# CHAPTER 102

# Physiology of Weight Regulation

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## Summary

Interest in the physiology of weight regulation has increased in recent years due to the major deleterious effects of the obesity epidemic on public health. A complex neuroendocrine network involving peripheral organs and the central nervous system (CNS) is responsible for maintaining a balance between energy intake and expenditure. Major changes in weight can result from an imbalance in this network. Gut and adipose tissue are the main peripheral organs involved in weight regulation. Hormones are secreted from these peripheral organs in response to nutrient intake and weight fluctuation, and are subsequently integrated by the CNS. Unraveling these peripheral and central signals and their complex interaction at multiple levels is essential to understanding the physiology of weight regulation.

## Introduction

According to the 2009–10 National Health and Nutrition Examination Survey (NHANES), the prevalence of obesity among adults in the United States was 35.7% and the prevalence of obesity and overweight was 68.7% [1, 2]. More than 110 000 deaths per year are attributed to obesity [3]. Furthermore, due to the substantial rise in the prevalence of obesity and its life-threatening complications, we may experience a decline in life expectancy in the United States in the 21st century [4]. Complex brain–gut interaction constitutes the basis of weight regulation. This involves intricate mechanisms, some of which are not fully elucidated at present and are the focus of extensive ongoing research. This chapter reviews our current understanding of the mechanisms of weight regulation, with emphasis on the role of the gastrointestinal (GI) system.

## Concept of Energy Homeostasis

Fat is the primary form of energy storage in the human body. According to the first law of thermodynamics, the amount of energy stored is equal to the difference between energy intake and energy expenditure. Under normal conditions, homeostatic mechanisms maintain the difference between energy intake and energy expenditure close to zero. A very small imbalance in those mechanisms over a long period of time can result in large cumulative effects, leading to a major change in weight. In order to keep a perfect balance between energy intake and expenditure, homeostatic mechanisms rely on neural signals that emanate from adipose tissue and from endocrine, neurological, and GI systems and are integrated by the CNS [5, 6]. The CNS subsequently sends signals to multiple organs in the periphery in order to control energy intake and expenditure and maintain energy homeostasis over long periods of time (Figure 102.1).

## Role of the Central Nervous System

In recent decades, extensive research has focused on the role of the CNS in the regulation of food intake and the pathogenesis of obesity. Eating in humans is thought to follow a dual model: "reflexive eating," which represents automatic impulses to overeat in anticipation of a coming food shortage, and "reflective eating," which incorporates a cognitive dimension involving social expectations of body shape and long-term health goals [7]. Reflexive eating is represented by the brainstem and the arcuate nucleus. Two populations of neurons are responsible for the regulation of food intake in the arcuate nucleus, one expressing neuropeptide Y (NPY) and agouti-related peptide (AgRP), which when activated leads to an orexigenic response and reduced energy expenditure, and the other containing pro-opiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART), in which increased activity results in an increase in energy expenditure and a decrease in food intake [8]. NPY is one part of the pancreatic polypeptide family, which includes two other hormones: pancreatic polypeptide (PP) and peptide YY (PYY). NPY is present in large quantities in the hypothalamus and is one of the most potent orexigenic factors [9]. Among NPY receptors, the Y5 receptors have been implicated as important mediators of the feeding effect and the Y5 receptors antagonists have been involved in recent weight-loss studies [10]. The brain cortex seems to play a role in the regulation of food intake and represents "reflective eating" [7]. The right prefrontal cortex (PFC) has been specifically involved in the cognitive inhibition of food intake.

## Role of Adipose Tissue

Insulin and leptin are adiposity signals that play an important role in the physiology of weight regulation.

Insulin receptors are widely present in the CNS. Insulin levels have been shown to correlate with body adiposity. Increases in food intake and adiposity can result from hypothalamic defects in insulin
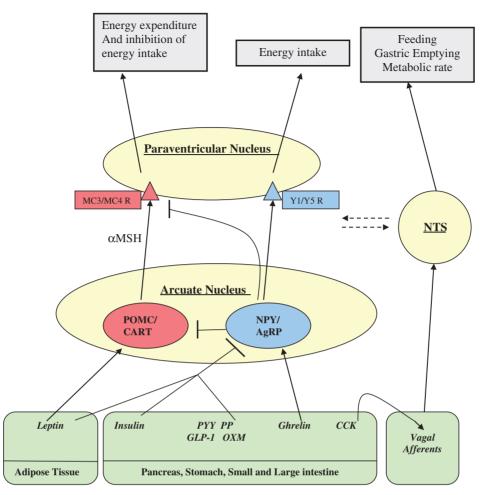
**Figure 102.1** Pathways of regulation of food intake. Representation of the potential action of gut peptides on the hypothalamus. Primary neurons in the arcuate nucleus contain multiple peptide neuromodulators. Appetite-inhibiting neurons (red) contain pro-opiomelanocortin (POMC) peptides such as α-melanocyte-stimulating hormone (αMSH), which acts on melanocortin receptors (MC3 and MC4), and cocaine- and amphetamine-stimulated transcript peptide (CART), whose receptor is unknown. Appetite-stimulating neurons in the arcuate nucleus (blue) contain neuropeptide Y (NPY), which acts on Y receptors (Y1 and Y5), and agouti-related peptide (AgRP), which is an antagonist of MC3/4 receptor activity. Integration of peripheral signals within the brain involves interplay between the hypothalamus and hindbrain structures including the nucleus of the tractus solitarius (NTS), which receives vagal afferent inputs. Inputs from the cortex, amygdala, and brainstem nuclei are integrated as well, with effects on meal size and frequency, gut handling of ingested food, and energy expenditure. →, direct stimulatory; –l, direct inhibitory; PYY, peptide tyrosine tyrosine; PP, pancreatic polypeptide; GLP-1, glucagon-like peptide 1; OXM, oxyntomodulin; CCK, cholecystokinin. Source: Badman 2005 [6]. Reproduced with permission of The American Association for the Advancement of Science.

signaling [11]. Insulin may also act outside the hypothalamus in the ventral tegmental area to suppress some aspects of feeding [12].

Circulating levels of leptin, an adipocyte-derived hormone, reflect the adipose tissue mass, as well as recent nutritional status. The action of leptin in the CNS results in a decrease in food intake and an increase in energy expenditure through the inhibition of NPY/AgRP neurons and activation of POMC neurons [13]. Most obese humans have elevated serum leptin levels, which suggests leptin resistance may be important in human obesity. Manipulating leptin resistance may provide an interesting target for obesity treatment. Recent research suggests that reduced responsiveness to leptin may result from a reduction in the POMC neuronal population and subsequent reactive gliosis in the hypothalamus in response to a high-fat diet [14].

Adiponectin and resistin are two other peptides produced by adipocytes. Low levels of the former are associated with insulin resistance, dyslipidemia, and atherosclerosis, whereas low levels of the latter have proinflammatory effects and have also been implicated in insulin resistance [15, 16].

## Role of the GI Tract

The GI tract elicits neural and endocrine signals that play a major role in food intake regulation. The interaction of GI hormones with the brain constitutes the gut–brain axis, which has been extensively studied in the past decade.

### Role of the Stomach in Food Intake Regulation

#### Gastric Distension

Gastric distension has been shown in multiple studies to serve as a signal for satiety. Instillation of a volume load in the stomach leads

to distension of gastric wall, which in turn induces satiety regardless of the nature of the load: in rats, studies have shown that equivalent volumes of saline or different nutrient solutions produce equivalent reductions in food intake [17, 18].

### Ghrelin

Ghrelin is a peptide predominantly produced by the stomach. Its secretion is increased by fasting and in response to weight loss and is decreased by food intake. Ghrelin is the only known circulating appetite stimulant. It stimulates appetite by acting on arcuate nucleus NPY/AgRP neurons and may also inhibit POMC neurons [19]. There is evidence that the vagus nerve is required to mediate its orexigenic effect.

Ghrelin plays a role in meal initiation, as demonstrated by a pre-meal surge in plasma ghrelin levels in humans and animals. It also appears to participate in long-term energy homeostasis, as suggested by its fluctuation in response to body weight variations [20]. It has been shown to play a role in stress-induced food reward behavior by acting on the ventral tegmental area of the brain [21].

### Role of the Pancreas and Small Intestine in Food Intake Regulation

### Cholecystokinin

Cholecystokinin (CCK) is the prototypical satiety hormone, produced by cells in the duodenum and jejunum. It is produced in response to the presence of nutrients within the gut lumen, specifically fat and protein. The satiating effect of CCK is mediated through paracrine interaction with sensory fibers of the vagus nerve. It inhibits food intake by reducing meal size and duration [22]. CCK has a short half-life, which makes it a very short-term modulator of appetite.

### Peptide Tyrosine Tyrosine and Pancreatic Polypeptide

PYY is secreted by enteroendocrine L-cells, mainly in the distal portion of the GI tract. It is released following meals (acting as a meal terminator) and is suppressed by fasting: exactly opposite to the pattern seen with ghrelin [22]. Increased levels of PYY are thought to play a role in the early weight loss observed after gastric bypass surgery [23]. PP is secreted in response to a meal, in proportion to the caloric load, and has been shown to reduce appetite and food intake [24]. It is mainly produced in the endocrine pancreas, but also in the exocrine pancreas, colon, and rectum.

### Glucagon-like Peptide 1 and Oxyntomodulin

GLP-1 and oxyntomodulin derive from the post-translational processing of proglucagon, which is expressed in the gut, pancreas, and brain. GLP-1 is secreted by enteroendocrine L-cells in the distal small bowel in response to direct nutrient stimulation in the distal small intestine, as well as indirect neurohumoral stimulation in proximal regions of the small intestine. The actions of GLP-1 include inhibition of gastric emptying, stimulation of insulin release, inhibition of glucagon release, and inhibition of appetite [25]. Furthermore, the effects of GLP-1 on weight and satiety are thought to be mediated in part by the presence of GLP-1 receptors in the CNS [26].

Oxyntomodulin is also secreted in the distal small intestine. It binds to the GLP-1 receptor, but with a lower affinity. It has been shown to decrease energy intake and, moreover, increase energy expenditure [27].

### Role of Gut Microbiota in the Development of Obesity

Recent evidence indicates that the commensal and symbiotic microbes that populate the gut (the gut microbiota) play a role in the development of obesity and insulin resistance. Several mechanisms are involved in this process, including increased energy extraction from diet, an effect on energy expenditure, and an effect on fat storage [28].

### Conclusion

The physiology of weight regulation involves intricate interactions between the brain and the gut. Tremendous progress has been made in our understanding of the different components of the gut–brain axis and extensive research is underway to create agents targeting these components in order to accomplish significant and lasting weight reduction.

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**Take Home Points**

- Understanding the physiology of weight regulation is fundamental in the fight against the obesity epidemic.
- Maintaining a stable weight involves complex homeostatic mechanisms responsible for balancing energy expenditure with energy intake.
- Signals originating from peripheral organs such as adipose tissue and the gastrointestinal (GI) system and integrated by the central nervous system (CNS) constitute the homeostatic mechanisms responsible for weight regulation.
- Gut hormones are produced in response to nutrient intake and weight fluctuation.
- The gut microbiota may play a role in energy regulation.
- Targeting the complex peripheral and central signals involved in weight regulation is the mainstay of the development of weight-reduction therapeutic agents.

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