Research Update

Leptin and the urge to eat

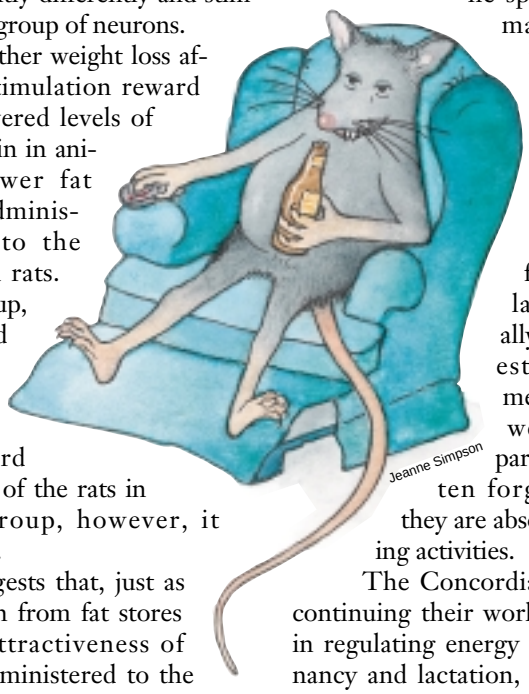
Leptin, a hormone secreted by fat cells, decreases food intake by animals. Now researchers at Concordia University's Centre for Studies in Behavioral Neurobiology (CSBN) in Montreal have found key clues to how it does this (*Science* 2000;287:125-8). They say leptin appears to regulate eating behaviour in 2 ways, one related to the rewarding effects of eating, the other to the rewards that come from competing activities.

Leptin has been the focus of intense research since it was identified as the product of the obese (*ob*) gene, sequenced in 1994. Scientists and pharmaceutical researchers hope this protein, which has been shown to have a role in body weight regulation, will eventually help control obesity. Previous studies have shown that it suppresses food intake and promotes weight loss. CSBN director Peter Shizgal explains that the goal of this study "was to learn about the brain mechanisms responsible for the decrease in food intake produced by leptin."

The researchers restricted the food given to a group of chubby, middle-aged rats until they lost 25% of their body weight, and then implanted electrodes in the lateral hypothalamus, a region of the brain involved in feeding and energy balance. When the rats pressed a bar, nerve cells near the electrode were stimulated, an effect known as brain stimulation reward. Shizgal suggests this effect is due to the activation of nerve cells involved in the evaluation of goals and actions. Given a weak stimulation, animals do not bother working at the bar, but they will press constantly to receive a strong stimulation. Researchers assess the sensitivity of the reward circuitry by measuring how strong the stimulation must be to convince the animal to work for it.

In the CSBN experiment, half the rats were more sensitive to the stimulation reward when they were slim than they were after they had been allowed to regain their normal weight. In the remaining rats, changes in body weight had no effect on brain stimulation reward. The researchers suspect that in this second group, the electrodes were positioned slightly differently and stimulated another group of neurons.

To test whether weight loss affected brain stimulation reward because of lowered levels of circulating leptin in animals with lower fat stores, they administered leptin to the slimmed-down rats. In the first group, leptin mimicked the effect of excess body fat and weakened the reward effect. In most of the rats in the second group, however, it strengthened it.



Shizgal suggests that, just as increased leptin from fat stores reduces the attractiveness of food, leptin administered to the first group reduced the rewarding effect produced by electrically activating nerve cells that normally signal the "goodness" of food. But the second group of rats provided the most striking and unexpected findings. In this case, he speculates, "leptin may contribute to the regulation of energy balance by biasing the rats to spend more time engaged in activities unrelated to feeding." Similarly, people usually lose their interest in having big meals after gaining weight at holiday parties, and they often forget to eat when they are absorbed by interesting activities.

The Concordia researchers are continuing their work on leptin's role in regulating energy balance, in pregnancy and lactation, and on the basic mechanisms of brain stimulation reward. — *Janice Hamilton*, Montreal

Briefly . . .

Secrets of long life

Researchers have extended the lifespan of mice by one-third, simply by removing a protein that usually reacts to oxidative damage (*Nature* 1999;402:309-13). The research provides clues to the aging process and hints at the possibility of greater longevity in mammals. Oxidation is known to contribute to aging and disease, and anti-oxidants such as vitamins C and E are touted as a way to stay healthier and live longer. Researchers have now found that a protein (p66shc) undergoes changes when faced with oxidative damage caused by ultraviolet light or hydrogen peroxide, for example. Mice genetically altered to lack the gene that creates the p66shc protein resist oxidative agents better and live much longer than regular mice, with no negative side effects yet identified. Hence, oxidation appears to play a key role in aging, and reaction to oxidative damage seems to be part of the mammalian make-up. But researchers are understandably reluctant to predict that this discovery will allow us to slow the aging process in humans.