Scientists Test Anti-obesity Vaccine

July 31 2006

In what may be the first published breakthrough of its kind in the global battle against obesity, scientists at The Scripps Research Institute have developed an anti-obesity vaccine that significantly slowed weight gain and reduced body fat in animal models.

The study is being published in an advanced, online edition of the *Proceedings of the National Academy of Sciences* during the week of July 31 to August 4.

In the new study, mature male rats immunized with specific types of the active vaccine ate normally yet gained less weight and had less body fat, indicating that the vaccine directly affects the body's metabolism and energy use. This finding may be especially important to stop what is commonly known as "yo-yo dieting," the cycle of repeated loss and regain of weight experienced by many dieters. The new vaccine, which is directed against the hormone ghrelin (pronounced "grell-in"), a naturally occurring hormone that helps regulate energy balance in the body, has shown the potential, in animal models at least, to put an end to that risky and often futile struggle.

These findings may mark a turning point in the treatment of obesity by confirming the effectiveness of immunopharmacotherapy to combat this serious and growing global problem. Immunopharmacotherapy engages the immune system, specifically antibodies, to bind to selected targets, directing the body's own immune response against them. This approach is being tested in a number of other areas including drug addiction, especially addiction to cocaine and nicotine.

"The study shows our vaccine slows weight gain and decreases stored fat in rats," said a senior author of the paper Kim Janda, Ph.D., who is Ely R. Callaway, Jr. Professor of Chemistry at Scripps Research, a member of The Skaggs Institute for Chemical Biology, and director of the Worm Institute of Research and Medicine. "While food intake was unchanged in all testing groups, those who were given the most effective vaccines gained the least amount of weight. To have an impact on appetite and weight gain, ghrelin first has to move from the bloodstream into the brain-where, over long periods, it stimulates the retention of a level of stored energy as fat. Our study is the first published evidence proving that preventing ghrelin from reaching the central nervous system can produce a desired reduction in weight gain."

Ghrelin, a gastric endocrine hormone produced primarily in the stomach, plays a physiological role in energy homeostasis, although the full extent of that role remains unknown. It was first identified in 1999 as a naturally occurring ligand-a molecule that binds to another to form a larger molecular complex-for a growth hormone secretagogue receptor. What is known is that ghrelin promotes weight gain and fat storage through its metabolic actions, decreasing the breakdown of stored fat for energy as well as curbing energy expenditure itself. During periods of weight loss, such as dieting, the body produces high levels of ghrelin to slow down fat metabolism, encourage eating, and promote fat retention, changes which normally make it difficult to lose weight and keep it off.

"We’re not claiming that our study answers the question of obesity treatment once and for all," Janda said. "What we are saying-and what our study confirms-is that this looks like a serious workable solution to the problem. And while much more research is needed to understand the full therapeutic potential of immunopharmacotherapy in combating obesity, these initial results are extremely positive. Right now it appears that active vaccination against ghrelin is one avenue that can slow weight gain and fat build-up in the body."

Producing an Active Vaccine

"Through our work in the development of immunopharmacotherapy-based vaccines against drug addiction, we became interested in the problem of obesity," Janda said. "While there were numerous possible hormones involved in obesity that could be targeted, we decided that ghrelin would be a good starting point to examine such a hypothesis."

The researchers developed three active vaccines (labeled Ghr1-2-3) to immunize adult male rats. Those animals immunized with Ghr1 or Ghr3 showed greater and more selective plasma-binding capacity for the active form of ghrelin-keeping the hormone in the blood and away from the brain and the central nervous system-as compared to Ghr2 or control models.

During the study, the rats immunized with Ghr1 and Ghr3 ate normally but, once antibody levels increased, accrued less body weight and fat, indicating an increase in the body's use of energy, a finding supported by studies of genetically altered mice. For example, the authors of the study write, "mice deficient for ghrelin or its receptor store less of their consumed food and resist accumulating body weight and fat on energy dense diets. [Ghrelin-deficient mice] also expend more energy and [are more active], [while] ghrelin receptor deficient mice show increased [utilization of fat as a key energy source]."

The study did note, however, that the immunized rats were fed low-energy, low-fat, and relatively less palatable chow diets and were comparatively lean. "Whether active immunization against ghrelin would help prevent the development of obesity caused by… high-fat 'Western' diets or would facilitate weight loss once obesity is established" remains uncertain, the study added.

Eric Zorrilla, Ph.D., a Scripps Research assistant professor, member of

the Harold L. Dorris Neurological Research Institute, and a lead author of the study, said, "The rats who received the most effective vaccines didn't eat differently than the others, including the control models. That makes our findings exciting therapeutically-the vaccine slows the rate of weight gain, while still allowing for normal eating habits. A vaccine against ghrelin also is particularly compelling in terms of the well-documented problems of human dieting. When you diet, the body responds as if it was starving and produces ghrelin to slow down fat metabolism and stimulate eating, changes meant to help retain and regain body fat. As a result, many people end up regaining the weight they lost and more once they go off their diets. This vaccine may have the real potential to prevent or seriously reduce yo-yo dieting, the repetitive cycle of weight loss and gain, because it interferes with ghrelin's ability to promote weight gain and fat accumulation."

There is broad speculation that ghrelin evolved as a response to the feast or famine conditions of early humans. Those who were genetically predisposed to eat heartily and store fat efficiently during periods of plenty were more likely to survive the next round of scarcity and passed this trait onto the next generation. In recent years, however, that powerful genetic legacy has come in direct conflict with the dangerous phenomenon of overeating in the developed world.

The Worldwide Threat of Obesity

Obesity remains a serious and growing problem for millions of people worldwide and is a contributing risk factor for a number of other diseases including heart disease, various cancers, Type 2 diabetes, stroke, arthritis, and depression. Although a number of pharmaceutical approaches have been taken to try to help people better control their body weight, few if any have been successful and several, including the drugs fenfluamine (a component of "Fen-Phen") and ephedrine, have been pulled from the market by the U.S. Food and Drug Administration.

According to recent reports from the World Health Organization, about 1 billion people worldwide are overweight or obese, most of them in the developed world. In the United States, for example, the National Health and Nutrition Examination Survey found that, in 2003 to 2004, approximately 66 percent of all American adults 20 years of age or older were overweight or obese. Almost four out of every five American men aged 40 to 59 were classified as overweight, according to a 2006 study published by the Journal of the American Medical Association. Even Japan, long a dietary exception, has experienced a rise in obesity and diabetes as Western-style eating habits continue to take hold in that country.

"The reason we looked at immunopharmacotherapy vaccines to treat obesity," Janda said, "was because drugs seeking to modulate obesity-driven receptors via agonist or antagonist effects have been remarkably unsuccessful. They are effective only while treatment is maintained and when treatment stops, weight returns. For obesity treatments to work, they must affect energy intake, absorption, expenditure, or storage. Our new vaccine works by changing expenditure or storage."

The ghrelin vaccine produced by Scripps Research scientists is not the only one being tested. Cytos, a Swiss-based biotechnology company, is currently testing a ghrelin-based vaccine in a combined phase I/II study with 112 obese patients. Like the Scripps Research vaccine, the Cytos vaccine produces antibodies that inhibit the uptake of ghrelin by the brain. However, Janda and Zorrilla noted, there are significant differences between the two vaccines.

"Compared to other ghrelin-based vaccines being studied," Zorrilla said, "our vaccine was designed to raise antibodies against the active form of ghrelin, which, we believe, makes it distinctive. "In addition," Janda stated, "the most effective forms of the vaccine contained an unnatural ester functionality-this not only increases water solubility, but minimizes

aggregation and micelle formation, which provides an additional, little-known therapeutic window for the success of a productive immune response. Simply stated, this translates into a better obesity vaccine."

In addition, Janda said, the Scripps Research vaccine did not produce a systemic inflammatory response. General inflammatory responses can occur with fevers or even cancers, causing lack of food intake and weight loss. That was not the case with the new vaccine.

Other authors of the study, titled "Vaccination against weight gain," include Shinichi Iwasaki, Jason A. Moss, Jason Chang, Jonathan Otsuji, and Michael M. Meijler of The Scripps Research Institute and its Skaggs Institute for Chemical Biology, as well as Koki Inoue of Osaka City University.

The study was supported by the National Institute of Diabetes, Digestive, and Kidney Disorders and The Skaggs Institute for Chemical Biology.

Source: Scripps Research Institute