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Scientists Link Energy Metabolism and Fertility

Scientists have discovered that a protein that translates insulin signals during carbohydrate metabolism also plays an important role in female reproduction and in the regulation of appetite and obesity in mice.

According to the researchers, the link between energy metabolism and fertility may underlie an evolutionarily conserved pathway that makes humans and animals fit for reproduction. Further study of the insulin receptor substrate-2 (IRS-2) protein may offer alternative avenues for the treatment of diabetes and infertility.

In an article published in the September 21, 2000, issue of the journal *Nature*, Howard Hughes Medical Institute investigator Morris F. White and colleagues at Harvard Medical School report that female mice that lack IRS-2 show severely impaired reproduction. Mice lacking *IRS-2* have defective ovaries that prevent egg release and they show abnormal production of the egg-releasing hormone from the pituitary gland.

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- **Morris F. White**

The IRS family of proteins mediates the transmission of the insulin signal to proteins in other tissues. The IRS proteins were discovered in White's laboratory at Harvard's Joslin Diabetes Center. "In earlier experiments in which we knocked out *IRS-2* in mice, we realized that it had broad effects on the neuroendocrine system," White said. "Male *IRS-2* knockout mice became diabetic within ten weeks, not just because their tissues were insulin-resistant, but because IRS-2 also played a major role in keeping beta cells in the pancreas alive to secrete insulin, compensating for the insulin resistance."

IRS-2-knockout mice mimic non-insulin-dependent diabetes, or type 2 diabetes, which accounts for more than 90 percent of the cases of human diabetes. "One of the most striking results in these knockouts was that the female mice don't develop diabetes until about 20 weeks after birth, whereas the males get diabetes at 10 weeks," said White.

Thus, when postdoctoral fellow Deborah Burks, lead author of the *Nature* paper, decided to examine fertility in the mice, she began with the female mice since they remained healthy longer. "One of the first things she found was that these mice overeat and gain weight, effects not observable in the males because when their diabetes kicks in, they begin to waste away," said White. "However, it wasn't until she tried to breed the females that she found they were terrible breeders. We realized that these female mice were infertile," he said. "So, what we thought was an uninformative animal turned out to be highly informative."

Detailed physiological studies of the females showed that their ovaries had few mature egg-containing structures called follicles and there was no production of luteinizing hormone that triggers egg release. Additional studies showed that the animals' brains were resistant to the appetite-regulating hormone leptin, causing the animals to overeat and become obese.

"So, if these findings in mice extend to people, it looks as if the *IRS-2* branch of the insulin-signaling system promotes a lot of processes that improve our fitness for reproduction," White says. "It controls our food intake, makes us more fertile and allows our beta cells to survive to secrete insulin that keeps carbohydrates and insulin gene expression under control. *IRS-2* coordinates reproduction, feeding behavior, and internal carbohydrate homeostasis, which is critical since pregnancy and reproduction is a very energy-intensive process," he said.

Earlier studies by other research teams showed that a similar linkage of reproduction and energy metabolism exists in the roundworm *C. elegans* and in the fruit fly *Drosophila*, suggesting that this theme is conserved throughout the animal kingdom, said White.

The discovery of *IRS-2*'s coordinating role suggests that insulin resistance might be an underlying trigger of obesity in diabetics, said White. "Insulin resistance may disrupt the leptin set point," he said. "The person starts to eat more and gain weight, and that elevated weight causes an additional layer of insulin resistance that causes the weight to mushroom out of control."

The key role of *IRS-2* highlights the importance of developing anti-diabetes drugs that enhance *IRS-2* activity, he said. Also, he said, the finding hints that *IRS-2* malfunctions may be at the root of polycystic ovarian syndrome (PCOS). Women with PCOS have a range of problems, including infertility, obesity and insulin-resistance. "While the role of *IRS-2* in these areas is

currently speculative, we will try to understand in detail how IRS-2 regulates the ovaries to promote fertility. We will also be looking at IRS-2 function in the brain and other tissues," said White.