

# Disabling mouse enzyme increases fertility

May 16 2008

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Changing the sugars attached to a hormone produced in the pituitary gland increased fertility levels in mice nearly 50 percent, a research group at Washington University School of Medicine in St. Louis has found. The change appears to alter a reproductive "thermostat," unveiling part of an intricate regulatory system that may one day be used to enhance human fertility.

"To adjust for the right amount of key reproductive hormones such as estrogen and testosterone, we may someday alter the sugars that are added to this hormone or others like it," says the group's leader, Jacques Baenziger, M.D., Ph.D., professor of pathology and immunology and of cell biology and physiology.

The report appeared recently in *The Journal of Clinical Investigation*.

Sugars are the most common addition to hormones and other proteins after they have been assembled from instructions in DNA. Nearly all proteins in the blood and on the surface of cells have sugars attached. Scientists believe sugar attachments modify and adapt proteins, enabling them to fill more than one job or changing the way they do their jobs in different contexts. But direct demonstration of such changes has been challenging.

Baenziger found a unique set of sugars consistently added to luteinizing hormone, which is part of a feedback loop between the pituitary, the reproductive organs and the liver. The loop cycles up and down over time, producing periodic peaks in other reproductive hormones and

triggering regular events such as the ovaries' release of eggs.

For their study, Baenziger's laboratory genetically disabled one of the enzymes that attaches sugars to luteinizing hormone in mice. This enzyme isn't the only one to add sugars to the hormone, so the alteration changes the mix of sugars rather than eliminating them completely.

“Initially, we didn’t seem to see much of a difference in the animals,” Baenziger says. “But then someone came to me and said, ‘We have too many animals. We’re constantly weaning mice!’”

A closer look showed that the mice were having nearly 50 percent more pups than normal, and that the liver removed the altered hormone from the blood more slowly. In addition, female mice were maturing earlier, were always receptive to male overtures for mating and had a disrupted ovulatory cycle. Males had higher levels of testosterone and females had higher levels of estrogen. Surprisingly, the altered female mice were also better mothers: They ate their pups less often.

"One could speculate that fertility problems in some humans may be partly related to a defect somewhere in this very complicated regulatory system," says Baenziger. "They may have the wrong proportion of some of these sugars, or the receptors that clear the sugar-hormone combination from the blood might not bind as well."

Baenziger, who recently won a five-year, \$3.3 million grant renewal from the National Cancer Institute, wants to learn more about the segments in the reproductive hormones that single them out for the addition of unique sugars. He hopes to use that information to search for other proteins that receive similar treatment.

"We know these systems for adding sugars are well-regulated, but we're just starting to get a sense for how they are controlled and how far-

reaching their effects can be," he says. "I think we're going to see much more of this kind of alteration and regulation of protein properties via added sugars in many other important areas of biology."

Source: Washington University School of Medicine

Citation: Disabling mouse enzyme increases fertility (2008, May 16) retrieved 18 April 2024 from <https://medicalxpress.com/news/2008-05-disabling-mouse-enzyme-fertility.html>

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