

Science/Medicine

Recent discoveries whet appetite for chemical research

Frontiers in Fighting Fat

By MARGIE PATLAK

Researchers, homing in on the chemistry behind putting on pounds, have come up with some compounds that hold promise for combatting obesity, middle-aged spread and more.

Recent findings on the hormones that govern waist size help explain why people tend to gain weight as they get older, despite no change in diet or exercise patterns, and why some people gain 10 pounds eating the same amount of food as someone who gains no weight.

Although the findings are preliminary and most involve animal research, some scientists are excited about the results.

"Research on obesity is at an exciting point in time," says Henry Lardy of the University of Wisconsin in Madison. "The different bits of information are all fitting together to give us a clear picture of the biochemistry behind weight gain."

Much of the new work involves three substances: DHEA, beta-agonists and adipsin.

Tests in humans are already under way for the naturally occurring hormone called DHEA, or dehydroepiandrosterone. A relative of the sex hormones, this compound was given to a small group of men for a month at the Medical College of Virginia in Richmond. The researchers reported last year in the *Journal of Clinical Endocrinology and Metabolism* that DHEA slashed by nearly one-third the percentage of body fat and increased muscle mass in the men. The compound, however, did not cause these men, who were at their ideal weights, to shed any pounds.

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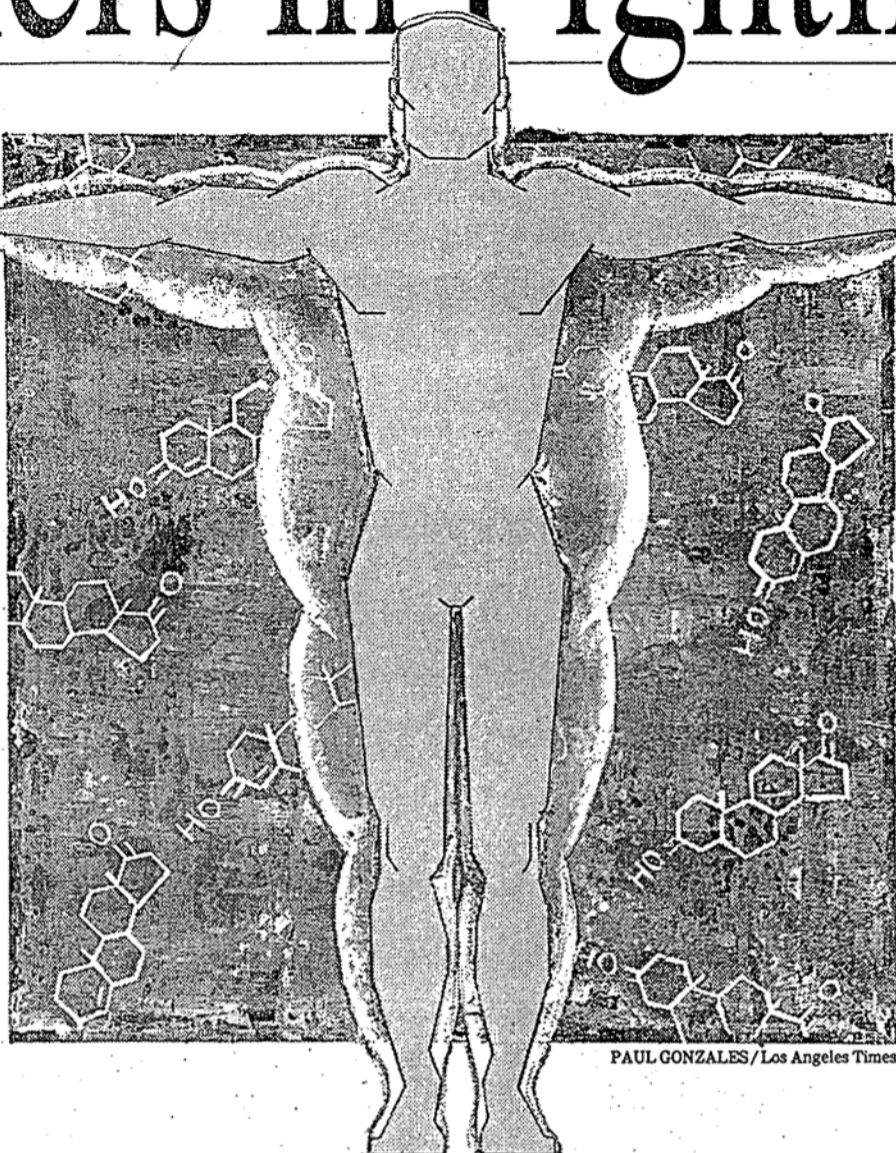
But as the researcher, John Nestler, points out, these men had peak levels of DHEA in their blood before they were given the experimental doses of the compound and more dramatic results may be garnered from giving DHEA to obese individuals. When DHEA is given to obese rats, dogs or monkeys, they lose substantial amounts of weight, even though their food intake does not change, studies at Madison show.

"DHEA stimulates metabolism, so we're optimistic it will be a useful weight-reducer compound for both the mildly and grossly obese," says Lardy, who pioneered studies on DHEA.

In animal studies, Lardy says, DHEA fosters weight loss by boosting the body's ability to burn off calories as heat, rather than store them as fat. Some people have a knack for burning up calories as heat, he explains, whereas many obese people are much more efficient at turning the calories into fat—a trait that is advantageous in a starvation-ridden community, but not usually of benefit in this country.

In a study by researchers at the University of Lausanne in Switzerland, for example, women obese since childhood generated much less body heat from a meal than did women of normal weight. DHEA may be able to help such people with fat-prone metabolisms.

But a number of questions have surfaced involving the safety and effectiveness of DHEA. While the hormone was reported to be associated with lower risk of heart disease and longer life span in men, UC San Diego researchers two years ago reported that DHEA was linked to a higher incidence



PAUL GONZALES/Los Angeles Times

Scientists are unlocking the secrets of the body's metabolism in an effort to explain why people tend to gain weight as they get older despite no change in diet or exercise patterns.

of heart disease and mortality rates in women.

And in 1985, the U.S. Food and Drug Administration ordered manufacturers and distributors of DHEA to stop the sale of the drug as a food supplement because research did not back up claims being made at that time that the product would enhance weight reduction efforts and sexual performance.

FDA spokeswoman Diane Walker said that the FDA has never approved DHEA for general use, and is now waiting for more extensive human studies before considering it for approval.

DHEA levels peak in the human body at about 25 years of age and then decline. The diminishing presence of the compound in the body as we age may partially explain why people tend to put on weight as they get older, Nestler says.

He and other investigators are now testing DHEA on people of varying ages and degrees of obesity to see in which groups, if any, it enhances weight loss.

Even if these studies prove promising, it will be several years before DHEA or a similar compound makes it to the market.

Another group of chemicals made by the body that hold potential for prompting weight loss are called beta-agonists. Animal studies by researchers at Merck, Sharp & Dohme Laboratories in Rahway, N.J., and Eli Lilly in Indianapolis suggest that these compounds prompt the animals to deposit food as muscle protein rather than fat and boost the burning of calories to give off heat.

For 18 weeks, Scottish researcher Allan Connacher gave a beta-agonist to 32 patients who were at least 20% overweight while maintaining them on a low-fat, high-fiber diet. At the end of the study, patients who received the beta-agonist drug lost an average of 34 pounds, compared to 22 pounds lost by patients who received a placebo drug while following the same diet. Further studies on the drug's safety and effec-

THE BODY'S FAT REGULATORS

DHEA

Short for dehydroepiandrosterone, DHEA is a naturally occurring hormone that stimulates metabolism, helping the body burn fat.

Current research has shown that doses of DHEA can be a useful weight-reducing compound for both the mildly and grossly obese. But a number of questions have surfaced involving the safety and effectiveness of DHEA. The hormone has been associated with a lower risk of heart disease and longer life span in men, but was the opposite for women.

Beta-agonists

Scientists believe this group of

chemicals cause the body to deposit food as muscle protein rather than fat and boost the burning of calories.

One recent study of 32 patients on a low-fat, high-fiber diet resulted in a higher weight loss for those who received the beta-agonists than those given a placebo.

Adipsin

A protein, it is thought to be the body's fat signal, essentially telling the body when to store more. When the levels of this molecule are up, a person's fat becomes severely depleted. Research now centers on what parts of the body adipsin acts upon and in what manner.

tiveness are needed, however, before it can be made available for general use.

A recently discovered compound thought to regulate fat storage is also being eyed as a potential anti-obesity drug. Years of research led scientists to hypothesize that animals must possess a natural weight-control mechanism whereby fat cells signal the body how much fat they are storing; the body responds by generating chemicals that affect appetite or metabolism so that more fat is stored or burned off, according to energy needs. Obese people, scientists surmise, have signaling mechanisms that have gone awry.

But evidence to support this hypothesis was scanty until Bruce Spiegelman of the Dana Farber Cancer Center in Boston and his colleagues reported two years ago in *Science* that the levels of a protein called adipsin, which is secreted into the blood stream by fat cells, differ between normal and obese mice. Normal mice make 100 to 200 times more adipsin than mice genetically prone to obesity, the researchers reported.

The researchers had apparently stumbled upon a promising fat signal. Adipsin may rein in the amount of fat an animal accumulates by essentially telling the body not to store more. If this turns out to be the case, adipsin may be a useful compound for countering obesity—"a tantalizing idea well worth pursuit," Spiegelman says.

Other researchers are equally excited by such prospects, including Rockefeller University obesity expert Jules Hirsch, who says Spiegelman's findings "are extremely interesting."

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The excitement was heightened recently when investigators at California Biotechnology Inc. in Mountain View, working with Spiegelman, found the human version of adipsin in mice. The scientists, who have not yet published their results, are now comparing the levels of this compound in the blood of obese individuals to that of normal-weight people.

Whether adipsin might also come to the aid of those not technically obese, but on the portly side, is open to debate. The animals Spiegelman found lacking adipsin were extremely overweight—most were born with a tendency to become obese. Some of these animals become obese even when they do not succumb to gluttony, for example, so they do not accurately model the human tendency to break out in fat after the holidays, among other things.

however, that adipsin helps fix the poundage of everyone, and not just those born with a tendency to obesity. Spiegelman discovered that adipsin is essentially the same as "complement factor D"—a molecule released by the immune system in response to infection. When the levels of this molecule are jacked up too far, medical case histories show, a person's fat becomes severely depleted. The fact that normal-weight individuals can develop this fat-wasting syndrome suggests that the effect of adipsin may not be limited to those people extremely obese, says Spiegelman, who is studying the protein further to see what parts of the body it acts on and in what manner.

Patlak is a free-lance writer based in Portland, Ore.