The Secret of Feeling FULL

A natural hormone turns out to be a powerful appetite suppressant. Could it lead to safe new anti-obesity drugs?

Christine Gorman

It sounds like a weight watcher's dream come true: a simple hormone, long thought to play an obscure function in the pancreas, turns out instead to be a powerful appetite suppressant – the body's way of telling the brain it's time to push the plate away. If a pharmaceutical company could put it in a pill and sell it at the drugstore, you might, just might, never again have to count calories or wrestle with your willpower. Just pop one of these things before a meal, and your stomach says – entirely on its own – "No, thank you, I've had quite enough." The scientific name for this remarkable substance is PYY 3- 36, or PYY for short, but the researchers who discovered its new function have dubbed it, appropriately enough, the fullness hormone. "If you take it prior to a meal, it switches off the appetite,: says Dr. Stephen Bloom, an endocrinologist at Hammersmith Hospital in London. "PYY is what makes you less hungry after a meal." But don't break out the cartons of Ben & Jerry's just yet. For one thing, the research reported in Nature last week was just a modest first step. A dozen volunteers in London were injected at various times with either the hormone or a placebo. Then they were led to an Indian-food buffet and invited to pack away all they could eat. Result: while on PYY, the grazers voluntarily consumed one-third fewer calories.

But getting results like this under lab conditions and making a drug that's safe and effective are two very different matters. For one thing, nobody is going to brave a hypodermic needle just to avoid eating a third helping of tandoori chicken; yet if you put PYY in a simple pill, it will quickly be destroyed by stomach acids. For another, nobody knows what the side effects of ingesting this hormone for months or years might be. It's quite possible, as with so many other biologically active substances, that the body will quickly build a tolerance to any excess PYY, rendering it ineffective.

After all, we have been down this road before. When scientists reported in the mid-1990s that the absence of a hormone called leptin triggered the development of some very fat mice, it seemed that a course for obesity was finally at hand. If these fat mice didn't make enough leptin, the reasoning went, then maybe fat people didn't make enough either. Would giving them leptin make them thin? The logic was so compelling that the pharmaceuticals firm Amgen reportedly paid tens of millions of dollars for development rights. It turned out, however, that most fat people – and fat mice – produce plenty of liptin. Their bodies, for reasons that are poorly understood, just aren't very sensitive to its effects. Even if PYY proves to be no miracle, it sheds light on how hunger works, and this comes at a time when Americans seem to be particularly confused about what makes us fat. The old arguments – is it too much fat, too many carbohydrates or too many calories? – were stirred up once again last month by an article in the New York Times Magazine suggesting that low-fat diets may be making us fatter. While the new information about PYY won't help you choose between a highprotein or low-fat diet, it goes a long way toward explaining how the brain and the digestive system conspire to keep the pounds on.

In essence, researchers are discovering, the digestive system tells the brain how much to eat by pumping various hormones, on of which is PYY, into the bloodstream. "There are at least half a dozen signals that we know about," says Michael Cowley, a neuroscientist at the Oregon National Primate Center in Beaverton and one of the co-authors of the Nature paper. Some of these biological traffic lights work in a very short time frame, affecting when you start and stop a meal. Some, like leptin, work over the longer term by helping the brain monitor how much fatty tissue the body has stored. PYY is a medium-term signal; it seems to suppress your appetite between meals, presumably so you can get some work done before you start eating again. What complicates things is that these signals are interconnected; if the level of one hormone falls or rises long enough, the whole system will shift until the hormones fall back to their original levels.

You know exactly what that feels like if you have ever tried to lose weight and then hit a plateau after a while. What is happening is that the changes in your digestive hormones have signaled the brain to lower your metabolic rate so that your body makes more efficient use of the calories you consume. Your appetite increases, and any further weight loss, takes just that much more effort and determination.

What gets neuroscientists excited is that most of these digestive hormones seem to effect the same group of neurons in the hypothalamus, a subsection of the brain that acts as a kind of master regulator of some of our more basic instincts – hunger, thirst, sleep, sex. That means if PYY fails to be a good candidate for a new anti-obesity drug, researchers may find another target in the brain that works better. Alternatively, studying PYY may help with the opposite problem – loss of appetite – which so often affects cancer patients and people with AIDS. Either way, a lot of work remains to be done. The 12 volunteers tested by Bloom and his colleagues were all healthy and of average weight. Perhaps the same biological factors that kept their weight under control also enabled them to respond to PYY. Bloom is already trying the hormone on two more groups of volunteers – one modestly overweight and the other slightly underweight – to see if the hormone will suppress their appetites as well. "We also want to move to long-term treatment and prove that over a week, say, you're still eating less," Bloom says. He is looking into the possibility that certain foods, particularly those high in fiber, may increase the level of PYY in the body naturally.

One thing seems pretty clear: any further medical treatment of obesity will probably require a combination of obesity will probably require a combination of drugs. Imagine for a moment, says Dr. Michael Schwartz, an endocrinologist at the University of Washington in Seattle, that scientists figure out a way to turn PYY into an easy-to-swallow pill, that the pill turns out to work for a wide range of people and that those who take it begin losing weight and shed, say, 5% to 8% of their body weight. At that point, some of the other hormones that affect long-term weight control, such as leptin and insulin, start dropping, and a shortacting hormone called ghrelin starts climbing, increasing your sense of hunger. "Now your body is competing with the effect of the drug." Schwartz says. "In the end, you may need two or three drugs to get the desired effect."

In the best of all possible worlds, of course, you would just pop a few pills and lose all the weight you want. In our world, better medications will probably still work best in combination with a healthy diet and plenty of exercise. The promise of the new drugs, whenever they are developed, is that we won't have to fight with ourselves quite so hard to get a little healthier. And that could be an important first step.

–With reporting by Aisha Labi/London

The Hunger Hormones

Some of these molecules make you feel hungry. Others make you feel full. All of them play off on another.

Short-term Signals

Ghrelin This hormone tells you it's time to start eating. Ghrelin is secreted by the stomach when it is empty and sends an "I'm hungry" signal to the brain.

Cholecystokinin This hormone tells you the meal is over. Cholecystokinin (CCK) is produced by the small intestine after food leaves the stomach. CCK triggers the release of enzymes from the gall bladder and pancreas.

Medium-term Signals

PYY 3-36 This hormone produced by the digestive tract helps you avoid snacking between meals. Once thought to regulate development of the pancreas, PYY 3-36 now appears to signal the brain to suppress the appetite.

Long-term Signals

Leptin Produced by your fat cells, this hormone works to keep the level of fat in your body constant. Under normal circumstances, the brain will ratchet up the body's metabolic rate and decreases appetite in response to a high leptin level.

Insulin Produced by the pancreas, this hormone controls the amount of glucose in the bloodstream. There is mounting evidence that insulin acts like leptin in regulating longterm body weight.

Source: Michael Cowley, Oregon National Primate Center