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# Obesity

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## Introduction

Obesity has become a worldwide health issue. In developed countries, the majority of people are either overweight or obese. We are reminded almost daily in newspapers and magazines about the magnitude of this problem. Despite efforts to increase public awareness and facilitate changes in lifestyle, the problem continues to worsen. Unfortunately, there are many other diseases that coexist with or are the result of obesity, including type 2 diabetes, coronary heart disease, dyslipidemias, gallstones, osteoarthritis, and some forms of cancer. Obesity is one of a cluster of diseases that constitute the metabolic syndrome. In addition, obesity may decrease the quality of life and lower self-esteem. The purpose of this theme issue section of *Endocrine* is to review the current status of the treatment of obesity, to describe the physiology of energy balance, and to cite new targets and modalities for body weight control that may contribute to improved treatment.

In the United States, the National Heart, Lung and Blood Institute in cooperation with the National Institute of Diabetes and Digestive and Kidney Diseases, developed federal evidence-based guidelines on the identification, evaluation, and treatment of overweight and obesity. Information on the clinical guidelines, and links to other resources for clinicians, researchers, and the public, can be accessed at http://www.nhlbi.nih.gov/guidelines/obesity/ob_home.htm. The following paragraph was distilled from the guidelines, with a focus primarily on treatment. For evidence categories one should consult the complete guidelines.

> Intentional weight loss will decrease blood pressure in overweight and obese persons with hypertension. Weight loss will decrease elevated total cholesterol, LDL-cholesterol, and triglycerides, and increases low levels of HDL-cholesterol in overweight and obese persons with dyslipidemia. Weight loss decreases elevated blood glucose levels in overweight and obese persons with type 2 diabetes. Low calorie diets are recommended for weight loss in overweight and obese persons. Reducing fat intake as part of a low calorie diet is a practical way to reduce calories. Increased physical activity contributes to weight loss and increases cardiorespiratory fitness. A combination of a low calorie diet and exercise is recommended. Behavior therapy may contribute to weight loss and weight maintenance. Pharmacotherapy for weight loss may be added to a comprehensive weight loss program including diet and exercise for patients with a BMI of ≥30 with no concomitant obesity-related risk factors or diseases (diabetes, hypertension, dyslipidemia, or cardiovascular disease), or for patients with a BMI of ≥27 with concomitant obesity-related risk factors or diseases. Currently, sibutramine and orlistat are approved for long-term use in the United States. Surgical interventions may be considered for select patients with severe obesity (BMI of ≥40, or ≥35 with comorbid conditions) when other treatments have failed and the patient is at high risk for obesity-associated morbidity and mortality. A standardized treatment approach may not be equally effective in diverse patient populations.

The theme issue is organized into several sections. The first section summarizes obesity non-pharmacological treatment, cardiovascular disease, and metabolic stress. The first review in this issue introduces the growing prevalence and associated medical issues of obesity and the metabolic syndrome. This is followed by a summary of medical nutrition therapy for management of obesity, and effects of changes in diet composition on weight regulation. An overview of the surgical treatment for obesity is next, including the history, current procedures and those in clinical trials. The beneficial and negative effects of surgery on endocrine function are discussed. Orlistat, which is an effective agent for long-term treatment of obesity, inhibits intestinal lipases, interfering with the absorption of dietary fat. While this issue does not specifically review this or other agents that interfere with nutrient absorption, the effectiveness of bariatric surgery and orlistat pharmacotherapy demonstrate the value of this strategy, although the endocrine effects of surgery unrelated to malabsorption may contribute to its efficacy. The vascular endothelial dysfunction associated with obesity, the postulated mechanisms tying obesity to cardiovascular disease, and beneficial effects of weight reduction are reviewed in the next article. This is followed by a review of the role of oxidative stress in obesity, type 2 diabetes, and aging. Future research will establish whether agents that target specific cardiovascular function in obesity, or agents that inhibit oxidative stress, will contribute to improved treatment for obesity, metabolic syndrome and other disorders.

The brain plays a critical role in the regulation of energy balance, and the next section of this issue discusses brain targets for treatment of obesity. The first review in this section discusses the regulatory pathways in the hypothalamus, including the melanocortin system, CART, neuropeptide Y, and MCH. It summarizes the role of the cannabinoid CB-1 receptor in regulation of energy balance, and discusses the efficacy of rimonabant in treatment of obesity. Topiramate, an antiepileptic agent with significant antiobesity effects in animals and humans, is also discussed. It is possible that the

antiobesity effects of rimonabant and topiramate are not exclusively mediated by brain targets, because there are effects upon adipose tissue as well. The effects of the cytokine CNTF, the synthetic analog Axokine, and the role of agents affecting AMP-activated protein kinase (AMPK) in the brain on energy balance were summarized. The next review article summarizes the control of energy balance by biogenic amines in the brain. The antiobesity effects of monoamine releasers (including amphetamines and phentermine), inhibitors of neuronal reuptake of serotonin, norepinephrine, and/or dopamine (including sibutramine), and the evaluation of other monoaminergic targets, including 5-$HT_{2c}$ and $H_3$ receptors are included. The hypothalamus integrates signals from other regions of the brain, and controls several signals involved in energy balance, including pituitary hormone secretion and sympathetic activation. Another important research topic not reviewed in this issue is the role of circadian controllers on energy balance, potential antiobesity targets, and the role of sleep in obesity.

Several regions in the brain detect circulating factors from the gastrointestinal tract, adipose tissue, pancreas, and other sources. These factors include hormones, cytokines, and specific metabolic products such as glucose and fatty acids. The specific brain targets may account for at least part of the effect of these factors on energy balance, although most of these factors also have peripheral metabolic effects. One may target secretion or degradation of the factor, or stimulate/block the molecular target for these factors. These agents and their molecular targets comprise the next section of this issue. The first article in this section discusses effects of several hormones from the gut, namely, ghrelin, peptide YY, and the glucagon-like peptide GLP-1 on food intake and energy balance. Ghrelin inhibits the hypothalamic melanocortin system and activates NPY neurons, resulting in stimulation of appetite. PYY has the opposite effect to activate the melanocortin system and inhibit NPY neurons. Ghrelin receptor antagonists or PYY agonists may be useful antiobesity agents. GLP-1 inhibits food intake at the hypothalamus and at the amygdala, and in addition activates insulin secretion. GLP-1 receptors can be activated by synthetic mimics of GLP-1, or by prolongation of GLP-1 levels with DPP-IV blockers that inhibit GLP-1 degradation. The role of cholecystokinin (CCK) in satiety and the development of agents to affect CCK function were not discussed in this review, but these agents may also be useful for treatment of obesity.

Several secretory products from adipose tissue are the topic of the next review. Leptin is the most thoroughly characterized adipokine, because the lack of leptin or its receptor in mice results in obesity and diabetes. Although leptin administration to obese patients does not result in adequate weight loss, study of leptin action has led to the identification of many other targets for antiobesity agents. Adiponectin, a complex protein with several molecular forms, improves peripheral insulin sensitivity and affects lipid metabolism at several levels, decreasing circulating triglyceride and free fatty acid levels, while increasing skeletal muscle fatty acid oxidation. Resistin decreases insulin sensitivity and may contribute to endothelial dysfunction. TNF-$\alpha$ and IL-6 promote inflammation; TNF-$\alpha$ also increases PAI-1 expression and decreases adiponectin expression. PAI-1 overexpression in adipose tissue may facilitate cardiovascular complications of obesity, but more interestingly it may participate in the obesity process itself. Angiotensinogen from adipose tissue increases blood pressure. Fatty acid secretion from visceral fat contributes to hepatic insulin resistance. Selective agents targeting either secretion of adipose tissue products or the receptors for these products may be useful antiobesity agents or useful adjuncts for treatment of other morbidities associated with obesity.

Mechanisms for improvement of insulin action and activation of AMP-activated protein kinase (AMPK) are discussed in the next review, the first of several papers that characterize peripheral targets in obesity. Both events increase whole body glucose disposal, beneficial in the treatment of hyperglycemia. Specific targets for improved insulin sensitivity include the inhibition of phosphotyrosine phosphatase, primarily PTP-1B, and inhibition of Jun N-terminal kinase. Physical training, metformin treatment, and adiponectin activate AMPK, and increase whole body glucose disposal independent of insulin. Activation of AMPK in the hypothalamus regulates appetite and body weight, as discussed in this review and the review of hypothalamic regulatory pathways. The second paper in this section describes several approaches for modulation of fatty acid metabolism. It also discusses the benefits of AMPK activation to decrease fat mass, ectopic fat accumulation in nonadipose tissues such as skeletal muscle and liver, and increase fatty acid oxidation. Acetyl-CoA carboxylase (ACC) is inhibited by AMPK activation. The cytosolic isoform of ACC (ACC1) mediates fatty acid synthesis and the mitochondrial isoform (ACC2) inhibits mitochondrial fatty acid oxidation. Inhibition of ACC would decrease fatty acid synthesis and increase its oxidation, theoretically resulting in decreased fat storage. Several other strategies for modulation of fatty acid metabolism and rationale were discussed, including blockade of fatty acid synthase, inhibition of steroyl-CoA desaturase isoforms, inhibition of hormone-sensitive lipase in adipose tissue, inhibition of diacylglycerol acyltransferase 1 (DGAT1), inhibition of ATP citrate lyase, and inhibition of mitochondrial acyl-CoA:glycerol-3-phosphate acyltransferase (mtGPAT).

The final review article concerns the inhibition of 11$\beta$-HSD1 for treatment of obesity. This enzyme converts inactive cortisone to cortisol, the active glucocorticoid. The adrenal cortex manufactures and secretes both agents, and locally expressed HSD1 can increase the amount of cortisol in the liver, fat, gonads, brain, and vasculature. Expres-

sion of HSD1 is increased in adipose tissue of obese patients and genetic animal models (Zucker fa/fa rat and ob/ob mice). The intentional overexpression of HSD1 in adipose tissue of mice results in obesity and insulin resistance. Overactivity of visceral fat HSD1 may increase the availability of fatty acids and other fat-secreted factors in the portal circulation, resulting in hepatic insulin resistance. Treatment of lean rats with a nonspecific HSD inhibitor resulted in weight loss and decreased circulating corticosterone levels, and healthy humans treated with nonspecific HSD inhibitors had improved insulin sensitivity. Lean and obese Zucker rats treated with carbenoxolone have decreased hepatic but not adipose HSD1 activity, and do not lose weight and improve insulin sensitivity, presumably because it is necessary to inhibit adipose HSD1 for these effects.

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