Fighting the origins of flab

Neuroscience: Although the practical applications are far off, research is shedding light on curbing obesity.

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SUN STAFF

As a neuroscientist at Johns Hopkins School of Medicine, Dr. Gabriele Ronnett fattens up mice in a search for ways to keep fat off people.

Ronnett's mice are programmed by nature to gain weight. "If you give them tasty food, they will eat until they get fat," she said as two furry black rodents scrambled around the palm of her hand. "Not all mice will do that."

Researchers have spent decades using mice, rats and humans in their search for a pill that will curb appetites and burn fat — long before federal officials released a study last month calling obesity a national epidemic.

"It's like looking for the holy grail. What's the one pill, with the right molecules, that's going to be a magic bullet?" Ronnett said.

For many researchers, the key to fighting obesity lies in understanding how the brain creates signals that tell us when to eat.

Scientists have known for years that brain cells, or neurons, send signals when our bodies need food and when we have eaten enough. Research in recent years has focused largely on receptors in the brain, such as leptin and serotonin, that alter signals in ways that can suppress our appetite for food.

But instead of looking at receptors, Ronnett and her group at Hopkins have focused on finding chemical compounds that will make enzymes in the brain suppress appetites and burn body fat.

Ronnett was part of a team of researchers who discovered two years ago that injecting mice with a new compound stimulated a brain enzyme known as CPT1 that prompted the mice to burn fat more quickly. They found that mice treated with the compound lost 50 percent more weight than a control group.

They had found in earlier research that the same compound, known as C75, shuts off another enzyme that plays a key role in food metabolism, cutting back on appetite. That enzyme, fatty acid synthase, or FAS for short, fires off neurons that send signals throughout the brain that make us feel hungry. By inhibiting FAS, the compound essentially fools the brain into thinking the body no longer needs food.

Ronnett says FAS also may fight cancer. The Hopkins studies show that FAS inhibitors kill off cancerous cells in tumors.

Researchers at Hopkins have formed a biotech company, FASgen Inc., to develop cancer and obesity treatments. They have narrowed their search from 400 potential compounds to a group of six that they say could prove effective as weapons to combat obesity. They have another six compounds they plan to test as cancer treatments.

The researchers say Food and Drug Administration approval of a drug for either cancer or obesity is years away. Finding marketable drugs and securing FDA approval can take years; researchers at Hopkins have been working with enzymes for 15 years. Any human trials of potential drugs to come out of the research would require FDA approval and are several years away, Ronnett said.

A pill that safely and effectively burns away fat or curbs appetites would have far-reaching health benefits — and reap huge profits.

Diet books, videos and other related products are a $30-billion-a-year industry, a figure that is expected to increase with the nation's ever expanding waistline. Health care costs to treat obesity-related ailments, such as diabetes, are estimated at $70 billion, according to a study by the Centers for Disease Control and Prevention.

"Obesity is such a horrendous health problem it needs to be addressed on several fronts," Ronnett said. "If it's not going to be a magic pill, I think what we have will be a good start."

The CDC announced last month that the number of U.S. deaths caused by poor diet and lack of exercise rose by 100,000 to 400,000 in 2000. The numbers make obesity a leading cause of premature deaths among Americans, second only to tobacco.

Almost 130 million Americans, or 64 percent, are overweight, according to government calculations, an increase from 47 percent in 1980. Moreover, a third of the U.S. population is obese, a category that means having a body mass index — a calculation of weight and height — that is 20 percent above recommended levels.

The numbers are no surprise to those who counsel the obese.

"I see it all the time," said Marilyn Tanner, a pediatric dietician who teaches health classes to obese children and parents at Children's Hospital in St. Louis.

Tanner blames the obesity epidemic on lifestyles that encourage big eating and discourage physical activity. Children are taught to clean their plates, food portions have become larger and people spend too much time watching television and using computers, she said.

"No one walks anywhere anymore. Kids and their parents are being driven everywhere," Tanner said.

The nation's unhealthy lifestyle has meant higher health care costs and has experts looking for new ways to make the nation slimmer and healthier.

Federal officials are studying whether health insurance rates should be higher for those whose weight means increased health care costs. Lawyers, basking in recent victories in suits against McDonald's and other food companies, are weighing whether to file additional suits focusing on what they say are failures to disclose warnings about the unhealthy contents of food ingredients.

But many experts say it's wrong to blame the food industry and advertising for the nation's weight problem. The problem is more deep-rooted, and responsibility lies with a culture focused so much around food and its consumption.

"Food is one of the few things you can reward yourself with almost anywhere, anytime," said Allen Levine, a neuroscientist at the University of Minnesota. "You can eat a doughnut at your desk, but you can't have sex in your office, or drink in public. Food is just so freely available."

Lab animals — a key to much of the scientific research — apparently don't face such inhibitions when it comes to sex. But like humans, they apparently like to eat.

Levine has experimented with rats to try to understand the parts of our brain that create cravings for sweets. He has worked with a group of neurotransmitters, known as endogenous opioids, that he and others think trigger the pleasure responses created by sweets.

His work has convinced him that cravings depend on individual circumstances.

"Rats will work harder for something with a sweet taste than something that tastes bland. But what you like is a flexible thing," he said. "If you're starving, even oatmeal tastes great."

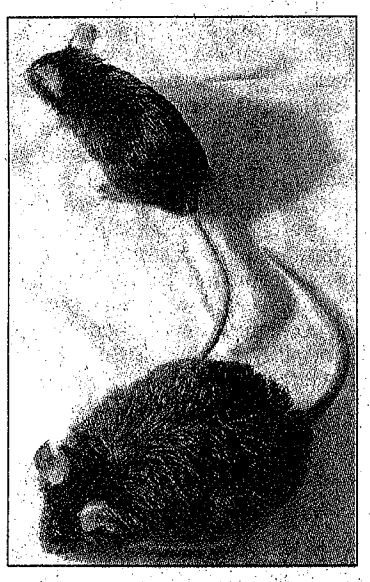
In Ronnett's lab, it's easy to see the difference between mice that are fed to become obese and mice on regular diets. After two months of feeding, the obese mouse is about twice the size of one with a regular appetite. It is also more lethargic, sniffing the air with less energy.

But there is a limit to the eating habits of even these mice.

"We don't fatten them up too much," she said. "That would be inhumane."

DOUG KAPUSTIN : SUN STAFF PHOTOS

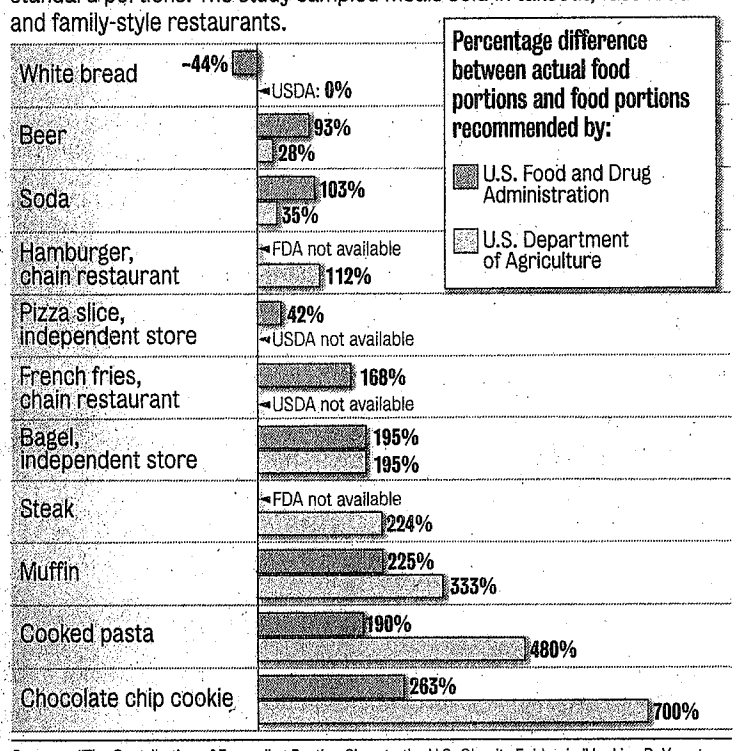
Neuroscientist Gabriele Ronnett and others at Johns Hopkins have found a chemical compound that makes brain enzymes suppress appetites and burn fat in mice. Research continues to determine whether the compound could have a similar effect in humans.



Without the compound, some of the mice grew twice as big.

Food portions in excess

With the exception of sliced white bread, all of the common foods measured in a study sponsored by New York University exceeded standard portions. The study sampled meals sold in takeout, fast-food and family-style restaurants.



Sources: "The Contribution of Expanding Portion Sizes to the U.S. Obesity Epidemic," by Lisa R. Young and Marion Nestle, *The American Journal of Public Health*, February 2002

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