Obestatin

A new hormone named obestatin may be used to help obese people control their appetite and lose weight.

Obestatin, a recently discovered anti-hunger peptide hormone, when injected into laboratory rats, reduced food intake and caused weight loss in the rats, according to a new report published in the Nov. 11 issue of Science.

Scientists have tried for years, yet failed to enlist other appetite-regulating hormones such as ghrelin and leptin to develop a treatment for obesity. In an article accompanying the report in the journal Science, Greg Barsh, genetics professor of Stanford University commented, "There are several known pathways that regulate body weight. This work is notable because it represents a completely new pathway."

For the study, scientists at Stanford University localized the gene sequence for the appetite-suppressing hormone obestatin, and then tested obestatin in normal rats for its function in regulating appetite or hunger.

After eight days of injection treatment of obestatin, rats ate only half as much as they did normally and lost 20 percent of their weight. Injection of obestatin also slowed the passage of digested food from the stomach to the small intestine, which in part delayed the hunger sensation long after a meal, the report said.

"To our surprise, we found that treatment with it suppresses food intake," said Dr. Aaron Hsueh, principal investigator of the study, an endocrinologist and professor of obstetrics and gynecology at Stanford. "It could have potential as an appetite-suppressing drug, by injection. Or it might be possible to deliver by nasal spray. It also allows us to screen for new drugs that might suppress appetite."

Obestatin is not the first appetite or hunger hormone ever found. A noteworthy hormone known as ghrelin, which was discovered in 1999, has been researched for its role in regulating hunger. Researchers had hoped that they could find a treatment for obesity based on ghrelin, but they could not.

Ghrelin, secreted from specialized stomach cells and the upper part of the small intestine, functions to carry messages between the brain and digestive system. It boosts hunger sensation and increases appetite. Its level gets high before a meal and becomes low after a meal.

Previously, ghrelin was considered the counterpart of leptin, an appetite-suppressing hormone produced in adipose tissue, which induces satiation at higher levels. However, leptin, which was found in 1994, did not seem a match for ghrelin and it wasn't effective in treating obesity in humans, although animal studies showed promise.

Obestatin, an anti-ghrelin appetite suppressing hormone, is produced from the same gene sequence from which ghrelin is also produced, according to the study. Ghrelin and obestatin share the same gene sequence, but have opposite effects on the regulation of appetite and hunger.

"That was the big surprise," said Professor Hsueh. It is rare for one gene to make two proteins. Scientists believed the gene encodes a protein which is in turn broken into two parts, forming ghrelin and obestatin.

The finding intrigued scientists like Dr. David Cummings at the University of Washington, who did not participate in the study, but have been researching ghrelin for a treatment for obesity.

The presence of obestatin helps solve the long-standing puzzle about mice (bred to lack the ghrelin gene sequence) live a fairly normal life. In contrast to what was expected, they do not lose their appetite and

weight and become skinny, Dr. Cummings said.

The explanation is, when the ghrelin gene was deleted, the obestatin gene was also deleted, this causing no net effect on appetite or hunger.

Hunger sensation may depend on a balance between ghrelin and obestatin. "A better understanding of the roles of ghrelin and obestatin in the intricate balance of energy homoeostasis and body weight control may be essential for successful treatment of obesity," the authors write.

Indeed, understanding ghrelin alone may not be enough. Previous studies by David Cummings found after dieters lost weight, the body tended to make more ghrelin than they did before dieting. The body seems to have a tendency of maintaining the status quo of the body weight. But options to tackle the problem have been limited.

Now, obestatin may come to rescue. Scientists may increase the level of obestatin to suppress the effect of ghrelin. Ghrelin and obestatin together may help find a way to treat obesity and potentially eating disorder anorexia nervosa in which patients tend to have high plasma levels of ghrelin.

Professor Hsueh said his discovery could lead to some potential applications. “Obestatin itself could have potential as an appetite-suppressing drug because one can use this small peptide by injection," he said. "The identification of the receptor for obestatin can also allow us to screen for new drugs that can also suppress appetite."

However, it is not clear how obestatin would affect body weight, although obestatin reduces appetite and forces lab rats to eat less. In an editorial accompanying the report, Dr. Matthias Tschöp, associate professor of psychiatry at the University of Cincinnati, commented that obestatin's "effect on body weight appears to be subtle."

"The effect of obestatin on body weight seems to be relatively limited," Tschöp commented. "Also, it might cause some sort of illness or nausea that causes a decrease in food intake."

The scientists involved in the study found rats, who were given the obestatin injection, ate much less, but they did not lose as much weight as expected. Further, it is unknown whether the lost weight came from fat or muscle tissue. The study tested obestatin in normal rats. How it would affect fat rats remain unknown.

One obstacle for obestatin to be used as an orally administered drug is that much of it can not survive in the stomach. For this, the hormone may be modified to avoid its breakdown in the stomach, which needs more work to be done.

Appetite-suppressing hormone obestatin may help fight obesity.

A new hormone named obestatin may be used to help obese people control their appetite and lose weight.

Scientists have tried for years, yet failed to enlist other appetite-regulating hormones such as ghrelin and leptin to develop a treatment for obesity. The finding re-kindles people's hope of defeating the global obesity epidemic in the foreseeable future.

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One obstacle for obestatin to be used as an orally administered drug is that much of it can not survive in the stomach. For this, the hormone may be modified to avoid its breakdown in the stomach, which needs more work to be done.

The importance of obestatin in human health is underlined by observations that: 1) it prevents the obesogenic actions of ghrelin, 2) it is elevated in patients with anorexia nervosa and 3) levels are unusually low in obese and post-gastrectomy subjects. Since obestatin does not appear to cross the blood-brain-barrier nor to act on pancreatic, hepatic or peripheral tissues it is believed that the majority obestatin's physiological effects are the result of direct actions on the

intestine. Actions of obestatin on the gastrointestinal tract have not yet been characterised.

Since that first description of obestatin, there has been some controversy in the literature about the exact role of obestatin and its significance in suppressing appetite, and some newer studies have failed to support a role for obestatin in suppressing appetite. While the exact role of obestatin in controlling appetite and weight remains to be determined, Park and co-workers show in a new paper that children with Parder-Willi Syndrome do not seem to have elevated levels of obestatin in their blood, despite having high levels of ghrelin.

These researchers have examined ghrelin levels before in people with PWS, and here they look at ghrelin, obestatin and insulin levels in 15 children with PWS and 18 controls. They find, as expected, total and acetylated ghrelin are high in children with PWS. For both those with PWS and controls, insulin levels are inversely related to ghrelin levels - this is also an expected result since it has been previously proposed that insulin regulates ghrelin in this manner. As has also been reported, after drinking glucose, insulin levels were lower in kids with PWS compared to controls. But there was much less difference between controls and those with PWS when it came to obestatin. There were no significant differences in obestatin levels in the blood in those with PWS or controls after glucose was given, nor did there seem to be a strong relationship between the levels of obestatin and insulin in either group. The authors conclude that obestatin is not elevated in PWS, nor does obestatin appear to be regulated in the same manner as ghrelin. At this time, then, there does not seem to be strong reason to suspect that obestatin plays a critical role in the excessive appetite associated with PWS.

Obestatin is not elevated in PWS

An article published last year described a new appetite suppressing peptide hormone, obestatin (see previous blog and reference here). One interesting feature about this peptide is that it appears to be derived from the same precursor as ghrelin, the hunger hormone elevated in PWS. Thus ghrelin and obestatin were proposed to originate from the same molecule, but have opposing effects - a Yin and Yang of the appetite world.

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The effect of obestatin peptides on intestinal contractility, peristaltic activity and food intake:

Obestatin is a newly discovered peptide hormone that decreases food intake and inhibits gastric emptying. The importance of obestatin in human health is underlined by observations that: 1) it prevents the obesogenic actions of ghrelin, 2) it is elevated in patients with anorexia nervosa and 3) levels are unusually low in obese and post-gastrectomy subjects. Since obestatin does not appear to cross the blood-brain-barrier nor to act on pancreatic, hepatic or peripheral tissues it is believed that the majority obestatin's physiological effects are the result of direct actions on the intestine. Actions of obestatin on the gastrointestinal tract have not yet been characterised.

Eating and Sleeping

Eating and sleeping—their relationship to ghrelin and leptin

EATING AND SLEEPING is two kinds of behavior that are essential for the survival of humans and higher animals. Whereas it is obviously excluded that they occur exactly at the same time, there appear to be common regulators of both phenomena. With the identification of ghrelin as the endogenous ligand of the growth hormone (GH)-secretagogue (GHS) receptor by Kojima et al. a new endogenous regulator of food intake and possibly also of sleep was found. In this issue of the American Journal of Physiology-Regulatory, Integrative and Comparative Physiology, Bodosi et al. report a sophisticated study on the relationship between sleep, feeding, ghrelin, and its antagonist in the energy balance, leptin.

The detection of ghrelin was preceded in the 1970s by the synthesis of GHSs and by the cloning of the GHS receptor. Although they act

on a different receptor, the GHSs and ghrelin share the capacity of GH-releasing hormone (GHRH) to stimulate GH. In addition to this endocrine effect, GHRH stimulates non-rapid eye movement (REM) sleep in various species including humans. Similarly sleep-promoting effects of synthetic GHS were found in humans. Furthermore, some hints exist for a stimulating influence of GHS on food intake and body weight.

Soon after the identification of ghrelin, which is displayed mainly in the stomach and also in other tissues including the hypothalamus, it became clear that it is the most powerful endogenous orexigenic factor known so far. Ghrelin stimulates food intake and conserves fat, resulting in increasing body weight in rodents. Similarly, appetite and calorie intake increased after ghrelin administration in humans. Ghrelin levels were found to be changed in eating disorders, with high concentrations in anorexia and Prader-Willi Syndrome and blunting in obesity. In contrast to ghrelin, leptin is an anorexigenic factor and it is thought that ghrelin and leptin regulate the energy balance in a reciprocal fashion.

Similarly to GHRH, non-REM sleep was enhanced after ghrelin in mice and humans. Intact GHRH receptors were shown to be the prerequisite for this effect in mice. Also, an effect of leptin on sleep was reported. Bodosi et al. compared plasma ghrelin and leptin levels and hypothalamic ghrelin contents, sleep, brain temperature, and feeding throughout the dark-light cycle in rats in three experimental conditions: free-feeding animals with normal diurnal rhythms, restricted feeding, and sleep deprivation. From their findings they conclude that intimate relations between feeding and plasma ghrelin and leptin are corroborated, whereas there are no strong links between sleep and these hormones in the rat. These study results are a challenge to search for the answers to new questions.

To what extent is ghrelin secretion under circadian regulation? In humans there exist controversial data whether ghrelin levels show major fluctuations throughout the day.

Whereas the fluctuations of hypothalamic ghrelin were not significantly under baseline conditions, according to the localization of ghrelin-containing neurons in the brain, Cowley et al. suggested a role of ghrelin in the regulation of rhythms, particularly in the timing of meals. Does ghrelin also play a role in the timing of sleep? This is not supported convincingly by the findings in the rat.

Sleep deprivation in the rat is accompanied by increases in ghrelin levels. In contrast, in humans a nocturnal ghrelin peak was found to be blunted during sleep deprivation. Findings in humans suggest dose-dependent differences in the behavioral effects of ghrelin. At night, a higher dose of ghrelin significantly induced hunger, whereas the lower dose promoted sleep. Interestingly, leptin peaks in humans and in rats during the night, whereas they have opposite sleep-wake patterns. Are there differences in the action of ghrelin and leptin between rats and humans?

So far little is known about gender differences in the effects of ghrelin. Given the fact that GHRH exerted sexually dimorphic effects on sleep-endocrine activity in humans similar studies appear to be necessary with ghrelin.

The GHS receptor appears to be an interesting target for pharmacological regulation of food intake, particularly for the treatment of obesity. During the development of such therapies side effects on sleep must be kept in mind.