What insulin (and leptin) say to the brain

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A report in the April issue of *Cell Metabolism* offers new evidence to explain just what message insulin delivers to our brains.

The study also shows that leptin, an appetite suppressant hormone produced in fat tissue, delivers at least a partially overlapping message to the neurons that critically control energy balance. It's only when both receptors go missing from those so-called POMC neurons in mice that the animals show signs of systemic insulin resistance as their blood sugar levels rise.

"Despite the long history of study of insulin action in the brain, it's been difficult to figure out what it actually does," said Joel Elmquist of the University of Texas Southwestern Medical School.

That's in part because removal of insulin receptors from the brain does essentially nothing, he explained; it causes no real difference in either body weight or blood sugar control. When leptin receptors alone are deleted from POMC neurons, animals become mildly obese, but again show little to no change in blood sugar.

Those results had called into question the physiological importance of leptin and insulin action in the brain as far as glucose balance goes, the researchers said. But more recent work by Elmquist's team did show that leptin and insulin provoke an electrophysiological response in POMC neurons (although in different cells).

To investigate further, the researchers produced mice whose POMC neurons couldn't respond to insulin or leptin. Unlike animals lacking one or the other receptor, these double knockout mice showed systemic insulin resistance. (Elmquist said the findings are consistent with a recent study by another group, suggesting that leptin therapy—in place of the standard insulin therapy—might hold promise for those with type 1 diabetes.)

The leptin and insulin receptor-deficient mice also showed something else that came as a total surprise, Elmquist said. They had clear signs of infertility, including smaller litter sizes and more matings that failed to produce offspring. Further investigation revealed that the ovaries of the mutant females had more degenerating follicles and occasional cysts. The animals also had elevated testosterone levels. Infertility, elevated testosterone, and insulin resistance are all features reminiscent of polycystic ovarian syndrome (PCOS) in humans.

"The high testosterone levels are what really got our attention," Elmquist said. "We don't know yet, but this may be a model for PCOS." That would be an important advance, since PCOS is quite common and animal models for its study have been hard to come by. Elmquist said the study's first author, Jennifer Hill, now at The University of Toledo, is continuing with that line of investigation. One of the first questions she will ask is whether metformin, an insulin-sensitizing drug often used in the treatment of PCOS, has fertility benefits for the mice.

More information: Hill et al.: “Direct Insulin and Leptin Action in Pro-opiomelanocortin Neurons Is Required for Normal Glucose Homeostasis and Fertility.” Publishing in Cell Metabolism 11, 286-297, April 7, 2010. DOI:10.1016/j.cmet.2010.03.002

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