MedicalXpress

# Scientists find molecular trigger that helps prevent aging and disease

November 18 2009

Researchers at Mount Sinai School of Medicine set out to address a question that has been challenging scientists for years: How do dietary restriction—and the reverse, overconsumption—produce protective effects against aging and disease?

An answer lies in a two-part study led by Charles Mobbs, PhD, Professor of Neuroscience and of Geriatrics and Palliative Medicine at Mount Sinai School of Medicine, published in the November 17 edition of the journal *Public Library of Science Biology*. The study, titled "Role of CBP and SATB-1 in Aging, Dietary Restriction, and Insulin-Like Signaling," examines how dietary restriction and a high-caloric diet influence biochemical responses.

Dr. Mobbs and his colleagues unraveled a molecular puzzle to determine that within certain parameters, a lower-calorie diet slows the development of some age-related conditions such as Alzheimer's disease, as well as the aging process. How the diet is restricted—whether fats, proteins or carbohydrates are cut—does not appear to matter. "It may not be about counting calories or cutting out specific nutrients," said Dr. Mobbs, "but how a reduction in dietary intake impacts the glucose metabolism, which contributes to oxidative stress." Meanwhile, a high calorie diet may accelerate age-related disease by promoting oxidative stress.

Dietary restriction induces a transcription factor called CREB-binding protein (CBP), which controls the activity of genes that regulate cellular

function. By developing drugs that mimic the protective effects of CBP - those usually caused by dietary restriction - scientists may be able to extend lifespan and reduce vulnerability to age-related illnesses.

"We discovered that CBP predicts lifespan and accounts for 80 percent of lifespan variation in mammals," said Dr. Mobbs. "Finding the right balance is key; only a 10 percent restriction will produce a small increase in lifespan, whereas an 80 percent restriction will lead to a shorter life due to starvation."

The team found an optimal dietary restriction, estimated to be equivalent to a 30 percent caloric reduction in mammals, increased lifespan over 50 percent while slowing the development of an age-related pathology similar to Alzheimer's disease.

The first part of the study looked at C. elegans, a species of roundworm, that were genetically altered to develop Alzheimer's disease-like symptoms. Dr. Mobbs and his team reduced the roundworms' dietary intake by diluting the bacteria the worms consume. In these types of roundworms, human beta amyloid peptide, which contributes to plaque buildup in Alzheimer's disease, is expressed in muscle, which becomes paralyzed as age progresses. This model allowed researchers to readily measure how lifespan and disease burden were simultaneously improved through dietary restriction.

The researchers found that when dietary restriction was maintained throughout the worms' adulthood, lifespan increased by 65 percent and the Alzheimer's disease-related paralysis decreased by about 50 percent.

"We showed that dietary restriction activates CBP in a roundworm model, and when we blocked this activation, we blocked all the protective effects of dietary restriction," said Dr. Mobbs. "It was the result of blocking CBP activation, which inhibited all the protective

effects of dietary restriction, that confirmed to us that CBP plays a key role in mediating the protective effects of dietary restriction on lifespan and age-related disease. "

In the second part of study, Dr. Mobbs and his team looked at the other end of this process: What happens to CBP in a high-calorie diet that has led to diabetes, a disease in which glucose metabolism is impaired? Researchers examined mice and found that diabetes reduces activation of CBP, leading Dr. Mobbs to conclude that a high-calorie diet that leads to diabetes would have the opposite effect of dietary restriction and would accelerate aging.

Dr. Mobbs hypothesizes that dietary restriction induces CBP by blocking glucose metabolism, which produces oxidative stress, a cellular process that leads to tissue damage and also promotes cancer cell growth. Interestingly, dietary restriction triggers CBP for as long as the restriction is maintained, suggesting that the protective effects may wear off if higher dietary intake resumes. CBP responds to changes in glucose within hours, indicating genetic communications respond quickly to fluctuations in dietary intake.

"Our next step is to understand the exact interactions of CBP with other transcription factors that mediate its protective effects with age," said Dr. Mobbs. "If we can map out these interactions, we could then begin to produce more targeted drugs that mimic the protective effects of CBP."

Source: The Mount Sinai Hospital