# Fat signals control energy levels in the brain

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Credit: Human Brain Project

An enzyme secreted by the body's fat tissue controls energy levels in the brain, according to new research at Washington University School of Medicine in St. Louis. The findings, in mice, underscore a role for the body's fat tissue in controlling the brain's response to food scarcity, and suggest there is an optimal amount of body fat for maximizing health and longevity.

The study appears April 23 in the journal *Cell Metabolism*.

"We showed that fat tissue controls brain function in a really interesting way," said senior author Shin-ichiro Imai, MD, PhD, professor of developmental biology and of medicine. "The results suggest that there is an optimal amount of fat tissue that maximizes the function of the control center of aging and longevity in the brain. We still don't know what that amount is or how it might vary by individual. But at least in mice, we know that if they don't have enough of a key enzyme produced by fat, an important part of the brain can't maintain its energy levels."

The findings may help explain the many studies that show a survival benefit to having a body mass index toward the low end of what is considered overweight.

"As we age, people who are slightly overweight tend to have fewer problems," Imai said. "No one knows why people categorized as being slightly overweight tend to have a lower mortality rate. But our study suggests that if you don't have an optimal amount of fat, you are affecting a part of the brain that is particularly important for controlling metabolism and aging."

Imai and his colleagues study how cells produce and utilize energy and how that affects aging. Past work of theirs and others demonstrated the importance of an enzyme called NAMPT in producing a vital cellular fuel called NAD. Traditionally, NAMPT is thought to be important for making this fuel inside cells. But Imai and members of his team noticed that fat tissue churned out a lot of NAMPT that ended up outside cells, circulating in the bloodstream.

"There's been a lot of controversy in the field about whether extracellular NAMPT has any function in the body," Imai said. "Some researchers have said it's just a result of leakage from dead cells. But our

data indicate it is a highly active enzyme that is highly regulated."

Such fine-tuned regulation suggests secreted NAMPT is doing something important somewhere in the body. To find out what that is, the researchers raised mice that lacked the ability to produce NAMPT only in the fat tissue.

"We were not surprised to see that energy levels in the fat tissue plummeted when fat tissue lacked this key enzyme," Imai said. "Other tissues such as the liver and muscles were unaffected. But there was one distant location that was affected, and that was the hypothalamus."

The hypothalamus is a part of the brain known to have important roles in maintaining the body's physiology, including regulating body temperature, sleep cycles, heart rate, blood pressure, thirst and appetite. Mice with low NAMPT in fat tissue had low fuel levels in the hypothalamus. These mice also showed lower measures of physical activity than mice without this defect.

Their findings suggest that fat tissue communicates specifically with the hypothalamus, influencing the way the brain controls the body's physiologic set points. Indeed, past work from Imai's group also supported an important role for the hypothalamus in whole body metabolism. They showed that increasing the expression of a protein called SIRT1 in the mouse hypothalamus increased the mouse lifespan, mimicking the effects of a calorie-restricted diet.

Imai suspects that all these processes influence one another. Their past work on the hypothalamus also had shown that SIRT1 function is dependent on energy levels in cells. And the new paper links energy levels in the hypothalamus to the fat tissue's newly identified function.

After examining what happens to mice with fat tissue that doesn't make

NAMPT, they performed the opposite experiment, studying mice that produced more NAMPT in fat tissue than is typical.

Mice that expressed high levels of NAMPT in the fat tissue were very physically active. Their activity levels were especially pronounced after fasting. The mice with low NAMPT in the fat tissue became even more lethargic after the fasting period. The mice with an overabundance of NAMPT in the fat tissue appeared unaffected by the period of time without food, remaining at activity levels similar to normal mice without food restriction. In fact, the mice with a lot of NAMPT produced in their fat behaved very similarly to the mice with a lot of SIRT1 in the brain.

Imai said they are now studying whether an overabundance of NAMPT in the fat increases lifespan, as they showed in the mice with an overabundance of SIRT1 in the brain.

The researchers also found they could temporarily boost the physical activity of the mice with low NAMPT in the fat tissue by injecting NMN, the compound that the enzyme NAMPT produces. Imai is investigating NMN as a possible intervention in diseases associated with aging.

Imai speculated that this NAMPT signal from the fat tissue, especially in response to fasting, may serve as a survival mechanism.

"This phenomenon makes sense in the wild," Imai said. "If you can't get food and you just sit around and wait, you won't survive. So the brain, working in conjunction with the fat tissue, has a way to kick in and let you move to survive, even when food is scarce."

**More information:** Yoon MJ, Yoshida M, Johnson S, Takikawa A, Usui I, Tobe K, Nakagawa T, Yoshino J, Imai SI. SIRT1-mediated

eNAMPT secretion from adipose tissue regulates hypothalamic NAD+ levels in mice. *Cell Metabolism*. April 23, 2015.

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