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Reducing insulin signaling in the brain can prolong lifespan

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One route to a long and healthy life may be establishing the right balance in insulin signaling between the brain and the rest of the body, according to new research from Children's Hospital Boston. The study, published in the July 20 issue of *Science*, not only reinforces the value of exercising and eating in moderation, but also helps explain a paradox in longevity research.

Insulin sends a vital signal throughout the body telling cells to use sugar from the blood. But when cells become less sensitive to insulin, which often happens as we age and gain weight, the body must make more insulin to keep sugar under control and avoid type 2 diabetes. For a long time, clinicians and scientists thought that "more insulin was a good thing," says Morris White, PhD, a Howard Hughes Medical Institute investigator in Children's Division of Endocrinology, who led the new study. "But the increased insulin also gets into the brain, where it can be detrimental."

Studies in the worm C. elegans and in fruit flies show that reducing insulin signaling lengthens lifespan. But in humans and rodents, reducing insulin signaling often causes diabetes. The view that insulin could reduce lifespan is difficult to reconcile with decades of clinical practice and scientific investigation to treat diabetes.

White suspected that the key to explaining this paradox—and to maximizing both health and longevity—is to reduce insulin signaling only in the brain. To test this idea, White's team measured longevity and

other characteristics in several groups of mice. In one group, they used a genetic trick to cut in half the amount of Irs2, a protein that carries the insulin signal inside the cell, in every cell of the body. Two other groups of mice were genetically engineered to have half, or nearly all, Irs2 removed only from the brain cells. Another group of normal mice served as controls.

“To our surprise, all of the engineered mice lived longer,” says Akiko Taguchi, PhD, first author of the study. Even more surprising, the mice lacking Irs2 only in the brain lived almost half a year longer than the normal mice – an 18 percent increase in lifespan – despite being overweight and having higher blood insulin levels, changes that usually reduce lifespan. These long-lived mice were more active in old age, retained youthful metabolic cycles (burning sugar by day and fat by night) and retained protective levels of anti-oxidant enzymes such as superoxide dismutase, which protect against oxidative stress, or “biological rusting,” in the brain and body.

The mice with normal brain Irs2 levels aged less gracefully – they lost the metabolic rhythms of youth, became more sedentary, and had reduced anti-oxidant enzymes after meals, leaving them vulnerable to cellular damage. Such damage correlates with a host of age-related diseases such as atherosclerosis, Alzheimer’s disease and cancer, notes White.

White believes the study findings suggest a new approach to preventing diseases that shorten lifespan. “The engineered mice live longer because the diseases that kill them –
cancer, cardiovascular disease and others – are being postponed by reducing insulin-like signaling in the brain,” he says, “regardless of how much insulin there is in the rest of the body.”

Drugs that regulate Irs2 signaling in the brain (but not elsewhere in the

body) are one possible preventive strategy, but no such drug has yet been found. Targeted drugs will be important because Irs2 is needed in other tissues, particularly the pancreatic beta cells that produce insulin.

“The easiest way to keep insulin levels low in the brain,” White says, “is old-fashioned diet and exercise.” Although obesity and sedentary lifestyles tune down the body’s sensitivity to insulin, exercise can bring it back and reduce blood insulin levels. Eating smaller meals keeps insulin low in the bloodstream, ensuring that less reaches the brain. The new drugs designed to fight insulin resistance and type 2 diabetes might have a similar effect.

“This study provides a new explanation of why it’s good to exercise and not eat too much,” says White. “It has less to do with how we look, and more to do with a healthy brain, especially in old age.”

The study also calls into question the long-term effects of insulin therapy for diabetes, White adds. “High insulin should be the short term solution to insulin resistance, because it might damage the brain in the long run,” he says. Better treatments for diabetes and healthy aging, he suggests, should concentrate on sensitizing the body’s cells to low amounts of insulin.

Source: Children's Hospital Boston