Insulin -- in need of some restraint?

March 7 2007

Knocking out the gene for a peptide associated with insulin secretion protects mice against the harmful effects of a high-fat diet, report researchers at the Salk Institute for Biological Studies. Their findings, detailed in the *Proceedings of the National Academy of Sciences*, suggest that urocortin 3, a new peptide recently discovered in the insulin secreting cells of the pancreas, plays a role in the increased production of insulin in response to high caloric intake in animals.

"Many normal mice eventually develop some signs of type 2 diabetes as they age," explains Wylie Vale, Ph.D., who conducted the study in collaboration with Kuo-Fen Lee, Ph.D., both professors in the Clayton Foundation Laboratories for Peptide Biology. "Interestingly, the mutant mice missing the urocortin 3 gene did not develop the age-related insulin resistance and high blood sugar we observed in the normal control mice," adds Vale.

After initial experiments had shown the importance of ucocortin 3 for the secretion of insulin, the Salk researchers bred mice missing the gene for urocortin 3 and compared their metabolism to that of normal mice. When placed on a high caloric diet for three months, the mutant mice packed on the same amount of weight and, as expected, had lower insulin levels. But, to the researchers' surprise, they also had lower blood sugar, improved glucose tolerance curves and didn't develop the fatty livers their unaltered counterparts suffered from.

"It is possible that restraining the abnormally high levels insulin secretion, which occurs with high caloric intake may help to maintain

insulin sensitivity and, thus, avoid some of the untoward consequences of the high food intake and weight gain," states first author Chien Li, the postdoctoral researcher who analyzed these mice and has since taken a faculty position at the University of Virginia.

Vale says the study reveals the "dark side" of high insulin production, the kind that results from over eating and obesity. "Insulin is very effective at lowering blood sugar, and promotes fat storage, preparing the animal for times when food may not be available," he says. "But when the hormone is produced at too high a level for too long, the body becomes insulin resistant and blood sugar and certain blood lipids gradually creep up, which can cause progressive damage to multiple organs."

Urocortin 3 is the second urocortin peptide that this laboratory has found to restrain insulin production or action. In a study published last October in *Proceedings of the National Academy of Sciences*, Vale, Lee and Alon Chen, Ph.D., a former postdoctoral researcher in Vale's laboratory, who is now at the Weizmann Institute of Science in Israel and Gerald Schuman, M.D., Yale School of Medicine, described a physiological function of urocortin 2.

They found that this peptide is highly produced in skeletal muscle, and functions as a negative regulator of insulin action and glucose use in those tissues. Mice lacking urocortin 2 had increased insulin sensitivity, and were protected against high calorie induced-insulin resistance over time – just like mice without urocortin 3. Additionally, the urocortin 2-deficient mice had less body fat and greater lean body mass.

Vale, Lee and their collaborators are now piecing together a global view of how these urocortin peptides, which are members of the corticotropin-releasing factor family, and their receptors regulate responses to physical and even psychological stimuli. The Salk group has been involved in the discovery of all of these peptide hormones as well as their receptors.

Urocortin 2 and urocortin 3 are part of the system that allows the body to secrete and respond to insulin as appropriate, Vale says. "We have found both ligands and their receptor that play important roles in insulin secretion and sensitivity. But they are not the only regulators in this very complex process and we must keep in mind that these metabolic studies have thus far only involved rodents," he cautions.

A study ongoing in Vale's laboratory aims to determine if knocking out both urocortin 2 and urocortin 3 in mice might offer additional benefits. "We know mice on a high-fat diet do better if either urocortin 2 or urocortin 3 is removed," he says. "We want to know if they do even better if both are missing. Such results may instruct us how best to develop therapeutic means to exploit these powerful effects," he adds.

Source: Salk Institute

Citation: Insulin -- in need of some restraint? (2007, March 7) retrieved 18 April 2024 from https://medicalxpress.com/news/2007-03-insulin-restraint.html

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