nature neuroscience

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Neurobiology of obesity

Food is a necessity, and it is also one of the pleasures of life. We eat to replenish energy stores, but we may feel hungry even when our needs for fuel are well met. And then we may feel satiated but eat some more because it tastes so good! Dieters know that it can be exceedingly difficult to limit food intake to the amount that the body actually needs. Morbid overweight—obesity—has reached epidemic proportions among affluent and less affluent populations around the world. Western societies spend enormous amounts of money to treat the health consequences of obesity. Desperate patients submit to radical surgeries in hopes of gaining control over their body weight. As our cover image shows, the problem isn't new, either—a Paleolithic artisan sculpted the 'Venus from Willendorf' figurine approximately 25,000 years ago.

Why is it so difficult to control food intake? What sort of tricks are our bodies and brains playing on us? It turns out that mammalian energy balance is controlled by an amazingly complex network of interacting feedback mechanisms that involve the hypothalamus, the brainstem, higher brain centers, and, in the periphery, the stomach, gut, liver, thyroid, and adipose (fat) tissue. We are just beginning to understand these circuits. In this focus issue, we highlight six areas where major progress has been made in the past few years.

The hypothalamus is the master regulator of energy metabolism, but how does it evaluate the nutritional status of the body? Apart from hormonal signals, the hypothalamus can sense nutrient levels directly. In their review, Tony Lam, Gary Schwartz and Luciano Rossetti describe how manipulations of lipid levels or lipid biochemistry in the hypothalamus affect the feeding behavior of mice and baboons. They discuss the evidence that a certain intermediate of fatty acid metabolism, LCFA-CoA, could serve to integrate fat and carbohydrate metabolic signals into an overall measure of energy status.

Roger Cone reviews our current knowledge of the melanocortin circuits in the hypothalamus and in the brainstem. Mutations in the melanocortin receptor MC4R are the most common genetic cause of inherited obesity. The hypothalamic melanocortin system responds to multiple signals from the periphery, especially hormones and nutrients. Activation of this system has a powerful anorexigenic effect, whereas its inhibition increases food intake and weight. Less is known about the function of the brainstem melanocortin neurons. They seem to pick up a distinct set of peripheral signals and work in concert with the hypothalamic melanocortin system in the regulation of food intake.

A perspective by Tamas Horvath highlights the unusual anatomy and plasticity of the hypothalamic melanocortin system. The synaptic input to several subclasses of modulatory neurons undergoes rapid rearrangement in response to fasting and feeding. Although a causal effect of this plasticity on feeding behavior has not yet been shown, deficiencies in neural plasticity could contribute to disorders of energy homeostasis.

Ten years ago, scientists identified the *ob* gene, a mutation of which causes obesity in a strain of laboratory mice. *Ob* codes for the hormone leptin, which is secreted from adipose tissue, signals via receptors in the hypothalamic arcuate nucleus and leads to activation of melanocortin neurons. Injected into mice, leptin causes reduced feeding and weight loss, but it does not have a significant slimming effect in obese patients. Overweight people or rodents have chronically elevated leptin levels because of the increased adipose tissue, but they seem to be resistant to leptin's anorexigenic effects. Heike Münzberg and Martin Myers in their review explain the intricacies of leptin signaling and how overactivation of a simple feedback loop by chronically high leptin levels might contribute to leptin resistance in obesity.

Marijuana, which acts on endocannabinoid receptors, stimulates appetite. The endocannabinoids themselves cause weight gain in animal experiments, and antagonists of the endocannabinoid receptor CB_1 cause weight loss. Vincenzo Di Marzo and Isabel Matias review the possible sites and mechanisms whereby endocannabinoids could affect feeding regulation. They also summarize the clinical trials of a specific CB_1 antagonist that may soon hit the market to treat obesity and metabolic syndrome (a condition that includes overweight, insulin resistance and high blood pressure and that predisposes people to developing diabetes and coronary heart disease).

Eating is a source of pleasure, and has been shown to activate reward circuits that are also involved in the response to drugs of abuse. A commentary by Nora Volkow and Roy Wise explores the parallels between drug addiction and pathological eating, including environmental and neurobiological factors.

Recognizing the threat to public health that is posed by the rise in obesity, the US National Institutes of Health (NIH) has established the Obesity Research Task Force, which encompasses 15 NIH institutes and several other NIH bodies, led by the National Institute for Diabetes and Digestive and Kidney Diseases (NIDDK) and the National Heart, Lung and Blood Institute (NHLBI). We are grateful to the NIH Obesity Research Task Force for generous financial support of this focus issue. With their help, we are making the content of the focus freely available on the web for three months at http://www.nature.com/neuro/focus/obesity/index.html.

Apart from the sponsors' foreword, the editorial team of *Nature Neuroscience* is entirely responsible for the content of the focus issue. We hope that our readers will find this collection of articles helpful and enjoyable and that it may contribute to advancing research in this important field at the interface of neuroscience, metabolism and medicine.

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