Abstract

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 due to 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, or CCK) 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: arcuate nucleus, body weight regulation, central nervous system (CNS), hypothalamus, neuropeptides, obesity.

INTRODUCTION

Body adiposity is a tightly regulated variable. To maintain fat stores over long periods of time, caloric intake must precisely match expenditure. Such a process relies on the complex interactions of many different physiologic systems. 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 peripheral fat stores comprise one side of the hypothesized feedback loop. The receiving side of this regulatory system includes multiple central effectors that translate this information into subsequent ingestive behavior. When the system detects low levels of adipose hormones, food intake is increased while energy expenditure is decreased. In the presence of high adiposity signals on the other hand, food intake is reduced and energy expenditure increased. In this way, the body’s negative feedback system can maintain energy balance or body adiposity over long periods of time.

THE DUAL-CENTERS HYPOTHESIS

The conceptual framework that historically dominated thinking about hypothalamic control of food intake was the dual-centers hypothesis proposed by Elliot Stellar in a very influential article in *Psychological Review* [1]. Years later, coinciding with the discovery of leptin, *Psychological Review* honored this article as one of the 10 most influential articles it had published in a century of publications. Stellar argued that hypothalamic nuclei are the central neural structures 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 supporting this hypothesis was that bilateral lesions of the VMH resulted in rats that ate more than controls and became obese. VMH-lesioned rats were thought to have a defect in satiety, and therefore the structure was termed the “satiety” center. Additionally, electrical stimulation of the VMH also caused the animals to stop eating. These experiments seemed to demonstrate a role for the VMH in enhancing satiety. In contrast with the VMH, the lateral hypothalamic area (LHA) was thought to be the “hunger” nucleus as lesions of the LHA resulted in rats that underate and lost body weight. Likewise, electrical stimulation of the LHA caused hyperphagia in sated animals. Based on data such as these, the VMH and LHA were respectively thought to be the satiety and hunger centers. This characterization, the dual-centers hypothesis, was the dominant conceptualization of CNS-controlled food intake for almost 30 years.

CHALLENGES TO THE HYPOTHESIS

As with all good theories however, challenges against the dual-centers idea emerged. The first was a realization that there were limitations to understanding of the neurocircuitry using the lesions as an experimental approach to understanding CNS function. Conclusions made about larger lesion studies were often difficult to interpret