

Hungering for Obesity Treatments

Jyoti Madhusoodanan

Will understanding the complex molecular signals involved in hunger yield better obesity drugs?

Fueled by chips, cookies, and other high-calorie snacks, our expanding waistlines pose a hefty problem. The World Health Organization dubbed obesity a global health epidemic in 2003. As of 2015, one-third of adults in the U.S. are obese, and an additional one-third are overweight. As obesity rates soar, so do their associated health problems, which include diabetes, heart disease, and more. With an epidemic of these proportions, researchers have long sought simpler cures—ones that can be bottled.

Early weight-loss drugs, which used molecules such as dinitrophenol and sibutramine, were introduced and later withdrawn due to their dangerous side effects. Until a few years ago, the only obesity medication approved in both the U.S. and Europe was orlistat—a molecule that blocks intestinal nutrient absorption but does little to abate appetite.

But that's changing. The discovery of two key hormones that control weight and appetite—leptin and ghrelin—in the 1990s electrified researchers hunting for obesity medications. Although drugs targeting these molecules met with little clinical success, their discovery paved the way to a better understanding of the complex mechanisms that control our cravings and how our bodies respond to food.

"A few years ago there were really no pharmaceutical treatments for obesity", says [Gregory J. Morton](#) of the University of Washington. "Now, there's a pipeline of certain viable treatments that act in part through the central nervous system—that's where a lot of the basic science is starting to reap some rewards." In addition to looking to the central nervous system (CNS) for targets, researchers are also testing combinations of medications that reach more than just one molecular mechanism as a way to finally effectively control obesity.

■ SEARCHING FOR HUNGER HORMONES

In 1994, [Jeffrey M. Friedman](#) of the Rockefeller University discovered leptin, a hormone secreted by fat cells that acts in



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the brain to suppress eating, keeping weight gain in check. Mice lacking the leptin gene are grossly overweight and can't stop eating. And when normal animals (or people) lose weight, leptin levels drop as fat cells disappear, so the individuals get hungrier, often leading to regaining weight.

Leptin acts over days and weeks. But what makes us hungry for lunch mere hours after breakfast, when we haven't lost any significant fat stores between the two meals?

Six years after leptin's discovery, researchers led by Masayasu Kojima of Kurume University found a clue: the so-called "hunger hormone", ghrelin. Kojima's and other researchers' work revealed that ghrelin is a peptide secreted by the stomach that spikes before meal times and travels to the brain via the bloodstream. There, among other things, it acts on the hypothalamus to boost appetite and triggers neurotransmitter release. Ghrelin was "the long-sought mediator of appetite and meal initiation signal", says [David E. Cummings](#) of the University of Washington, who did some of the early work on ghrelin.

To this day, ghrelin is the only known appetite-stimulating hormone; other molecules signal satiety or suppress appetite.

Published: March 14, 2017

Several studies have proven its dramatic effects: Animals lacking ghrelin eat less and are resistant to diet-induced weight gain, while humans and animals who are given doses of ghrelin eat more and pack on the pounds. A human genetic condition (Prader–Willi syndrome) that spikes ghrelin levels can cause uncontrollable eating and obesity in children.

Ghrelin's potent effects led to a flurry of research on ghrelin-blocking molecules as a new route to potential antiobesity drugs. But, in animal studies, even when ghrelin antagonists were found to be safe and block the hormone's activity, they failed to treat obesity. "No one has designed a ghrelin receptor antagonist that actually suppresses feeding behavior", says [Roy Smith](#) of The Scripps Research Institute in Florida.



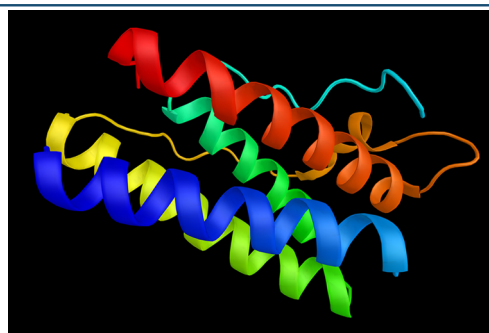
Ghrelin is the only known hormone that stimulates appetite. Credit: ibreakstock/Shutterstock.

In addition to leptin and ghrelin, other factors that control feeding behaviors were discovered over the decades, some as early as the 1970s. Intestinal endocrine cells release a slew of hormone signals when they encounter food, including glucagon-like peptide (GLP-1), peptide YY, and oxyntomodulin. Physical cues from stretch, pressure, and volume sensors activated when food enters the stomach create a sense of fullness. "All these peptide hormones have been considered as potential drug targets to treat obesity", Cummings says.

Such potential drugs failed, in part, because our responses to food are surprisingly complex. The drive to eat is powerful; over millennia, it has motivated humans and animals—both predator and prey—to venture beyond safe shelters to hunt and forage in the wild. To encourage these risky behaviors, many of the gut and brain signals that trigger hunger and satiety also evolved to be intricately linked to motivators such as stress, fear, and reward-seeking. The hormonal, neural, and physical signals that sync up to control eating create multiple—often redundant—links between short-term eating behaviors and long-term body weight.

But shifts over time mean many people now eat as reward, to control stress, or in response to other cues. "The human brain has a much more complex reaction to food and control of appetite than rodent or primate brains", says [Olivia M. Farr](#) of Harvard Medical School. "To get at the heart of obesity, we really need to study the human brain."

Recent studies are starting to show how intestinal peptides, hormones like leptin and ghrelin, and other cues converge in the brain. In addition to these peripheral secretions, common neurotransmitters such as dopamine, serotonin, and norepinephrine also tweak sensations of hunger and satiety. And all these signals act in concert across multiple brain regions.



Leptin, a hormone secreted by fat cells, suppresses eating behavior. Credit: ibreakstock/Shutterstock.

Farr, who works in [Christos S. Mantzoros's](#) lab at Harvard, uses brain imaging techniques to study how different hormones and foods trigger distinct responses. For example, they've found that [short-term treatment with a leptin analogue](#) "increased the activity of brain centers related to the importance of food cues during fasting", she says. "We saw that leptin acts in many areas of the human cortex—not just the hypothalamus—and all of these areas are potentially targets for where leptin is unable to alter eating behaviors in obesity." Being able to pin these CNS pathways down, and to identify drugs that could target these specific sets of neurons, could lead to powerful new therapies, according to Cummings.

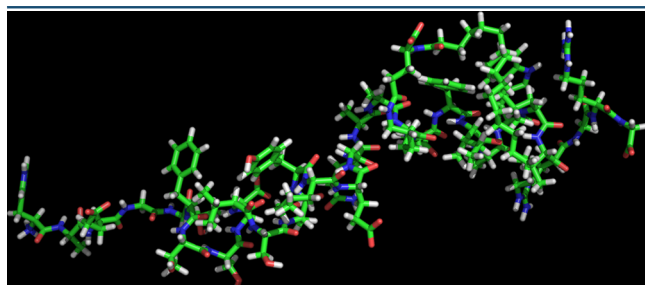
■ BOTTLING A CURE

So far, treatments targeting either leptin or ghrelin alone have proved ineffective except in those individuals with genetic disorders affecting these hormones' functions. Some [ghrelin analogues](#), such as macimorelin, are now being tested in clinical trials for another extreme problem: cancer cachexia, a form of severe weight loss and wasting that occurs in patients on chemotherapy.

Now, researchers are looking for drugs that target the CNS that could affect the entire hormonal symphony that regulates hunger, satiety, stress, and reward. Newer therapies

aim to reach neurons that carry a medley of receptors and are responsive to gut hormones such as leptin or ghrelin, neurotransmitters such as dopamine and serotonin, and neuropeptides such as pro-opiomelanocortin (POMC), which decreases appetite, agouti-related protein, which increases it, and neuropeptide Y, which decreases energy expenditure. Since these molecules act in concert to control appetite-specific pathways, drugs that target these networks have met with greater success than older drugs with less specific modes of action.

For example, in 2013, the FDA approved lorcaserin, which is thought to work by activating satiety-linked POMC neurons. Liraglutide, which mimics the actions of the satiety-signaling peptide GLP-1, was initially approved as a diabetes medication but, in 2014, was cleared for use at a higher dose to treat obesity. Farr and her colleagues have found that liraglutide decreases activity in parts of the brain that react to French fries, cake, or other enticing treats.



The drug liraglutide, which mimics the actions of glucagon-like peptide, is approved as an obesity treatment. Credit: A2-33/Wikimedia Commons.

Further improving obesity treatment will likely involve targeting more than just one hormone, researchers say, because of the diversity of signals that control appetite and eating behaviors. “In a redundant system, it’s hard to imagine that removal of any one determinant is going to overpower the others”, says Cummings.

For now, [combination therapies](#) rely on simply giving two already known medications together. One combination prescribed by doctors is a mix of amphetamine-based phentermine, which stimulates the sympathetic nervous system and suppresses feeding behavior, and the epilepsy drug topiramate, which increases energy expenditure. The second is a mix of bupropion and naltrexone, which work together on POMC neurons to decrease appetite and reduce food cravings by acting on reward pathways.

In addition to mixing independent molecules, pharmaceutical companies are also trying to design compounds that can either bind to two independent receptors or cross-link two receptors at once. “Most companies recognize that combination therapies are the future, but they’re also very

challenging to develop clinically”, says Kevin Grove, vice president of obesity research at Novo Nordisk, one of the makers of liraglutide. First you have to develop the two individual molecules separately and then prove that their combined action is even more effective, he explains, a process that can be very expensive for manufacturers.

But designing a single peptide that can bind two distinct targets at the same time is not easy either, and most such work is still in animal studies. One such effort stems from Smith’s lab at Scripps, where his team has found that cross-linking a dopamine receptor known as D2 to the ghrelin receptor can suppress feeding behavior in mice. The ghrelin receptor antagonist they use is one that previously failed to work as an antiobesity drug. But it works when complexed with a D2-binding antagonist.

None of these medications are free of side effects, and, importantly, none are as effective as bariatric surgery. Typically, obesity drugs cause an average weight loss of 5–15% when combined with diet and exercise, while bariatric surgery results in losses up to 30%. Although researchers initially thought the surgery worked purely because of physical changes—the stomach is reduced to a smaller size and simply cannot hold as much food—studies increasingly show that it also affects multiple hormonal systems. For example, ghrelin levels remain consistently low, and the body’s response to GLP-1 is several fold higher after the procedure.

“There’s a significant morbidity and mortality associated with surgery, but that’s considered more acceptable with surgery than it would be with drugs”, says [Jonathan R. S. Arch](#) of the University of Buckingham. So ongoing efforts to create combination drugs that mimic the actions of two or more hormones simultaneously could capture the benefits of bariatric surgery without the risk of complications.

Like eating itself, the drug combinations that best control obesity will need to target more than just hunger and satiety, researchers say. In the long term, combination therapies that prove successful will likely need to simultaneously suppress appetite, boost the body’s energy use, and tamp down the reward cravings induced by the temptation of delicious treats. Clinical proof of such drugs’ utility may take a few years still, according to Grove. “But now, we understand the targets that we need to hit to get there”, he says.

Jyoti Madhusoodanan is a freelance contributor to [Chemical & Engineering News](#), the weekly newsmagazine of the American Chemical Society.