Treatment of the Obese Patient

Edited by
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Treatment of the Obese Patient is a timely and informative text for all health care providers challenged with helping patients manage weight. This volume includes insight into recent scientific advances in obesity research and provides the most up-to-date reviews of current treatment issues and strategies.

The volume is divided into two parts. Part I covers new discoveries in the physiological control of body weight, as well as the pathophysiology of obesity. Expert authors discuss pathways that control food intake, energy expenditure, and peripheral nutrient metabolism, including a look at the emerging evidence of the role of adipose tissue as an endocrine organ. Part II covers issues central to clinical management. Authors in this section discuss polycystic ovarian syndrome, diabetes, energy density, glycemic index, low-carbohydrate diets, the role of physical activity, and novel approaches to pharmacotherapy, surgery, and management of micronutrient deficiencies in the post-obese patient.

An essential, practical text that sorts, synthesizes, and interprets the latest information on obesity-related topics, Treatment of the Obese Patient is an essential volume for clinical endocrinologists and other health care providers.

Features
- Evidence-based, state-of-the-art discussion of physiological control of body weight and the pathophysiology of obesity
- Authoritative advice on a full range of issues central to clinical management
- Illustrative case studies

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- Energy Expenditure and Obesity

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The rising prevalence of obesity among children and adults is one of the most significant threats to our nation’s health as we enter the 21st century. Among a host of disorders associated with obesity that affect multiple organ systems, the escalating prevalence of type 2 diabetes and conditions associated with the metabolic syndrome and cardiovascular disease are the most worrisome. For these reasons, it is increasingly important for clinical endocrinologists and other health care providers to be informed about breakthroughs in obesity research and to become engaged in the clinical care of the obese patient. Although our medical journals and the popular press are including more and more articles about obesity-related topics, there is a need to sort, synthesize, and interpret this information into a single readable text. Thus, the primary purpose of this volume of Contemporary Endocrinology, entitled Treatment of the Obese Patient, is to inform clinicians of recent scientific advances in obesity research and to provide an up-to-date review of current treatment issues and strategies. To provide the most useful and authoritative text, we have selected chapter authors who are not only experts in their fields of study but who are also able to translate important and emerging concepts to the practicing clinician.

The volume is divided into two parts. Part 1 covers new discoveries in the physiological control of body weight, as well as the pathophysiology of obesity. The most exciting breakthroughs in obesity research over the past decade have come from a growing appreciation of the critical pathways that control food intake, energy expenditure, and peripheral nutrient metabolism including the emerging evidence of the role of adipose tissue as an endocrine organ. Each of these evolving areas is covered in its entirety in this volume. Chapters 1 through 3 address the neuroregulation of appetite, the role of gut peptides in providing peripheral signals of nutrient balance to the brain, and the new biology of the endocannabinoid system. In Chapters 4 and 5, the pathophysiology of adipokines and role of free fatty acids, insulin, and ectopic fat in the metabolic dysregulation of obesity are reviewed. Chapter 6 examines the provocative role of fetal origins and birth weight in the causation of obesity. Finally, Chapters 7 and 8 provide a comprehensive review of new developments in body composition in health and disease, and the role of alterations of energy expenditure in the development of obesity.

In Part 2, we turn to a range of issues that are central to the clinical management of obese patients. This section begins with an informative review of the socioeconomic aspects of obesity. Chapters 10 through 12 address the comprehensive assessment and evaluation of the obese adult patient, the pathophysiology and approach to the patient with polycystic ovarian syndrome, and management of the obese patient with diabetes. Chapters 13 through 15 provide an excellent review and discussion of three dietary approaches that have been advocated in the treatment of obesity—energy density, glycemic index, and low-carbohydrate diets. The role of physical activity is covered in Chapter 16. Communication, counseling, and motivational interviewing, keys to changing patient behavior, are considered in Chapter 17. Chapters 18 through 20 turn our attention to new developments in the pharmacotherapy of obesity, surgical approaches and outcomes, and management of micronutrient deficiencies in the postbariatric surgical patient. Lessons
learned from individuals who have succeeded in losing weight and maintaining a reduced obese state long term: members of the National Weight Control Registry are discussed in Chapter 21. Lastly, a succinct summary of evaluation and management of the pediatric obese patient is reviewed in Chapter 22.

Treatment of the Obese Patient is a timely and informative text for all health care providers facing the challenges of helping their patients manage their weight. Our intention is to provide a resource that will both stimulate and engage clinicians to take part more successfully in the obesity-care process. We hope we have accomplished this goal.

Robert F. Kushner, MD
Daniel H. Bessesen, MD
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Physiology and Pathophysiology
Neuroregulation of Appetite

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Summary

This chapter reviews current literature on hormonal and neural signals critical for the regulation of individual meals and body fat. Body weight is regulated via an ongoing process called energy homeostasis, or the long-term matching of food intake to energy expenditure. Reductions from an individual’s “normal” weight owing to a lack of sufficient food lowers levels of adiposity signals (leptin and insulin) reaching the brain from the blood, activates anabolic hormones that stimulate food intake, and decreases the efficacy of meal-generated signals (such as cholecystokinin) that normally reduce meal size. A converse sequence of events happens when individuals gain weight, adiposity signals are increased, catabolic hormones are stimulated, and the consequence is a reduction in food intake and a normalization of body weight. The brain also functions as a “fuel sensor” and thereby senses nutrients and generates signals and activation of neuronal systems and circuits that regulate energy homeostasis. This chapter focuses on how these signals are received and integrated by the central nervous system.

Key Words: Hypothalamus; arcuate nucleus; body weight regulation; neuropeptides; central nervous system (CNS); obesity.

Introduction

Body weight (or, more accurately, body adiposity) is a tightly regulated variable. To maintain body fat stores over long periods of time, caloric intake must precisely match expenditure. Such a process relies on the complex interactions of many different physiological systems. As an example, one negative feedback system is composed of hormonal signals derived from adipose tissue that inform the central nervous system (CNS)
about the status of peripheral energy stores. These signals from adipose tissue or peripheral fat stores form one side of the hypothesized feedback loop. The receiving side of this regulatory system includes one or more central effectors that translate adiposity information into appropriate subsequent ingestive behavior. When the system detects low levels of adipose hormones, food intake is increased, whereas energy expenditure is decreased. On the other hand, in the presence of high adiposity signals, food intake is reduced and energy expenditure increased. In this way, the negative feedback system can maintain energy balance or body adiposity over long periods of time by signals in the CNS.

THE DUAL-CENTERS HYPOTHESIS

Historically, the conceptual framework that dominated thinking about the role played by the hypothalamus in the control of food intake was the dual-centers hypothesis proposed by Stellar in 1954 (1). In the same year that the discovery of leptin refocused attention on the role of the hypothalamus in energy balance, Psychological Review honored this article as one of the 10 most influential articles it had published in a century of publications. Stellar eloquently argued that the hypothalamus is the central neural structure involved in “motivation” generally and in the control of food intake more specifically. This control is divided into two conceptual categories controlled by two separate hypothalamic structures. The first category was “satiety” and was thought to be controlled by the ventromedial hypothalamus (VMH). The most important data that contributed to this hypothesis were that bilateral lesions of the VMH resulted in rats that ate more than controls and became obese. These lesioned rats were thought to have a defect in satiety; therefore, the VMH was described as being a “satiety” center. Additionally, experimentally the lesion could be replicated by electrical stimulation of the VMH, which also caused the animals to stop eating—in other words, these experiments demonstrated a role for the VMH in enhancing satiety. In contrast to the VMH, the lateral hypothalamic area (LHA) was thought to be the “hunger” nucleus, as lesions of the LHA resulted in rats that under-ate and lost body weight. Additionally, electrical stimulation of the LHA caused eating in sated animals. Therefore, the VMH was thought to be the satiety center and the LHA was considered the hunger center. This characterization of the brain was called the dual-centers hypothesis and was the dominant conceptualization of how the CNS controlled food intake for almost 30 yr.

CNS Regulation of Food Intake

CNS regulation of food intake was originally thought to be controlled by the VMH and the LHA; however, several challenges were made to this early hypothesis. The first was a realization that there are limitations to our understanding of the neurocircuitry using the lesions as an experimental approach to understanding CNS function. Conclusions made about larger lesion studies were difficult to interpret because lesions usually destroyed all fibers in the nuclei, not just those fibers of specific interest. An additional problem was that there are consequences of the lesion not directly tested. For example, although lesions of the VMH result in hyperphagic and obese rats, they also result in rapid and dramatic increases in insulin secretion from pancreatic β-cells (2). Indeed, exogenous peripheral insulin administration results in increased food intake, and repeated administration can result in rapid weight gain (3). Therefore, in addition to regulating
“satiety,” the VMH also appears to have an important role in the regulation of insulin secretion (2). Further research supported the VMH’s role in regulating additional functions other than satiety. In particular, later data indicated that it was not cell bodies in the VMH but rather fibers running from the paraventricular nucleus (PVN) to the brainstem that were critical for the effect of VMH lesions on insulin secretion (4,5). So although the changes in insulin secretion were potentially responsible for the effects of VMH lesions on food intake and body weight, this control of insulin secretion may not be directly mediated by the VMH.

Another challenge to the dual-centers hypothesis came from work out of Grill’s lab, which focused on transection of the neuraxis at different levels by utilizing the chronic decerebrate rat. The chronic decerebrate rat has a complete transection of the neuraxis at the mesodiencephalic junction that isolates the caudal brainstem, severing all neural input from more rostral structures such as the hypothalamus. Hence, neither the VMH
nor LHA (nor any other hypothalamic nuclei, for that matter) could exert direct influence on the motor neurons in the brainstem critical for executing ingestive behavior (6). Despite a complete loss of neural input from the hypothalamus, the chronic decerebrate animal has the ability to engage in consummatory behavior and to adjust that behavior in response to both external and internal stimuli. Chronic decerebrate rats respond appropriately to taste stimuli (6–9). More importantly, chronic decerebrate rats demonstrate satiety, and the size of the meals is influenced in the same manner as in a normal rat (6,8). The caudal brainstem is therefore sufficient to integrate internal regulatory signals that limit meal size into ongoing ingestive behavior independent of the hunger and satiety centers of the hypothalamus. These data suggest that there are several regions in the CNS that mediate the control of food intake and that no single brain area constitutes either a “hunger” or a “satiety” center.

**CNS Regulation by Adiposity Signals and Effector Pathways**

These challenges to the dual-centers hypothesis led to new models for understanding the role of the hypothalamus in the control of food intake. Other research has focused on emphasizing factors and signaling pathways that control long-term energy balance. Adult mammals typically match their caloric intake to their caloric expenditure in a remarkably accurate fashion. In the 1950s Kennedy postulated that animals could regulate their energy balance by monitoring the major form of energy storage in the body, adipose mass (10). When caloric intake exceeds caloric expenditure, fat stores are expanded; when caloric expenditure exceeds caloric intake, fat stores are reduced. In other words, if the size of the adipose mass could be monitored, energy intake and energy expenditure could be adjusted to keep adipose mass constant and thereby keep the energy equation balanced over long periods of time.

There are at least two peripherally derived hormones that provide key afferent information to the CNS for body weight regulation. Leptin, a peptide hormone secreted from adipocytes in proportion to fat mass, has received tremendous attention during the last decade. Considerable evidence has been derived that implicates leptin as one of the body’s adiposity signals (11–14). Leptin levels in the blood correlate directly with body fat, and peripheral or central administration of leptin reduces food intake and increases energy expenditure.

Importantly, leptin levels are better correlated with subcutaneous fat than with visceral fat in humans, such that the reliability of leptin as an adiposity signal varies with the distribution of body fat. There is a sexual dimorphism with respect to the way in which body fat is distributed. Males tend to have more body fat located in the visceral adipose depot, whereas females tend to have more fat in the subcutaneous depot. Because females tend to have more subcutaneous fat than males, on the average, leptin is therefore a better correlate of total adiposity in females than in males (15). Further, when energy balance is suddenly changed (for example, if an individual is fasted for a day), plasma leptin levels decrease far more than body adiposity in the short term (16–18). Hence, although much has been written about leptin as an adiposity signal, it is not ideal in and of itself, suggesting that other signals may exist. One candidate is the pancreatic hormone, insulin.

Insulin is well known for its role in regulating glucose homeostasis; however, an often under-represented role for insulin is as an adiposity signal. Plasma insulin levels also directly correlate with adiposity, and although leptin is a better correlate of subcutaneous
adiposity, insulin correlates better with visceral adiposity (19–22). Moreover, when energy balance changes, there are changes in plasma insulin that closely follow changes in homeostasis (23). Therefore, both leptin and insulin can be considered adiposity signals, each indicating something different to the brain; insulin is a correlate of visceral adiposity and leptin is a correlate of subcutaneous adiposity and, together or separately, they are markers of changes of metabolic status.

CONTROL OF ENERGY INTAKE

Food intake in mammals, including humans, occurs in distinct bouts or meals, and the number and size of meals over the course of a day comprises the meal pattern. Food intake is thought to be regulated by signals from the gut, brainstem, and hypothalamus. Most humans are quite habitual in that they eat approximately the same number of meals, and at the same time of day (24,25). Factors or signals that control when meals occur are different from those that control when they end—i.e., different factors control meal onset and meal size (25,26). Historically, meal onset was thought to be a reflexive response to a reduction in the amount or availability of some parameter related to energy. Changes in glucose levels were posited to stimulate meals; this was coined the “glucostatic” theory. This theory put forth the idea that a reduction of glucose utilization by sensor cells in the hypothalamus of the brain caused the sensation of “hunger” and a tendency to start a meal (27,28). An additional hypothesis was generated about what stimulates “hunger”; this was associated with changes in fuel, either from changes in body heat, upon fat utilization by the liver, or upon the generation of adenosine triphosphate (ATP) and other energy-rich molecules by cells in the liver and/or brain (29–32).

Food intake may be stimulated for reasons other than simple changes in energy substrates. An alternative hypothesis for meal generation is that most meals are initiated at times that are convenient or habitual, and thus based on social or learned factors as opposed to fluxes of energy within the body (33). In this schema, the regulatory control over food intake is exerted on how much food is consumed once a meal is started rather than on when the meal occurs (34,35). Therefore, individuals have flexibility over their individualized meal patterns, and this is influenced by their environment and lifestyle. Hence, there are factors and signals that are regulatory controls that determine meal size, and this is generally equated with the phenomenon of satiety or fullness (26).

Satiety

Meals are considered to be regulated—there are initiation and cessation cues that signal the beginning and completion of the meal, respectively. If the cessation cue is controlled by signals that arise from the brain and gut, then the individual must have a means of measuring reliably how much food has been eaten—i.e., the number of calories consumed, or perhaps the precise mix of carbohydrates, lipids, and proteins, and/or other food-related parameters. Consumption must be monitored as the meal progresses so the person knows when to say “I’m full” and put down the fork (26). Some parameters or signals might provide the important feedback during an ongoing meal. These signals may be in the form of vision, smell, or taste to gauge the amount of energy consumed. However, several types of experiments have found that any such input is minimal at best. To determine whether the gut conveys a signal to end the meal, animals have been experimentally implanted with a gastric fistula (36). When the fistula is closed, swallowed food enters the stomach, is processed normally, and moves into the duodenum.