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Innovations

When Enough Is Too Much:
New Strategies to Treat Obesity

US government organizations estimate the US adult overweight and obese population at 65%; 13% of children. The Centers for Disease Control and Prevention now classify obesity as nearly equal to tobacco use as the number one health threat for Americans. However, the choices for prescription products aimed at combating the new "obesity epidemic" are limited to only two: Meridia (sibutramine) and Xenical (orlistat). Though the obesity market is certainly demanding medications, few overweight or obese people maintain long-term therapy with either drug, largely because of side effects. This leaves the door open for any company that can come up with an effective and relatively side-effect-free solution. In pursuit of this goal are two small companies located on either coast of the US, both with naturally occurring compounds geared toward reducing overall calorie intake by producing feelings of satisfied hunger, or satiety, sooner rather than later.

Nastech Pharmaceuticals

Nastech, a 20-year-old company based in Bothell, WA, has evolved its focus toward novel drug delivery solutions. "We're trying to use molecular biology tools to solve drug delivery problems," says Steven Quay, MD, PhD, Nastech's President and CEO. "Currently, we are focusing on intranasal delivery." Nastech's obesity therapy, PYY3-36, a naturally occurring protein found in the gut, is a member of the neuropeptide Y family known to be associated with feelings of hunger and satiety. "PYY is the peptide that gives you the feeling of fullness," says Quay.

About 10 years ago, investigators discovered that PYY3-36 appears in the bloodstream after oral food intake, typically within 35–60 min. "One of the most impressive studies with PYY3-36 showed that its blood concentration was strictly related to the number of calories being eaten," says Quay. Researchers found that PYY3-36 levels rose correspondingly with calorie intake. "Researchers at Hammersmith Hospital in London then did the reciprocal experiment showing that if you infused PYY3-36 into obese volunteers, they would eat significantly fewer calories after taking PYY3-36 as compared to placebo," says Quay [1]. Specifically, they found that in both obese and lean people, PYY3-36 reduced overall calorie intake by 30% 2 hr post-transfusion. They also discovered that endogenous levels of PYY3-36 were low in obese volunteers, suggesting that PYY3-36 deficiency may contribute to obesity. Interestingly, other researchers have very recently questioned some of the earlier animal studies done with injected PYY3-36 by the Hammersmith group, claiming that calorie reduction and weight loss could not be replicated in test animals [2]. But Quay is not fazed by the ongoing publications controversy because of the proven results of PYY3-36 in human tests, including Nastech's own. "It is an interesting controversy, one that would be more worrisome if we didn't have human data that was positive, showing PYY3-36 reduces calorie intake and has a substantial effect on scores of satiety," he says.

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"You have to think of the brain as a computer room with no windows," says Quay. "Everything we think or experience is really a series of receptors being activated." It is believed that after a meal, PYY3-36 produces satiety by occupying the Y2 receptor in the arcuate nucleus, a collection of nerve cells located in the hypothalamus. If these receptors are not blocked, nerve cells are activated releasing neuropeptide NPY, producing ongoing sensations of hunger. Quay explains that the arcuate nucleus does not have a blood-brain barrier, so the PYY3-36 peptide gets into the bloodstream, diffuses to the arcuate nucleus, and binds tightly to the Y2 receptor with picomolar affinity within 35–60 min of eating. "Then your brain says 'I'm full and I don't need to eat anymore'," says Quay. "But one of the problems with obesity today has to do with the very high-density diets (with respect to calories) people are eating now. The problem is that if you go to a fast-food restaurant you can get two days of calories in 45 min, usually more quickly than the PYY3-36 can tell you to stop eating."

Nastech now seeks to match the results of the infused PYY 3-36 studies using its own intranasal formulation. To date, three phase I studies have been performed, the most recent reported in late June 2004. That week-long phase IC study among 37 obese people showed an average weight loss of 1.3 pounds in those who sniffed one dose of PYY3-36 1 hr before eating. That may not seem impressive, but Quay asserts that "if you talk to doctors who counsel people on weight loss, 1 to 2 pounds of true body weight loss per week is where you should be. More than that and you are losing water, which is a transient thing." Depending on the number of doses received, volunteers reduced daily calorie intake from 77 to 648 calories.

He is also pleased with the pharmacodynamics of the intranasal formulation, which uses the same nasal actuator found in at least 20 different commercial nasal sprays, including Flonase for allergy. "In our human studies, we have gotten better bioavailability than we had predicted, and we were able to get up to nine times the dosage you usually get after a big meal," says Quay. "So we

have a lot of dynamic range in terms of what we can deliver into the bloodstream.

Looking forward, Nastech will begin a phase II placebo-controlled trial examining weight loss over a six-month period. "This is planned for later in 2004," says Quay.

Manhattan Pharmaceuticals

Manhattan Pharmaceuticals, based in New York City, was founded in August 2001 with one specific goal. "It was built specifically to develop an improved obesity therapeutic," says Leonard Firestone, MD, Manhattan's President and CEO. In this case, the therapy is oleoyl estrone (OE), a naturally occurring fatty acid ester of estrone first developed by researchers at the University of Barcelona, including Dr. Maria Alemany, well known for his research into the study of calorie intake, appetite, and fat deposition regulation. "Dr. Alemany began to look for the true mediators of satiety in the blood and in the process focused on the steroids coming up with the esterified steroids, particularly the fatty aceyl estrone," says Firestone. He explains that molecules like OE are signaling molecules that can affect neurons in the peripheral nervous system and the CNS. "There is accumulating evidence that OE is a blood-borne molecule that works to depress appetite centrally," he says.

OE is present in the plasma of mammals—rodents and man—in the ng/ml level and exists in plasma roughly in proportion to the amount of body fat. "That relationship holds until you get to a body mass index (BMI) of 30 or greater," says Firestone. "Once you get to the obesity level, the OE level remains flat. Obese people have relatively less OE in their blood than their body mass and fat content would predict."

For as yet unexplained reasons, obese individuals appear to manufacture inadequate amounts of OE. "The conclusion we reach is that perhaps OE is one of those coarse controls on the storage of calories, like leptin—something manufactured in fat that feeds back to the brain that says 'I have sufficient fat stores'," explains Firestone. And the hypothesis is that obese people synthesize less OE per unit of body weight than is needed. "Less of it circulates in blood, which probably means less of it is feeding back to the brain. Then whatever appetite signals go out from the brain are inadequate in obese people." Researchers at Manhattan have evidence that giving exogenous OE reduces appetite, both in obese and normal-weighted animals. The plan at Manhattan in the future is to try to find out why OE levels fall in obese people, but their first priority is to investigate what happens when test subjects are given more.

"Aside from their side effects, drugs like Xenical and Meridia are only minimally effective: only 5%–8% loss of body mass can be expected," says Firestone. "Frankly, we need something that helps you lose 15%–20% of body mass and is not riddled with side effects." Manhattan's researchers claim that in the laboratory OE has reduced caloric intake between 40%–70%, and that translates over time into a 15% body mass reduction. A single-person study from Barcelona published in October 2003 found that OE reduced body mass by 22% in the obese male volunteer [4]. Firestone claims that in rat studies an approximately 15% body mass reduction is routine. "And the weight they lose consists of white adipose tissue, not bone or skeletal mass, not parenchymal organ mass, not extracellular fluid," he says.

"We don't yet know a great deal about the natural biology of OE, other than it exists in plasma in proportion to body mass and body fat up to a certain point and then its levels seem to be relatively low in obese people," says Firestone. He also knows OE is synthesized in peripheral fat, released into blood, and interacts with hypothalamic neurons, all together something like a peripheral lipid signaling molecule that will stimulate the appetite control center in the brain.

Manhattan will file an IND for OE in late 2004, with human phase I clinical studies set to begin by 2005 in the US.

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