Activating protein enhances average lifespan, limits age-related disease in mice

December 4 2007

Metabolism researchers at Washington University School of Medicine in St. Louis have found that although it does not extend maximum lifespan in mice, activating a protein in muscle tissue increases average lifespan and prevents some age-related diseases. The researchers believe a similar approach may someday help people avoid age-related problems such as atherosclerosis, diabetes, hypertension and even some cancers.

In a series of experiments, the research team bred large numbers of mice, fed them a normal chow diet and followed each mouse until its natural death. Half were genetically engineered to make more of a protein in their muscle tissue called uncoupling protein-1. Their littermates did not make excess uncoupling protein. In muscle tissue, uncoupling protein-1 converts the energy from food into heat and mimics the effects of exercise.

Past research conducted in the laboratory of Clay F. Semenkovich, M.D., the Herbert S. Gasser Professor and chief of the Division of Endocrinology, Metabolism and Lipid Research, had found that mice with extra uncoupling protein-1 in muscle tissue are protected from diabetes and obesity.

Because the experiments took so long for this study and involved the breeding and following of so many mice, Semenkovich was joined on the paper by three first authors: Alison C. Gates, Ph.D., a former postdoctoral fellow in the lab now studying at Southern Illinois University Edwardsville; Carlos Bernal-Mazrachi, M.D., assistant

professor of medicine and of cell biology and physiology; and Sharon L. Chinault, Ph.D., former postdoctoral fellow and now assistant professor of biology at MacMurray College in Illinois. The findings are published in the December issue of the journal *Cell Metabolism*.

"Uncoupling basically means generating inefficient metabolism," says Semenkovich. "We knew years ago that when mice manufactured uncoupling protein in muscle, they didn't become obese. The next challenge was to see whether the protein would be relevant to some of the major problems that affect humans, namely aging and age-related disease."

The longest-lived animals in each group lived for 39 months and died within two weeks of one another. What was different was the median lifespan for the mice. Median survival in the uncoupled mice was 30 months, compared to 27 months for their wild-type littermates.

"We were a little bit disappointed because we had hoped uncoupling in muscle would slow aging, but maximum lifespan didn't increase," Semenkovich says. "However, the odds of reaching that maximum lifespan did improve in the uncoupled mice."

Semenkovich says the mice with the genetic alteration were more likely to live longer, presumably because they were able to avoid age-related diseases. One result appeared in all of the experiments: Decreasing body fat and inflammation in the animals by accelerating muscle metabolism with uncoupling protein delayed death and diseases, including atherosclerosis, diabetes, hypertension and even cancer.

The researchers examined the mice after each animal died. They were surprised to find that female mice with the uncoupling protein mutation were less likely to develop a type of cancer called lymphoma. None of the genetically engineered females did. No differences in lymphoma

rates were found in male mice. Increased uncoupling protein-1 in muscle also reduced markers of chronic inflammation.

In a second set of experiments, the researchers found that the uncoupled mice were less likely to have vascular disease. That was the opposite of what Semenkovich and his colleagues previously had found in mice engineered to overproduce uncoupling protein-1 in the wall of the aorta, the body's primary artery. Rather than being protected from damage, those mice were prone to develop high blood pressure and atherosclerosis.

"Where the uncoupling occurs has a big impact," he says. "If this principle someday becomes a therapy, it will be very important to target the proper tissues to produce the desired effects."

The team also generated a line of mice that made extra uncoupling protein only after the animals received drug therapy. They genetically modified a line of mice that already were prone to become obese. When the researchers gave these animals an antibiotic drug called doxycycline, they manufactured more uncoupling protein in muscle tissue and reversed their problems with glucose metabolism and hypertension related to their obesity.

Prior to these experiments, the researchers hypothesized that uncoupled mice might experience the type of increased survival seen in animals on calorie restriction. "Here at Washington University, we have Dr. John Holloszy, one of the world's leaders in aging research," Semenkovich says. "Calorie restriction prolongs lifespan in animals, and Dr. Holloszy has elegantly begun to translate caloric restriction studies to humans."

In landmark studies in the 1980s, Holloszy's team also had shown that rodents getting a great deal of exercise tended to live longer, but unlike calorie-restricted rodents, their maximum lifespan did not change.

Uncoupled mice, Semenkovich says, resemble the animals that exercised.

"Uncoupling in muscle may be a substitute for exercise," he says. "If that's true in humans, and if uncoupling can be done safely, this could be an important therapy because it's sometimes very difficult to get people to exercise."

Source: Washington University