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New clue into how diet and exercise enhance longevity

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The traditional prescriptions for a healthy life—sensible diet, exercise and weight control—extend life by reducing signaling through a specific pathway in the brain, according to Howard Hughes Medical Institute researchers who discovered the connection while studying long-lived mice.

They said their findings underscore the importance of maintaining a healthy lifestyle and may also offer promising research directions for understanding and treating diabetes and Alzheimer's disease.

Howard Hughes Medical Institute investigator Morris F. White and his colleagues published their findings in the July 20, 2007, issue of the journal *Science*. Akiko Taguchi and Lynn Wartschow in White's laboratory in the Division of Endocrinology at Children's Hospital Boston and Harvard Medical School were co-authors of the research article.

In their experiments, the researchers sought to understand the role of the insulin-like signaling pathway in extending lifespan. This pathway governs growth and metabolic processes in cells throughout the body. The pathway is activated when insulin and insulin-like growth factor-1 switch on proteins inside the cell called insulin receptor substrates (Irs).

Other researchers had shown that reducing the activity of the pathway in roundworms and fruitflies extends lifespan. Despite those tantalizing clues, White said, "The idea that insulin reduces lifespan is difficult to

reconcile with decades of clinical practice and scientific investigation to treat diabetes."

"In fact, based on our work on one of the insulin receptor substrates, Irs2, in liver and pancreatic beta cells, we thought more Irs2 would be good for you," said White. "It reduces the amount of insulin needed in the body to control blood glucose, and it promotes growth, survival and insulin secretion from pancreatic beta cells.

In earlier work, the researchers had found that knocking out both copies of the Irs2 gene in mice reduces brain growth and produces diabetes due to pancreatic beta cell failure. However, in the new study, when the researchers knocked out only one copy of the gene, they found the mice lived 18 percent longer than normal mice.

Because reducing insulin-like signaling in the neurons of roundworms and fruitflies extends their lifespan, the researchers decided to examine what would happen when they knocked out one or both copies of the Irs2 gene only in the brains of mice.

Mice lacking one copy of the Irs2 gene in brain cells also showed an 18 percent longer lifespan, and the near complete deletion of brain Irs2 had a similar effect. "What's more, the animals lived longer, even though they had characteristics that should shorten their lives—such as being overweight and having higher insulin levels in the blood," said White.

However, both sets of Irs2 knockout mice exhibited other characteristics that marked them as healthier, said White. They were more active as they aged, and their glucose metabolism resembled that of younger mice. The researchers also found that after eating, their brains showed higher levels of superoxide dismutase, an antioxidant enzyme that protects cells from damage by highly reactive chemicals called free radicals.

“Our findings put a mechanism behind what your mother told when you were growing up—eat a good diet and exercise, and it will keep you healthy,” said White. “Diet, exercise and lower weight keep your peripheral tissues sensitive to insulin. That reduces the amount and duration of insulin secretion needed to keep your glucose under control when you eat. Therefore, the brain is exposed to less insulin. Since insulin turns on Irs2 in the brain, that means lower Irs2 activity, which we’ve linked to longer lifespan in the mouse.”

White and his colleagues are planning their next studies to better understand how healthy aging and lifespan are coordinated by Irs2 signaling pathways in the body and the brain. White speculated that the insulin-like signaling pathway in the brain might promote age-related brain diseases.

“We are beginning to appreciate that obesity, insulin resistance, and high blood insulin levels are connected to Alzheimer’s disease, Huntington’s disease, and dementias in general,” he said. “It might be that, in people who are genetically predisposed to these diseases, too much insulin overactivates Irs2 in the brain and accelerates disease progression. Thus, insulin resistance and higher insulin levels might be the environmental influences that promote these diseases,” he said.

Source: Howard Hughes Medical Institute