Obesity: Reviving the promise of leptin

January 6 2009

(PhysOrg.com) -- The discovery more than a decade ago of leptin, an appetite-suppressing hormone secreted by fat tissue, generated headlines and great hopes for an effective treatment for obesity. But hopes dimmed when it was found that obese people are unresponsive to leptin due to development of leptin resistance in the brain. Now, researchers at Children's Hospital Boston report the first agents demonstrated to sensitize the brain to leptin: oral drugs that are already FDA-approved and known to be safe. Findings were published January 7 by the journal *Cell Metabolism*.

In 1995, researchers reported in Science that they had isolated a protein that is present in normal mice, but not in an obese strain of mice called ob/ob, which lacked a gene also called ob. When either obese or normal mice were directly injected with the protein - now called leptin - they ate less and lost weight.

"Everyone in the field thought they would get the Nobel," says Umut Ozcan, MD, of Children's Division of Endocrinology. Unfortunately, when obese humans took the hormone, they lost weight only temporarily - then rebounded back. "Most humans who are obese have leptin resistance," says Ozcan. "Leptin goes to the brain and knocks on the door, but inside, the person is deaf."

For years, industry and academic laboratories have been searching for a drug to make peoples' brains sensitive to leptin again, without success.

In the new study, Ozcan's group first showed that the brain cells of obese mice have increased stress in the endoplasmic reticulum (ER) - a structure within the cell where proteins are assembled, folded into their appropriate configurations, and dispatched to do jobs for the cell. In the presence of obesity, the ER is overwhelmed and can't function properly. This stress triggers a signaling cascade (the "unfolded protein response") that tries to relieve the stress by increasing the level of molecular "chaperones," which assist in protein folding, and by blocking more proteins from coming in.

Ozcan and colleagues then showed that ER stress, and the resulting activation of this signaling cascade, blocks leptin action in the brain. Most intriguingly, they showed that using chemical chaperones to reduce ER stress can re-sensitize the brain to leptin, and lead to weight loss when used in conjunction with leptin. "I think our study will bring new hope for the treatment for obesity," says Ozcan.

Working first with mice made obese through a high-fat diet, they demonstrated that the animals developed ER stress in the hypothalamus, the main area of the brain where leptin signals. This in turn initiated the unfolded-protein response, rendering the mice extremely leptin-resistant. The team also created a strain of mice whose ER was weakened in the brain through deletion of a gene called XPB1 specifically in the neurons.

These mice also developed ER stress and leptin resistance, and also became obese, despite having some of the highest leptin levels ever reported. As expected, the mice also ate more and gained more weight.

But when Ozcan and colleagues pretreated either group of mice with a chemical chaperone (either 4-PBA or TUDCA) leptin sensitivity increased as much as 10-fold, and the mice had significant weight loss with leptin treatment even when fed a high-fat diet.

Children's researchers hope to eventually move the discovery to human trials. Both 4-PBA and TUDCA are safe in humans and already FDA-approved for clinical use. 4-PBA (Buphenyl) used in urea cycle disorders and in cystic fibrosis; TUDCA (tauroursodeoxycholic acid), used for centuries in traditional Chinese medicine, is currently used in some liver diseases. Both agents are under study for use in neurologic disorders such as Alzheimer's disease and Huntington's disease.

In related work in 2006, Ozcan and colleagues reported in Science that chemical chaperones reduce ER stress in a mouse model of type 2 diabetes, normalizing blood sugar and restoring insulin sensitivity.

In 1995, Amgen, Inc. (Thousand Oaks, CA) paid $20 million for commercial rights to recombinant human leptin, a record amount for a deal with an academic institution. In 2006, Amgen sold the rights to Amylin Pharmaceuticals (San Diego, CA). Amylin is testing leptin in combination with its diabetes drug, pramlintide.

Provided by Harvard University