Mouse study prompts experts to revisit the promise of leptin

Fifteen years ago, the groundbreaking discovery of the appetite-suppressing hormone leptin provoked a buzz of excitement and promise. Rumors of a possible Nobel Prize were in the air, and the world anticipated leptin-based therapies for a growing number of people struggling with obesity.

Initial experiments in rodents hinted that this type of treatment might work. But hopes of creating a wonder diet drug dwindled after a decade of trials found that—with the exception of people with rare leptin-associated metabolic disorders—the vast majority of obese individuals were resistant to exogenous leptin. Disappointing results continued, and the California-based company Amgen sold its commercial rights to leptin, which it initially bought for $20 million in 1995.

Over the past few years, researchers have desperately been looking for a mechanism that explains this leptin resistance. A new study by Umut Ozcan at Harvard Medical School in Boston and his colleagues may well have hit the nail on the head—the researchers have found a method of resensitizing the brain to leptin (*Cell Metab.* **9**, 35–51; 2009).

In mice fed a high-fat diet, the researchers found evidence of increased stress in the endoplasmic reticulum (ER), a cell organelle where proteins are made, on the basis of levels of a molecule known as phosphoric acid. ER stress tends to occur when demand for protein synthesis exceeds normal ER production capacity, and proteins begin to pile up within the organelle. This stress triggers a cascade of signals that block leptin from acting in the brain.

During ER stress, chaperone molecules try to stabilize protein synthesis by overseeing intracellular protein folding. So Ozcan's group reasoned that chaperone molecules could help overcome ER stress and increase leptin sensitivity.

The researchers turned to two chaperone molecules, phenyl butyric acid and tauroursodeoxycholic acid, both used to treat liver ailments. They injected these drugs directly into obese mice that were genetically engineered to be leptin resistant. The mice were then treated with leptin. Whereas the control mice lost about 25% of their body weight over two weeks, the mice pretreated with chemical chaperones lost more than 40% of their body weight within the same timeframe.

Ozcan and his colleagues hope that this finding will help translate into a long-sought leptin-based treatment for obesity in humans. "Lots of molecular mechanisms that are identified in mice are also the mechanisms seen in humans," he says, noting that the proteins involved in the ER stress pathway are similar in mice and humans.

"This is an elegant piece of science and raises the possibility that ER stress might underpin leptin resistance," says Stephen O'Rahilly from the University of Cambridge Metabolic Research Laboratories in Britain.

However, other researchers are skeptical. David Ron of the New York University Langone Medical Center in New York speculates that ER stress might not have a direct relationship with leptin signaling. Ron says that chemical chaperones are simple compounds that "may have many targets in the cell," adding that it is "far from proven" that these chaperones affect leptin resistance by alleviating ER stress.

Whether this new study will translate to clinical benefits for obese individuals will have to be further tested, but it looks like leptin can be put back on the table for possible therapeutic potential, particularly as a study involving 177 obese and overweight individuals published last spring (*PNAS* **105**, 7257–7262; 2008) found that a combination treatment of leptin and the diabetes drug pramlintide caused significant weight loss over a six-month period.

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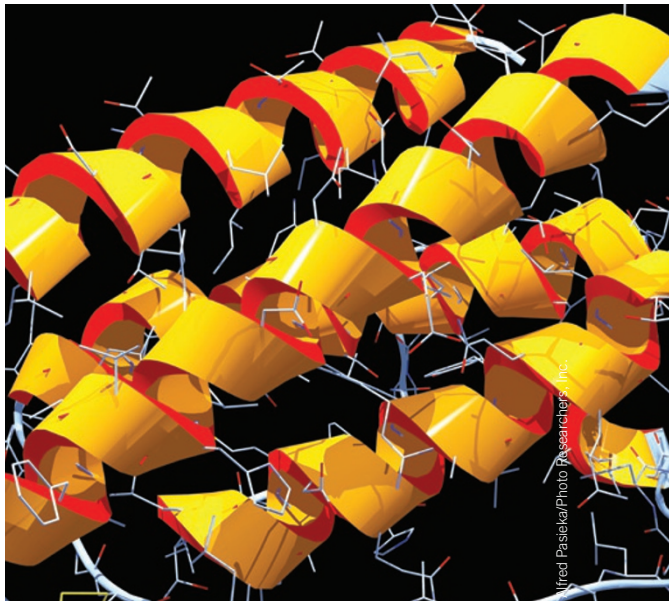

Tricky hormone: Leptin has thrown researchers for a loop

Branded baubles to become history

Say goodbye to the pens, stress balls, mugs and other trinkets emblazoned with pharmaceutical brand names that have been a common sight in doctors' offices for nearly three decades. As of 1 January, a new voluntary code issued by the Pharmaceutical Research and Manufacturers of America (PhRMA) has put a kibosh on the branded baubles.

"Although our member companies have long been committed to responsible marketing of the life-enhancing and life-saving medicines they develop, we have heard the voices of policymakers, healthcare professionals and others telling us we can do better," Billy Tauzin, president and chief executive officer of PhRMA, said in a written statement.

However, not everyone is convinced that this move will remove industry influence from clinics. The change in code does little to affect the overall business model of how pharmaceutical company representatives market their products to physicians, says Allan Coukell, the director of policy at the Prescription Project, a nonprofit organization funded by the Pew Charitable Trusts to promote the recommendations of a 2006 article in the *Journal of the American Medical Association* that criticized how drugs are marketed to doctors (*JAMA*, doi:10.1001/jama.295.4.429; 2006).

"The fact is that, after the Vioxx debacle, all those pens and coffee mugs just became blatant reminders of how caring about people can fall to the wayside when pharmaceuticals are pushed like any other business product," says Coukell. "Now, they're not going to give doctors 99-cent pens. But they're still going to give them expensive dinners and other perks."

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