Editorial Comment

Sweet Preference, Obesity and Genetic Polymorphism of Leptin and the Leptin Receptor

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Obesity is a risk factor for lifestyle-related and cardiovascular diseases, since it is closely associated with increased morbidity and mortality in the patients with cardiovascular disease and hypertension (*1*). Obesity results from an abnormal accumulation of fat in the white adipose tissue. Recent research utilizing genetic models of obesity in rodents has implicated leptin as playing a major role in obesity. Leptin is a 167–amino acid peptide hormone encoded by the obese (Ob) gene (*2*), which is secreted by adipocytes and plays an important role in regulating food intake, energy expenditure and adiposity. Leptin exerts its biological activity by interacting with leptin receptors (*3*). Leptin receptors belong to the class 1 cytokine receptor family, members of which act mainly through the JAKs and STATs signaling pathways. Leptin receptors are expressed in the central nervous system—mainly in afferent satiety centers of the hypothalamus—and in peripheral organs such as adipose tissues, skeletal muscles, pancreatic β-cells and liver, thus indicating the autocrine and paracrine role of leptin in energy regulation.

Leptin has dual regulatory functions in weight maintenance. When energy intake and output are equal, the leptin level reflects total body fat mass. In conditions of negative and positive energy balance, the dynamic changes in plasma leptin concentration function as a sensor of energy balance and influence the efferent energy regulation pathways as follows: 1) leptin inhibits insulin secretion and biosynthesis; 2) leptin inhibits gluconeogenesis; 3) leptin reverses insulin resistance; 4) leptin potently decreases intramyocellular lipid levels by enhancing mitochondrial fatty acid β-oxidation; and 5) leptin suppresses the hypothalamus-pituitary-thyroid axis.

It has been well demonstrated that leptin inhibits food intake. Leptin regulates energy homeostasis mainly by acting on the hypothalamic neuropeptides. POMC neurons producing anorectic α-MSH are believed to be key mediators of the actions of leptin. Transgenic overexpression of leptin has been shown to result in markedly decreased food intake and body weight gain with complete disappearance of white adipose tissue and brown adipose tissue. In humans, treatment with recombinant leptin reduces the marked hyperphagia in leptin-deficient subjects and results in weight loss. Leptin suppresses sweet preference by suppressing the neural and behavioral responses to sweet substances (*4*) through its action on the leptin receptors in the taste bud cells of mice, in addition to suppressing central appetite regulation. Since the imbalance between regulation of food intake and energy expenditure lead to the obesity, the impairment of sweet preference regulated by leptin may cause the obesity.

The intriguing and timely article by Mizuta *et al*. in the present issue of *Hypertension Research* (*5*) provides new evidence that leptin and leptin receptor gene polymorphisms are associated with sweet preference and obesity. The authors investigated the sweet preference and clinical characteristics of a total of 3,653 residents randomly selected from the general population, including obesity and serum leptin levels, and polymorphisms of the leptin gene and leptin receptor gene and determined the associations among the parameters using logistic regression analysis, in order to consider potential confounding factors in the relation between these parameters and

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sweet preference and/or obesity. They determined that the *LEP* A19G and *LEPR* R109K polymorphisms were associated with sweet preference, whereas serum leptin was not. Further, the *LEPR* 109KK genotype was found to be associated with obesity along with sweet preference.

What is the role of leptin receptors in sweet preference? Sweeteners activate transduction cascades in sweet-responsive cells through both cAMP and inositol triphosphate in taste bud cells. It was reported that leptin increased the K^+ conductance of taste cells, leading to hyperpolarization and reduction of cell excitability, and leptin suppressed the behavioral response to sweet substances (*6*). In this issue, Mizuta *et al*. considered that the *LEPR* R109 or the *LEP* A19G polymorphism might affect the molecular mechanisms of leptin activation of K^+ currents as in the case of pancreatic β cells and hypothalamic neurons (*5*).

The findings of all of these studies, when taken together, suggest that polymorphisms of the leptin gene and leptin receptor gene would be significantly related to the sweetness sensitivity through the leptin-regulated ion channel activity of taste bud cells, indicating these polymorphisms might predict the risk for obesity. Therefore, determining the single nucleotide polymorphisms of leptin and its receptor and a pharmacological intervention based on information on a gene for sweet preference in humans may open a new avenue for the treatment of obesity and lifestyle-related disease.

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