tion of fat around the body that could be an omen of other, more serious side effects. The most detailed of these studies, reported by clinician Andrew Carr of St. Vincent Hospital in Sydney, Australia, involved 116 patients taking protease inhibitors for an average of 10 months. Of these, 72 (64%) had fat wasting of the limbs and face with fat accumulation in the gut, a syndrome called lipodystrophy. "I don't think anyone has a good concept of what the mechanism is, or how reversible it is," says Henry Masur, who heads the critical-care unit at the Clinical Center of the National Institutes of Health, where he and his colleagues have studied 18 patients with the disorder.

"The data from [the Australian group] have struck all of us," says clinician Scott Hammer of Harvard Medical School in Boston. "The excitement of success we've experienced has to be tempered by the toxicity." Carr notes that although lipodystrophy by itself does not appear to be dangerous, it suggests that the powerful protease inhibitors are producing a systemic effect that could lead to more severe problems later on. "Are these people going to get heart attacks and strokes in 10 years' time?" Carr asks. He also worries that the drugs could cause metabolic imbalances that lead to insulin resistance.

Such concerns led Carr and others to question the common wisdom that treatment should begin as soon as patients learn they are infected with HIV. "These people are going to be on drugs for years," says Carr. Once again, Faulkner's observation could apply: The common wisdom may not be complicated enough.

–Jon Cohen

OBESITY RESEARCH

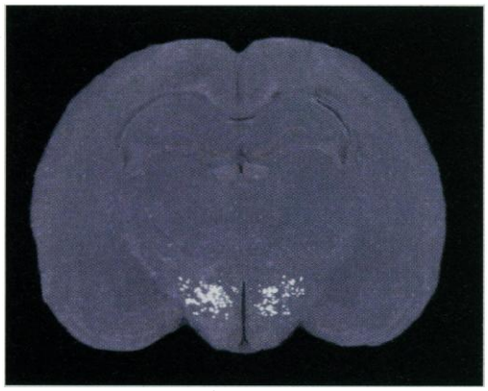
New Appetite-Boosting Peptides Found

As the popularity of the ill-fated diet drug combination fen/phen showed, people who are morbidly, or just unhappily, overweight are hungry for a pill to help them shed pounds. At the other end of the spectrum, people whose health is threatened by a lack of appetite, because of chemotherapy or illness, would benefit from an appetite-boosting drug. Given what's likely to be a billion-dollar demand, pharmaceutical companies are scrambling to find drugs to control appetite. Now, researchers at the University of Texas Southwestern Medical Center in Dallas and SmithKline Beecham Pharmaceuticals have found a potential new drug target: In today's issue of *Cell*, the team, led by Masashi Yanagisawa of UT Southwestern, reports the discovery of two related peptides, from the brains of rats, that trigger eating by the animals.

The peptides—which the researchers named orexins, from the Greek word for appetite—aren't the first ones found to turn up hunger, but researchers see them as especially intriguing. For one thing, unlike most of the others, these peptides are made only in a brain area called the lateral hypothalamus (LH), previously identified as the brain's "feeding center" because its destruction caused experimental animals to stop eating and starve to death. The orexins may be key to that brain area's normal function.

What's more, because researchers already know the identity of the receptors through which these peptides work, they can begin to look for drugs that either mimic or block their appetite-enhancing effects. "I think it's terrific," says Jeffrey Friedman, of Rockefeller University in New York City, whose team discovered the appetite-suppressing protein leptin. "All the available evidence says there are many molecules" involved in the control of eating behavior, "and these two clearly need to be added to that list."

Yanagisawa's team members weren't planning to enter this hot field when they began their work. They were collaborating with researchers at SmithKline Beecham's labs in Pennsylvania and the United Kingdom in a search for peptides that activate so-called "orphan receptors." These are proteins whose amino acid sequences show the structural hallmarks of cell surface receptors but whose triggering molecules are as yet undiscovered.



Hunger zone. Orexin messenger RNA (bright spots) is concentrated in the lateral hypothalamus.

S. WILLIAMS, M. DAVIS, J. RICHARDSON, M. YANAGISAWA/UT SOUTHWESTERN MEDICAL CENTER AND HHMI

Out of this search came two related peptides that activate two related orphan receptors. Further study revealed that the peptides seem to be made exclusively in the lateral hypothalamus. "That was the obvious clue that they may be involved in feeding behavior," says Yanagisawa.

To test that hypothesis, Yanagisawa's team injected the peptides directly into the brains of rats. They proved to be powerful appetite boosters, causing the animals to eat from three to six times more than control rats did for several hours. Next, the researchers looked to see what effect starvation has on brain levels of the orexins. If the peptides really govern feeding, Yanagisawa says, those levels should go up when the animals are hungry. "We did the starvation experiment," says Yanagisawa, "and lo and behold [orexin] was upregulated."

The discovery should give physiologists new clues to the puzzle of how the brain controls appetite. "Every new discovery [like the orexins] adds to an understanding of how the system works," says physiologist Larry Bellinger, who studies feeding behavior at the Baylor College of Dentistry in Dallas.

Until recently, the LH has been overshadowed by a neighboring area, the ventromedial hypothalamus (VMH). Dubbed the "satiety center" because experiments done in the 1940s showed that its destruction turns animals into chronic overeaters, the VMH has been a hot spot of research for the past few years. Not only are receptors for leptin found there, but so are neurons containing a molecule called peptide Y, which is known to enhance appetite.

But the idea of satiety or feeding centers is now recognized as too simplistic. Indeed, Bellinger says, the hypothalamus is criss-crossed with "a huge wiring diagram" of neurons receiving and passing on information about the body's nutritional state, such as how many fat cells there are or how much sugar the blood contains. And the LH is almost certainly relaying some of these signals. For example, low blood-sugar levels activate some LH neurons. When triggered, those neurons might release the orexins or another appetite-stimulating peptide discovered 2 years ago in the LH—melanin-concentrating hormone.

A better understanding of the wiring that controls feeding is essential to developing safe appetite-controlling drugs, says Bellinger. But there is already reason to hope that the orexins and their receptors will make good targets for such drugs. Because the orexins appear to be only in the LH, they may have fewer other functions in the brain than does peptide Y, whose broad distribution and multiple functions make it harder to find drugs that block only its appetite-inducing effects. "There is no guarantee that [the orexins] won't do other things either," says Friedman, but the fact that they seem to be restricted to the LH is "good news." And it's the kind of news that drug companies are sure to pounce on.

–Marcia Barinaga