Chapter 11
Control of Body Weight and the Modern Metabolic Diseases

The increase in the body weight in the world population has become one of the most important public health problems, as it is a major risk factor for several pathologies such as cardiovascular diseases and diabetes.

A systematic analysis evaluating the worldwide changes in the body mass index (BMI, defined as the body mass divided by the square of the height) was performed by the Global Burden of Metabolic Risk of Chronic Diseases Collaborating Group. They used health examination surveys and epidemiological studies from 199 countries and territories in the world, including 9.1 million participants, and showed that the mean worldwide BMI increased by 0.4 kg/m^2 per decade for men and 0.5 kg/m^2 per decade for women. Figure 11.1 shows the results of the percentage of the obese ($BMI \geq 30\ kg/m^2$) or overweight ($BMI \geq 25\ kg/m^2$) people, between 1980 and 2008, in distinct areas of the globe. It is clear that although there are some differences among the regions, the increase in body weight seems to be a global phenomenon.

Body weight is a result of the balance between food intake and energy expenditure. Several peripheral mediators secreted by different cells in the body act on the central nervous system, influencing the feeding behavior by controlling appetite or satiety, as well as regulating body energy expenditure by changing the metabolic rate and controlling thermogenesis. In this chapter we will discuss the mechanisms by which the body weight is controlled as well as the main proposals on how the impairment of this control may cause the modern metabolic diseases.

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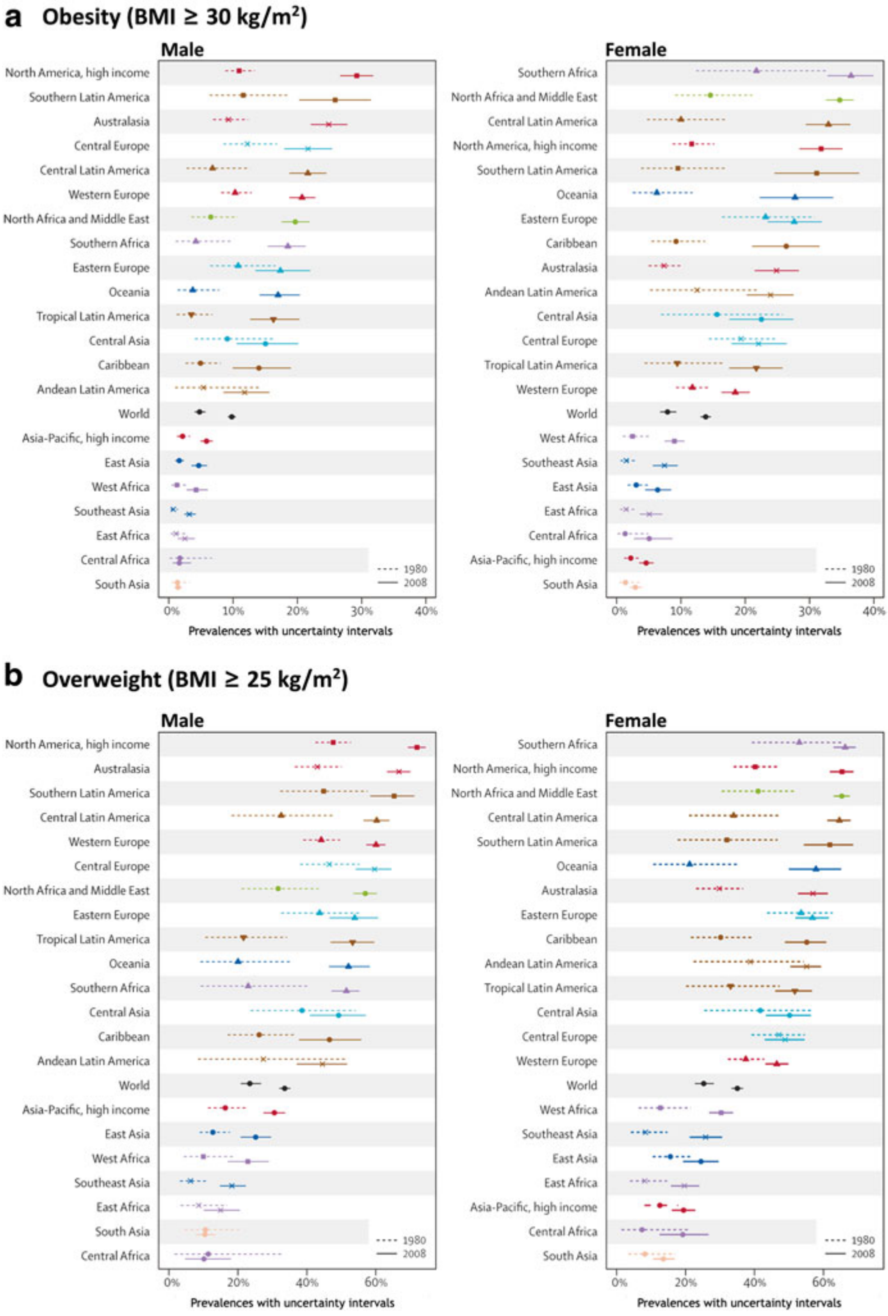


Fig. 11.1 Prevalence of obesity (**a**) or overweight (**b**) in 1980 and 2008 among males (*left*) and females (*right*) in different areas of the world (Reproduced from Finucane et al., Lancet 377:557–567, 2011, with permission from Elsevier)

11.1 Humoral Control of Food Ingestion

Although eating is a complex behavior that involves distinct areas of the brain, including the sensory areas that process the information of food taste, smell, and appearance, and the cortex, which is responsible for the psychological component of the appetite and satiety, the hypothalamus may be seen as a central player in the control of feeding.

The hypothalamus is located below the thalamus, just above the brain stem, in the ventral part of the diencephalon (Fig. 11.2). Anatomically, it is divided in several regions; the following ones are directly involved in the control of energy balance: ARC, arcuate nucleus; VMH, ventromedial hypothalamus; DMH, dorsomedial hypothalamus; PVN, paraventricular nucleus; and LH, lateral hypothalamus (Fig. 11.2).

The hypothalamus induces anorexigenic (appetite-suppressing) or orexigenic (appetite-stimulating) behaviors by sensing several substances that are secreted by different cells in the body as a response to food intake or to the increase in adiposity. For instance, leptin, insulin, cholecystokinin (CCK), and peptide YY (PYY) provide the anorexigenic signals, while ghrelin is the main orexigenic mediator, as it will be discussed in the next sections.

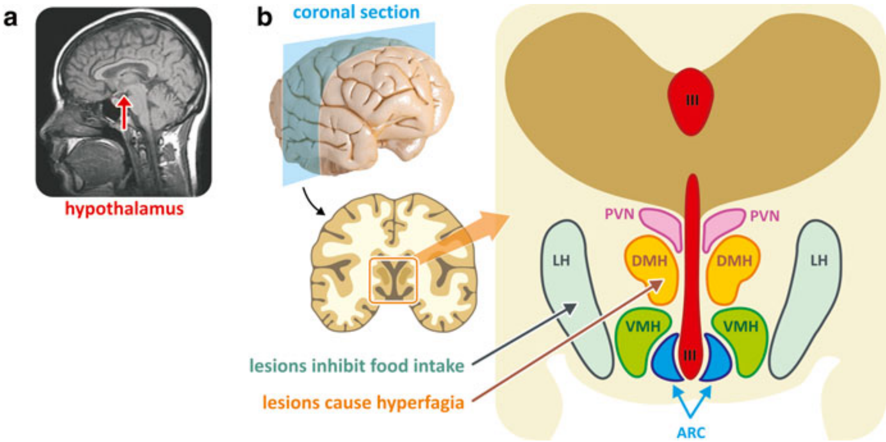


Fig. 11.2 (**a**) Magnetic resonance image of the human brain showing the localization of the hypothalamus (reproduced from the free media repository Wikimedia Commons). (**b**) Human brain section showing the anatomical localization of the hypothalamic regions. The *blue arrow* indicates the area whose lesion caused hyperphagia and the *orange arrow* indicates the area whose lesion caused the inhibition of food intake. *III* third ventricle, *ARC* arcuate nucleus, *VMH* ventromedial hypothalamus, *DMH* dorsomedial hypothalamus, *PVN* paraventricular nucleus, *LH* lateral hypothalamus

11.1.1 A Historical Perspective of the Role of Hypothalamus in Food Intake

The first evidence showing that the hypothalamus controls the body energy balance came from a number of studies conducted in the 1940s. These experiments showed that lesions in areas of the medial-basal hypothalamus caused either hyperphagia and obesity or anorexia, depending on the specific region that was lesioned (as indicated in Fig. 11.2).

More than just revealing its role in the control of food ingestion, these experiments led to the hypothesis that the hypothalamus would act as a sensor of the feeding status of the organism, stimulating or inhibiting food intake depending on the amount of the energy stored in the body. A question that was immediately raised was how this sensing mechanism would operate. An attractive hypothesis was that it occurred through the circulating metabolites detected by the hypothalamus.

At that time, a common approach to investigate the participation of a circulating mediator in a given phenomenon was through parabiosis experiments. In these experiments, the blood vessels of two animals were surgically connected to allow the exchange of circulating factors between them. In a classical experiment performed in 1959, parabiotic pairs of rats were subjected to a lesion in the hypothalamus of one of the animals. While the lesioned rats became obese, as expected, the unlesioned partners stopped eating and lost weight, indicating that a circulating factor produced by the obese animals, for which the lesion turned the animal unresponsive, inhibited food intake in the normal ones (see the result of this experiment in Fig. 11.3).

Other parabiosis experiments were performed in the 1950s taking advantage of the description of two spontaneous recessive mutations in mice that result in a phenotype of extreme obesity caused by hyperphagia. The two mutated genes were called *ob* (from the obese phenotype; Fig. 11.4) and *db* (from diabetic, and also obese, phenotype).

When a homozygotic mouse for a mutation in the *ob* gene (*ob/ob* mouse) was joined through parabiosis to a normal mouse, the obese animal stopped eating in excess and tended to normalize its weight. This suggested that the product of the *ob* gene, which is defective in the *ob/ob* mouse, would be the circulating factor that signalizes to the hypothalamus the excess of body weight, leading to the inhibition of food intake. In contrast, when a *db/db* mouse was connected to a normal mouse, only the normal animal lost weight, suggesting that the mutation caused a failure in the response to the “obesity” factor, which acts in the normal mouse inhibiting food ingestion (Fig. 11.5).

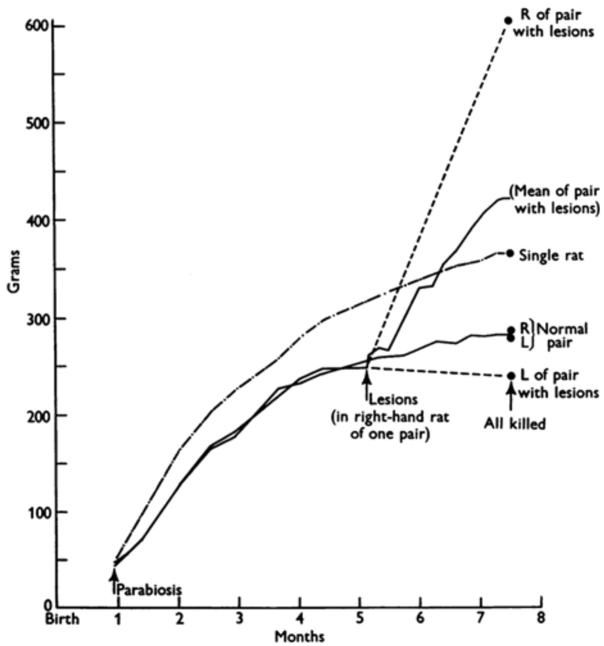


Fig. 11.3 Growth curves of parabiotic rats. When the animals were 5 month old, lesions were made in the hypothalamus of the right-hand member of the parabiotic pair. The last point in the curve corresponds to the individual body weights after death and separation of the parabiotic pairs. The *dashed lines* indicate the presumed body weight of each member of the pair based on the weight at the end of the experiment. The growth curve of a single rat is also shown for comparison. Figure reproduced with permission from Hervey, J. Physiol. 145:336–352, 1959

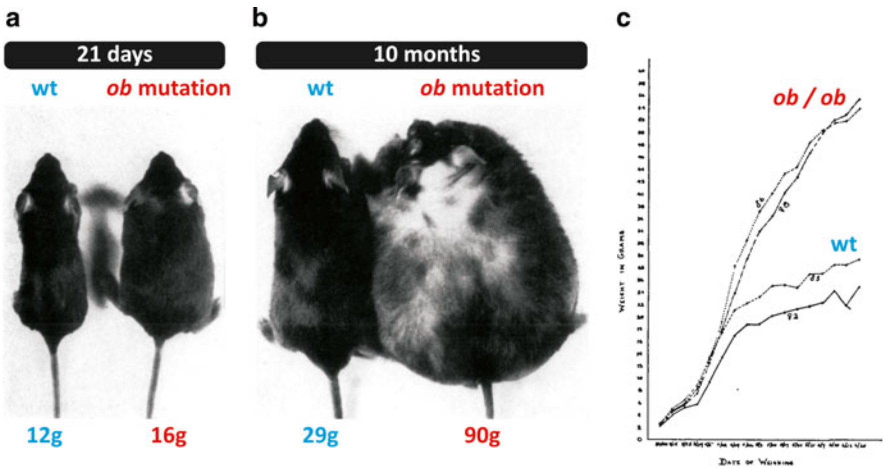


Fig. 11.4 Photographs and growth curves reproduced from the original article that described the phenotype of the animal with the spontaneous mutation in the *ob* gene. (**a**) Normal and *ob/ob* mice at 21 days of age. (**b**) Normal and *ob/ob* mice at 10 months of age. (**c**) Growth curves of two normal and two *ob/ob* mice from birth to 4 months of age. Figures reproduced with permission from Ingalls et al., J. Hered. 41:317–318, 1950

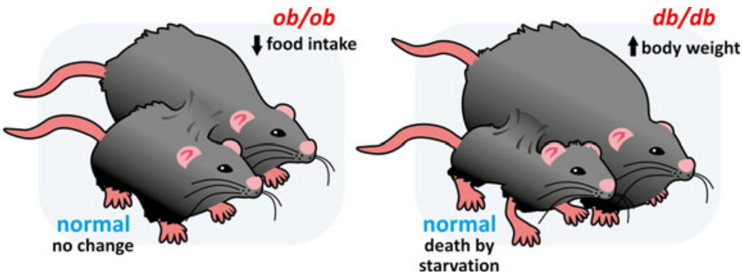


Fig. 11.5 Schematic representation of the parabiosis experiments with *ob/ob* and *db/db* mice. When an *ob/ob* mouse was connected to a normal mouse, the obese animal stopped eating in excess and lost weight, while no changes occurred in the normal mouse. When a *db/db* mouse was connected to a normal one, only the normal mouse lost weight

11.1.2 Leptin: A Hormone Indicative of Adiposity

The parabiosis experiments with the *ob/ob* and *db/db* mice described in the previous section indicated that the amount of adipose tissue accumulated in the body was regulated by the endocrine system. However, the hormone (the circulating factor) responsible for the transmission of the information of the increase in body weight to the hypothalamus remained unknown until 1994, when the product of the *ob* gene was finally discovered. More interestingly, it was found that this protein is expressed almost exclusively in the adipose tissue. This protein was named leptin (from the Greek word *leptos*, which means thin), and its discovery represented a revolution in the study of obesity both due to the expectations it raised on the pharmaceutical industry and because it revealed a complete new function for the adipose tissue, whose role changed dramatically from an inert tissue of energy storage to an endocrine organ (Box 11.1).

Immediately after the discovery of leptin, massive investments were made in the development of new treatments that envisaged the elimination of obesity by simply administrating leptin to obese people. However, as high as the expectations were the disappointments when it became clear that in humans the mutations in the leptin gene accounted for a very small number of obesity cases, and the simple administration of leptin in the remaining obesity cases did not lead to weight loss.

Despite the failure of using leptin to treat obesity, it soon became clear that the plasma levels of leptin directly correlated with the BMI and to the percentage of fat in the body, showing that the increase in the amount of adipose tissue determined the increase in plasma leptin (Fig. 11.6).

Leptin is a small protein of 167 amino acid residues forming an α-helical structure that resembles the structure of some cytokines (Fig. 11.7). Leptin effects are mediated by its binding to specific receptors expressed by neurons in the central nervous system, the inhibition of appetite being mainly due to its binding to receptors of the hypothalamic neurons (see also Sect. 11.1.5).

Box 11.1 The Adipose Tissue as an Endocrine Organ

The discovery of leptin opened the way to the identification of a series of proteins secreted by the adipose tissue, which were named adipokines (see table). These proteins act as hormones or cytokines and are mainly involved in the regulation of energy metabolism or in inflammation. This made the white adipose tissue to be recognized as a dynamic endocrine organ besides being a lipid storage tissue.

Active polypeptides secreted by the adipose tissue

Name	Molecular nature	Main features and functions
Leptin	16 kDa protein	Expressed mainly in adipocytes. Controls energy balance (see main text)
Adiponectin	30 kDa protein that forms multimeric complexes	Expressed exclusively in adipocytes. Blood levels inversely correlate to adiposity. Increases lipid catabolism and insulin sensitivity
Resistin	75 kDa protein	Expressed mainly in adipocytes. Secreted during adipogenesis. Increases insulin resistance
Visfatin	52 kDa protein	Extracellular isoform of the enzyme nicotinamide phosphoribosyltransferase of the NAD biosynthesis pathway. Stimulates insulin secretion
Apelin	55 amino acid precursor that generates several active fragments	Expressed in many cell types including adipocytes. Increases cardiac contractility and lowers blood pressure
Retinol-binding protein-4 (RBP-4)	20 kDa protein	Expressed mainly in hepatocytes and adipocytes. Transports retinol in the blood but also decreases insulin sensitivity
Tumor necrosis factor-α (TNF-α)	17 kDa protein that forms soluble trimers	Pro-inflammatory cytokine secreted mainly by macrophages but also by many other cells including adipocytes. Triggers the inflammatory response and regulates cell death, but also increases insulin resistance (see Sect. 11.3.1)
interleukin 6 (IL-6)	24 kDa protein	Produced by many cell types. Acts as a pro-inflammatory cytokine
Monocyte chemotactic protein-1 (MCP-1)	13 kDa protein	Produced by many cell types. Acts on the inflammatory process, but also impairs insulin signaling in skeletal muscle cells
Plasminogen activator inhibitor-1 (PAI-1)	47 kDa protein	Expressed in endothelium but also in other cell types such as adipocytes. Inhibits the proteases involved in the degradation of blood clots

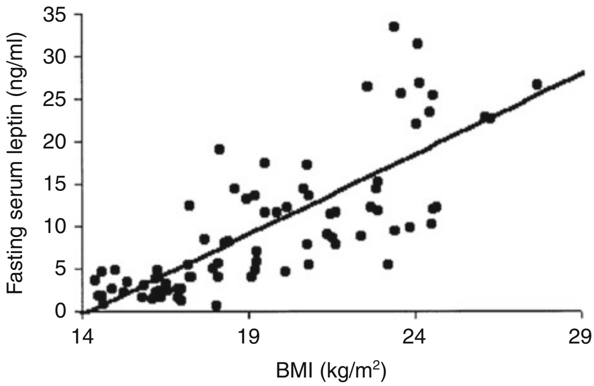


Fig. 11.6 Correlation of plasma leptin concentrations with BMI in a sample of 41 obese children (aged 6–9 years old) and the same number of nonobese children (control group), matched by age and sex (Reproduced with permission from Valle et al., Int. J. Obes. Relat. Metab. Disord. 27:13–18, 2003)

The leptin receptor is a homodimeric transmembrane protein that is constitutively associated to the enzyme Janus kinase 2 (JAK2, Box 11.2). Leptin binding promotes conformational changes in the receptor that mediate an increase in the tyrosine kinase activity of JAK2, resulting in its autophosphorylation and in the phosphorylation of different intracellular targets, leading to the activation of different signaling pathways, including the JAK/STAT3, the phosphatidylinositol-3-kinase (PI3K), and mitogen-activated protein kinase (MAPK) pathways (Fig. 11.7).

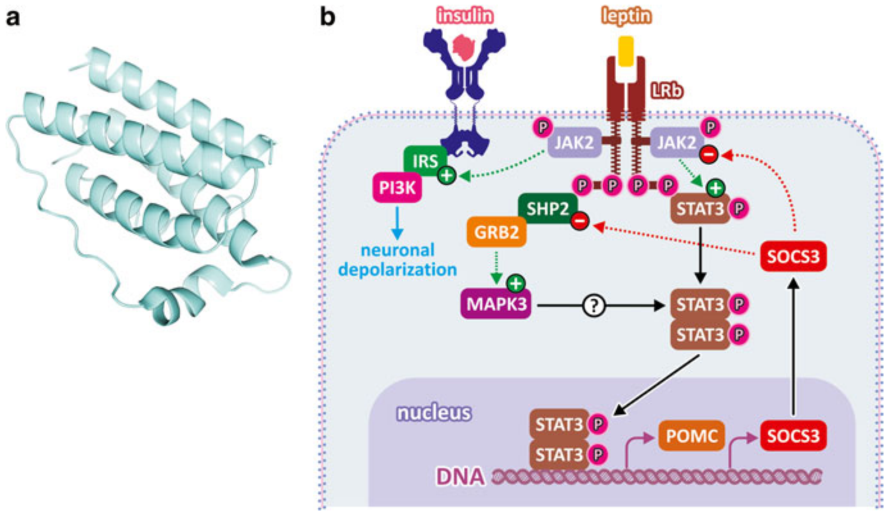


Fig. 11.7 (**a**) Leptin structure. (**b**) Leptin signaling pathway. Leptin binding to its receptors in the hypothalamus leads to the activation of JAK2 and to the recruitment of STAT3, IRS, and SHP, which become active. STAT3 migrates to the nucleus, inducing the expression of POMC and the feedback inhibitor of the pathway SOCS3. IRS mediates the activation of PI3K, which induces neuronal depolarization involved in the rapid responses independent on gene expression. Activation of MAPK pathway is mediated by SHP recruitment

JAK/STAT3 is the predominant pathway that mediates leptin effects. When STAT3 is phosphorylated by JAK2, it migrates to the nucleus, where it regulates the expression of several genes. This includes those encoding some important

Box 11.2 The Origin of the Janus Kinase Name

In the Roman mythology, Janus (in Latin, *Ianus*) is the god of the gateways, beginnings, and transitions, who keeps the door of Heaven. He is represented as having two faces looking in opposite directions (see figure with Janus representation in an old Roman coin), meaning that he can see the future and the past simultaneously. The first month of the year is named after him, as in January we look back at the last year and forward to the next. The reference to Janus in JAK's name is related to the fact that the members of this family of kinases possess two near-identical phosphate-transferring domains, one with kinase activity and the other that negatively regulates the kinase activity of the first.

Janus head represented in a Roman coin dated 225–214 BC (Reproduced from the free media repository Wikimedia Commons)

neuropeptides involved in the appetite control, such as neuropeptide Y, which has its expression inhibited, and the pro-opiomelanocortin (POMC), corticotropin-releasing hormone (CRH), and the cocaine- and amphetamine-regulated transcript (CART), which have their expression induced (see Sect. 11.1.5 for details on the role of these neuropeptides in the appetite control). STAT3 also induces the expression of feedback inhibitors of the signaling pathway, such as SOCS3 (suppressor of cytokine signaling 3) (Fig. 11.7).

The active JAK2 also recruits proteins from the family of the insulin receptor substrates (IRS), which mediate the activation of the PI3K pathway (for more details about this pathway, see the mechanism of insulin action in Sect. 8.4.2). Thus, there is a cross talk between the signaling pathways triggered by leptin and insulin at the hypothalamic level, so that the leptin action on the hypothalamus is positively modulated by insulin and vice versa. PI3K regulates the electrophysiological properties of the hypothalamic neurons, modulating the release of neurotransmitters in the synapses, which also contribute to the reduction of feeding. It is important to mention that the blood concentration of both insulin and leptin are increased in response to food ingestion. Since the hypothalamic neurons are also rich in insulin receptors, both leptin and insulin contribute to the triggering of the anorexigenic responses after feeding.

In summary, the action of leptin on the hypothalamic neurons alters the gene expression pattern in these cells and causes cell depolarization, resulting in the activation or inhibition of the secretion of different neuropeptides (see Sect. 11.1.5). It is important to mention that leptin effects can be seen as part of the long-term effects on the control of the body weight. Leptin does not promote an abrupt interruption in food ingestion, but influences the amount of food intake and its relationship with the body energy expenditure over time. There are other hormones and mediators that directly promote the postprandial satiety or trigger appetite. These mostly short-term mediators are mainly secreted by the gastrointestinal tract, as discussed in the next sections.

11.1.3 Intestinal Peptides: Triggers of Postprandial Satiety

The satiety feeling just after a meal is a result of several signals, mainly arising from the gastrointestinal tract, that act on the brain, providing information regarding the quality and the quantity of food ingested. These signals are involved in the short-term regulation of food ingestion, especially the control of the meal size.

The first experiments suggesting the role of the intestine in promoting satiety were performed using a surgical procedure previously developed by Ivan P. Pavlov in his classic experiments of the decade of the1890s, which revealed the role of the central nervous system in the regulation of gastric secretion in dogs (see Box 11.3).

Box 11.3 Pavlov and the Sham Feeding Experiments

Ivan Petrovich Pavlov was a Russian scientist whose research on the physiology of digestion led him to be awarded the Nobel Prize in Physiology or Medicine in 1904. Pavlov developed a surgical method that establishes fistulas in various organs, enabling the continuous observation of their functions. This opened a new era in the development of physiology, whose procedures until then were based essentially on vivisection methods, which allowed only an instantaneous picture of the analyzed process. The classical Pavlov's experiments were performed on sham-fed dogs, to which a gastric fistula was applied (see figure). Within a few minutes after the beginning of sham feeding, gastric juice begins to flow without ceasing for hours.

Pavlov demonstrated that when the vagus nerves were lesioned, secretion of gastric juice during sham feeding was absent, showing the reflex nature of the first phase of gastric juice secretion.

Pavlov's esophagostomy associated to the application of a gastric fistula used in the sham-feeding experiments

This procedure consists of establishing an esophagic fistula in animals, so that when they eat, the food is tasted and swallowed, but does not accumulate in the stomach and does not pass into the small intestine, which is usually referred as sham feeding (Box 11.3).

A number of experiments performed in the 1970s showed that when the animals were sham fed, satiety did not occur, revealing that the satiety feeling originates from the passage of food through the gastrointestinal tract. These experiments allowed the subsequent identification of several intestinal peptides involved in triggering satiety and whose plasma levels rapidly increase after a meal (Fig. 11.8). In this section we will comment on the secretion profile and the action of three of these peptides: cholecystokinin (CCK), glucagon-like peptide 1 (GLP-1), and peptide YY (PYY).

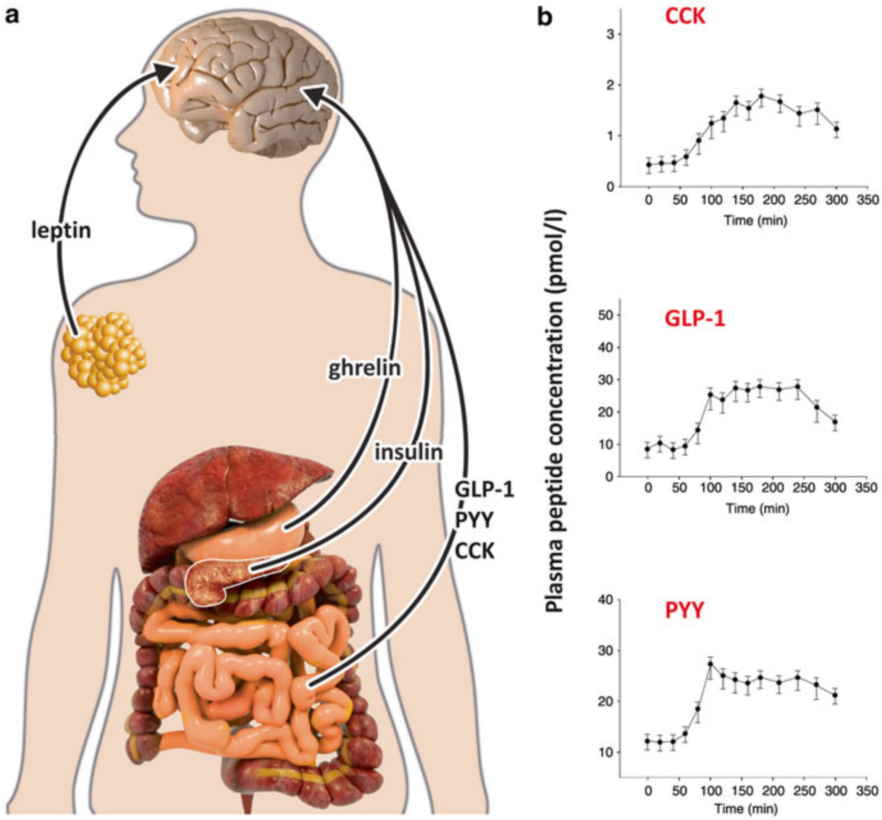


Fig. 11.8 (**a**) Sites of secretion of the peripheral factors that modify food intake and energy expenditure through direct effects on the brain: ghrelin is secreted by the stomach prior to the meals, inducing food intake (Sect. 11.1.4); CCK, GLP-1, and PYY are secreted by the intestine just after the meals, interrupting eating; leptin is secreted by the adipose tissue as a signal of adiposity (Sect. 11.1.2); and insulin is secreted by the pancreas in response to nutrient ingestion (Sect. 8.4). (**b**) Plasma concentrations of intestinal peptides in response to breakfast ingestion, which occurred 60 min after the beggining of the measurements. Data are from 12 subjects, presented as mean ± SEM. CCK, cholecystokinin; GLP-1, glucagon-like peptide-1; PYY, peptide tyrosine tyrosine (Reproduced with permission from Vidarsdottir et al., Eur. J. Endocrinol. 162:75–83, 2010)

CCK is secreted by the I cells, mainly located in the proximal duodenum, suppressing food intake and decreasing meal size. CCK was one of the first gastrointestinal peptides to be demonstrated as an important trigger of the postprandial satiety. Experiments in the 1970s using sham-fed rats, which ate continuously due to the absence of intestinal stimulation, showed that the intraperitoneal injection of CCK suppressed feeding in a dose-dependent manner (Fig. 11.9).

Long-chain fatty acids and proteins are particularly effective in inducing CCK secretion, although carbohydrate-rich meals also promote an increase in CCK plasma levels. CCK seems to act on the brain through a paracrine stimulation of the vagal afferent nerve fibers, whose terminals are proximal of the intestinal I cells, suggesting that the CCK plasma levels are not the best indicator of its potential action.

The L cells of the distal intestine secrete both GLP-1 and PYY, although the regulation of the release of each of these peptides differs. PYY is a 34 amino acid residue peptide named after its tyrosine content. PYY secretion is triggered by the direct contact of the L cells with the nutrients, as well as in response to duodenal lipids. This latter stimulus is probably mediated by CCK. PYY binds to Y receptors in the arcuate nucleus neurons inhibiting NPY release and thus causing anorexigenic effects (see Sect. 11.1.5). GLP-1 is a peptide derived from the pro-glucagon precursor and its secretion is stimulated especially after a carbohydrate-rich meal, although fats are also potent secretagogues. A body of evidence suggests that, as CCK, GLP-1 reduces food intake and promotes satiety by acting on vagal afferent nerve terminals close to the L cells. The satiety promoted by the increase in secretion of both GLP-1 and PYY seems to be the main reason for the success of bariatric surgeries, currently considered to be the most effective surgical treatment for morbid obesity (see Box 11.4).

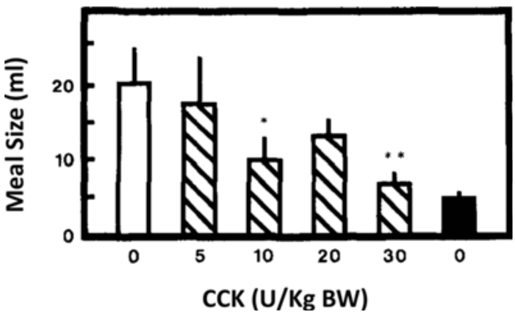
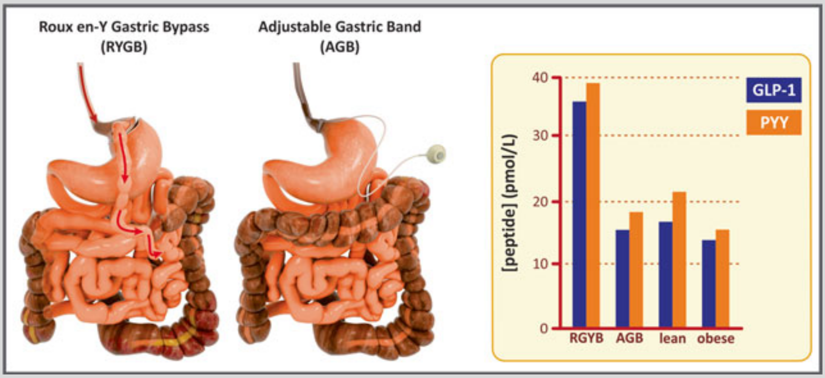


Fig. 11.9 Result of an experiment in which sham intake of a liquid diet was quantified in rats ($n=8$) upon intraperitoneal injection of CCK in the concentrations indicated in the figure (*hatched bars*), with the "0" (*white bar*) corresponding to saline injection. Animals in which the gastric fistula was maintained closed were used as control (*black bar*). The animals were submitted to food deprivation for a period of 3 h after which the ingested food volume was quantified until the animal stops eating. *Vertical lines* are the standard errors with * corresponding to $p=0.05$ and ** corresponding to $p<0.01$ for CCK vs. saline. (Copyright © 1978 by the American Psychological Association. Reproduced with permission from Kraly et al., J. Comp. Physiol. Psychol. 92:697–707, 1978)

Box 11.4 Bariatric Surgery

Bariatric surgery is a weight loss procedure based on the removal of a portion of the stomach (gastrectomy), the reduction of its size through the introduction of a medical device (gastric banding), or the creation of a small stomach pouch which is connected to the intestine skipping the duodenum (gastric bypass). It has become the treatment of choice for individuals with severe obesity, being recommended for people with BMI > 40 or BMI > 35 when serious coexisting medical conditions occur. Bariatric surgery may be classified as purely restrictive (as in the case of the adjustable gastric band) to mostly malabsorptive (as occurs in the biliopancreatic diversion), which usually results in clinical complications related to malabsorption of macronutrients. The surgical approaches predominantly used today are the Roux-en-Y gastric bypass and the adjustable gastric band (see figure). The Roux-en-Y gastric bypass produces better results in terms of weight loss, probably because it is associated to an increase of the plasma concentrations of the satiety peptides PPY and GLP-1 (see figure). More recently, a variation of this procedure was proposed, in which a gastric fundus resection is combined to the bypass. This promotes a more consistent decrease in ghrelin secretion together with an increase in PPY and GLP-1 release, which makes the response even more effective.



Schematic representation of the predominantly used bariatric surgery: the Roux-en-Y gastric bypass (*left*) and the adjustable gastric band (*right*) and changes in plasma concentrations of GLP-1 and PYY 1 h after breakfast in lean ($n = 15$) or obese ($n = 12$) subjects or patients submitted to RYGB ($n = 6$) or GB ($n = 6$) (Based on data from the study described in le-Roux et al. Ann. Surg. 243:108–114, 2006)

11.1.4 Ghrelin: The Main Orexigenic Hormone

Ghrelin was discovered in 1999 as an endogenous ligand of the *g*rowth *h*ormone secretagogue *r*eceptor, from which its name is derived. Indeed, one of the actions of ghrelin is to stimulate growth hormone release, but its role in the control of appetite seems to be independent of this previously identified function.

The active form of ghrelin is an acylated peptide of 28 amino acid residues, secreted mainly by the stomach (Fig. 11.10a). Ghrelin concentration in blood increases during fasting and reaches its lowest level just after a meal, indicating a physiological role for this hormone in meal initiation (Fig. 11.10b). Measurements of plasma ghrelin levels in gastrectomized patients confirmed that the stomach is a major source of circulating ghrelin in humans (Fig. 11.10b). Indeed, the fact that ghrelin is an important signal to start feeding may explain the decrease in feeding behavior after gastrectomy (see Box 11.4).

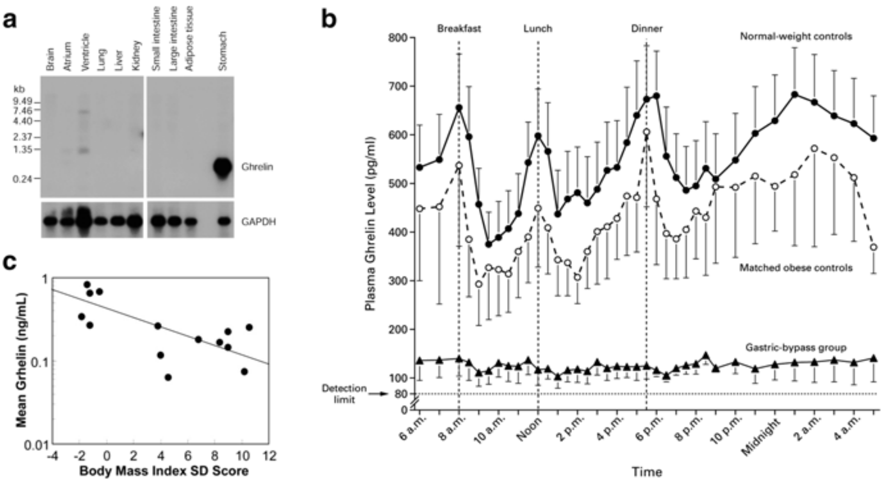


Fig. 11.10 (**a**) Analysis of the expression of ghrelin mRNA in different rat tissues. The figure shows the result of a Northern blotting, a technique in which the mRNA for a specific gene is radioactively labeled and detected by autoradiography (Reproduced with permission from Kojima et al., Nature 402:656–660, 1999). (**b**) Mean 24-h plasma ghrelin concentration during a day in 10 normal-weight human subjects and 5 obese subjects who underwent a proximal Roux-en-Y gastric bypass and 5 obese subjects who had recently lost weight by dieting and were matched to the subjects in the gastric-bypass group according to final body mass index, age, and sex. The *dashed lines* indicate breakfast, lunch, and dinner (Reproduced with permission from Cummings et al. N. Engl. J. Med. 346:1623–1630, 2002). (**c**) Relationship between the mean 24-h plasma ghrelin concentration and BMI in five lean and nine obese girls (Reproduced with permission from Foster et al. Pediatr. Res. 62:731–734, 2007)

Many studies have shown that ghrelin administration into the brain ventricle in rodents induces food intake through the increase of the expression of hypothalamic neuropeptide Y, an opposite effect of that observed for leptin. In agreement, the relationship of blood ghrelin concentrations and BMI is the opposite of that observed for leptin: plasma ghrelin concentrations inversely correlate with BMI (Fig. 11.10c).

Ghrelin receptor, the growth hormone secretagogue receptor (GHSR), belongs to the class of G protein-coupled receptors (for more details on G protein-coupled receptors and their different signaling pathways, see the description of adrenaline receptors in Sect. 10.5.1). GHSR may be coupled to different types of G protein, including type G_q, which mediates changes in ion currents in the neurons through the activation of phosphatidylinositol-specific phospholipase C. Phospholipase C hydrolyzes the phosphatidylinositol 4,5-bisphosphate (PIP_2) in inositol 1,4,5-triphosphate (IP_3) and diacylglycerol (DAG), which induce Ca^{2+} release from ER and the activation of protein kinase C (PKC), leading to the inhibition of K^+ channels and causing neuronal depolarization (Fig. 11.11). Additionally, GHSR, through G proteins type G_q or G_i, mediates the activation of the MAPK or PI3K pathways, leading to changes in neuronal gene expression, which includes the induction of expression of the orexigenic neuropeptide Y (NPY, see next section) (Fig. 11.11).

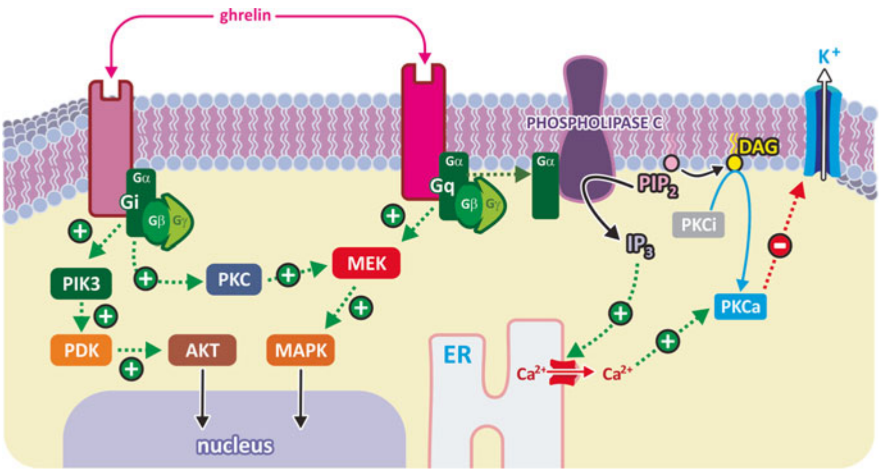


Fig. 11.11 The binding of ghrelin to GHSR results in the release of GDP and binding of GTP to the G protein α-subunit coupled to the receptor. Neuronal depolarization is triggered by ghrelin binding to GHSR coupled to G protein-type G_q, which activates PLC, generating IP_3 and DAG, resulting in an increase in the intracellular Ca^{2+} concentration and the activation of PKC, which inhibits the K^+ channels. Changes in the neuronal gene expression are achieved through ghrelin binding to GHSR coupled to G protein-type G_q or G_i, which activates MAPK or PI3K pathways

11.1.5 The Arcuate Nucleus and the Melanocortin System

The main target of the peripheral mediators in the hypothalamus is the arcuate nucleus (ARC). ARC is a region of the medial-basal hypothalamus adjacent to the third ventricle (see Fig. 11.2). The blood–brain barrier in this region seems to be more permeable, facilitating the contact of the ARC neurons with humoral and metabolic factors coming from the peripheral circulation, including the anorexigenic and the orexigenic factors discussed in the previous sections.

Two subsets of ARC neurons play a central role in the regulation of energy balance: the NPY/AgRP neurons and the POMC neurons (Fig. 11.12). It is important to mention that the name of these neuron populations is derived from the name of the neuropeptides secreted by them, which, in turn, were named as a reference to an initial function described for them, usually unrelated to their role in the energy balance control. Thus, although we will point out the origin of these peptides'

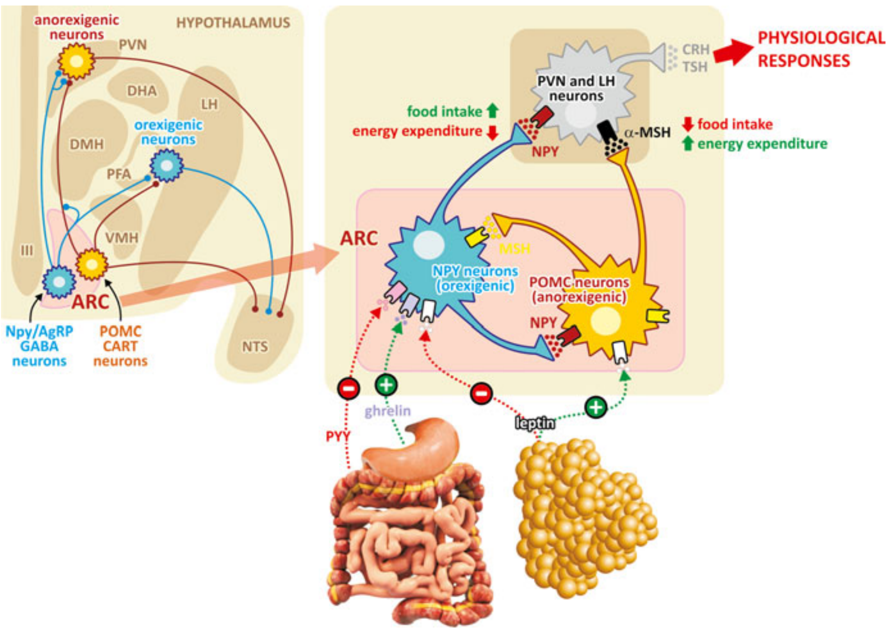


Fig. 11.12 Schematic representation of the subpopulation of the ARC neurons: the NPY/AgRP and the POMC neurons. PYY and leptin inhibit NPY/AgRP neurons, decreasing appetite by the reduction of NPY release. Leptin activates POMC neurons, leading to the release of POMC-derived peptides, such as α-MSH, which bind to melanocortin receptors (such as MC4R) in other hypothalamic areas (mainly in the PVN and LH), promoting satiety. Ghrelin stimulates NPY/AgRP neurons, inducing the expression and secretion of NPY and AgRP, which are antagonists of melanocortin receptors, triggering hunger and decreasing energy expenditure

nomenclature, the names themselves will not be useful for the understanding of their functions in the energy balance control.

The NPY/AgRP neurons express the neuropeptide Y (NPY), a neuropeptide with strong orexigenic properties, which stimulates food ingestion. These neurons also express the Agouti-related protein (AgRP), a protein related to fur pigmentation in rodents that when mutated causes obesity in mice.

The POMC neurons express pro-opiomelanocortin (POMC), whose cleavage originates several endocrine- and neuroendocrine-active peptides, including the anorexigenic peptides α- and β-melanocyte-stimulating hormones (α-MSH and β-MSH) and the adrenocorticotropic hormone (ACTH). Among these peptides, α-MSH and β-MSH are directly related to the increase in energy expenditure in the organism, as it will be detailed in Sect. 11.2.

Food ingestion behavior is established by a concerted action of the anorexigenic and orexigenic hormones on these two neuron populations. During fasting, ghrelin is secreted by the stomach cells leading to an increase in its blood level. In ARC, ghrelin binds to NPY/AgRP neurons, stimulating the synthesis and secretion of NPY, which results in an increase in appetite (Fig. 11.12). During feeding, gastrointestinal peptides, such as PYY, are released from the intestine cells. PYY also acts on NPY/AgRP neurons, but its binding to these neurons inhibits NPY release, diminishing appetite. As a response to the increase of adiposity, the adipocytes secrete leptin, which binds to both NPY/AgRP and POMC neurons. The effects of leptin binding to each of these neurons are antagonic: it inhibits the NPY/AgRP neurons and stimulates POMC neurons, stopping food ingestion by a simultaneous decrease in the NPY-induced appetite and increase in satiety promoted by anorexigenic POMC-derived peptides (Fig. 11.12).

The next question to be posed is how the ghrelin and leptin signals are deciphered by the hypothalamus producing their respective physiological responses: the changes in the feeding behavior and the energy expenditure rate in the body. The answer resides in the fact that both NPY/AgRP and POMC neurons are also connected to neurons in other hypothalamic areas (mainly in the PVN and LH; Fig. 11.12, see also Fig. 11.2), which mediate the recognition of the feeding status to a systemic response in the organism. The PVN and LH neurons express the melanocortin receptors (MCR1–MCR5), whose agonists are the POMC-derived peptides and the antagonist is NPY. Upon stimulation by POMC-derived peptides, PVN and LH neurons secrete the corticotropin-releasing hormone (CRH) and thyrotropin-releasing hormone (TRH), which mediate anorexigenic, thermogenic responses, and even physical activity (behavioral) responses.

In summary, the orexigenic and anorexigenic signals (such as ghrelin and leptin) bind to the ARC neurons leading to the secretion of POMC-derived peptides or NPY. These peptides act on the PVN and LH neurons, stimulating or inhibiting the release of CRH and TRH, which in turn regulate the anorexigenic and thermogenic responses in the organism. The integration of these events and players is known as the melanocortin system, which is considered the most efficient model to explain the neuronal control of the long-term energy balance in the organism.

11.2 Control of Energy Expenditure

Energy metabolism in animals can be resumed as the chemical processes through which the energy obtained from food—energy intake—is converted to work and heat—energy expenditure. The total energy expenditure in an organism can be subdivided for didactic purposes in three components: (a) the basal metabolic rate, which corresponds to the energy involved in all metabolic reactions required for the cellular functions; (b) the adaptive thermogenesis, which consists in the production of heat in response to cold or diet; and (c) the physical activity, both the spontaneous, such as that necessary to maintain posture, and the voluntary, including exercise in sports, leisure, and other activities (Fig. 11.13).

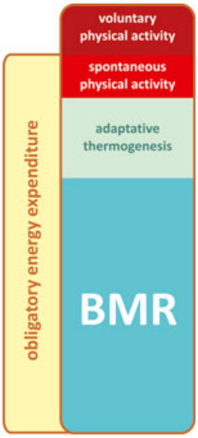


Fig. 11.13 The three components of energy expenditure: the basal metabolic rate (BMR), represented in *blue*, corresponds to energy involved in the metabolic reactions necessary to maintain cellular functions; the adaptive thermogenesis, represented in *green*, corresponds to the regulated energy release in the form of heat as a response to changes in ambient temperature or diet; and physical activity, represented in *red*, corresponds to the energy expenditure during voluntary or involuntary physical activities

11.2.1 Adaptive Thermogenesis

The adaptive thermogenesis is one of the components of energy expenditure and can be defined as the production of heat due to a regulated increase in the metabolic rate. It is controlled by the brain, both through the stimulation of the sympathetic system and through the hypothalamus–pituitary–thyroid axis, as a response to triggering signals including cold exposure and food intake (Fig. 11.14).

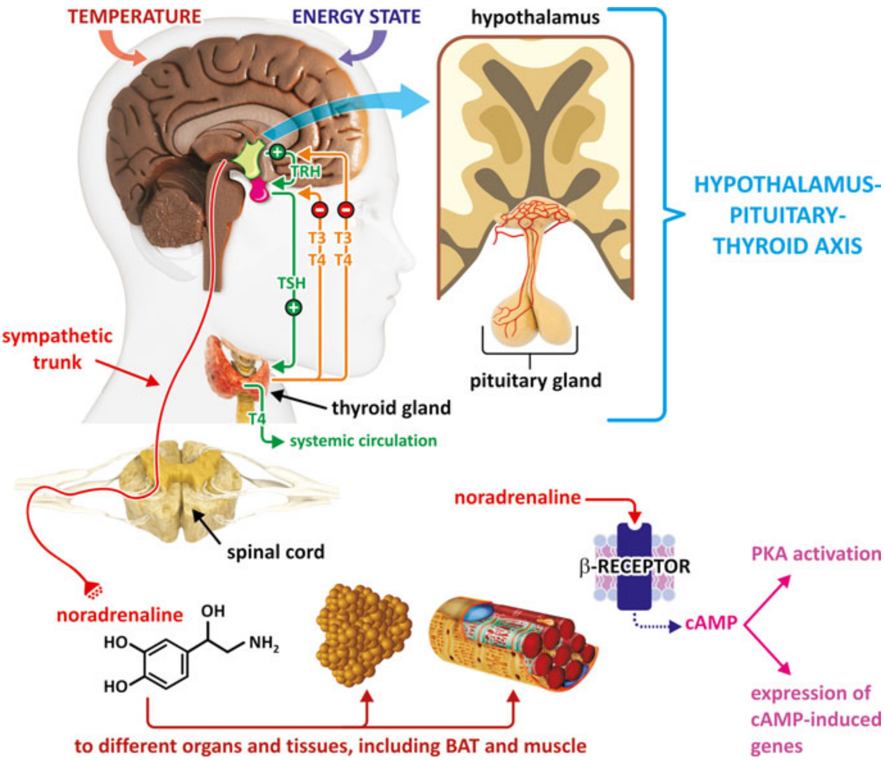


Fig. 11.14 Changes in the ambient temperature and in diet are sensed by the brain resulting in noradrenaline release by the sympathetic nerves and in the activation of hypothalamus–pituitary–thyroid axis. Noradrenaline acts on brown adipose tissue (BAT) and muscles through its binding to adrenergic receptors, which leads to an increase in intracellular AMPc concentration and the consequent modulation of the activities of some PKA-regulated enzymes as well as the induction of the expression of the AMPc-induced genes. Thyroid hormones (T3 and T4) play a major role in controlling energy expenditure (see Sect. 11.2.2). They are released by the thyroid gland as a response to the thyroid-stimulating hormone (TSH) produced by pituitary, whose secretion is stimulated by the hypothalamic thyrotropin-releasing hormone (TRH). T3 and T4 exert a negative feedback control over the hypothalamus and pituitary

11.2.1.1 Cold-Induced Thermogenesis

Shivering is one of the most primitive responses induced by exposure to cold, which is especially important to the adaptive thermogenesis in adult humans and large mammals. However, in human newborns and other small mammals, the most important cold-induced adaptive thermogenesis involves the release of noradrenaline by the sympathetic nerve terminals, particularly within the brown adipose tissue (BAT).

BAT thermogenic capacity is mainly sustained by the high activity of the uncoupling protein 1 (UCP1 or thermogenin) in this tissue (see Sect. 6.2.5). Binding of noradrenaline to BAT adrenergic receptors leads to an increase in the intracellular cAMP concentration, which in turn mediates the modulation of enzymatic activities, as well as the expression of the cAMP-induced genes (Fig. 11.14), including the gene for UCP1 and those that codify the deiodinase 2 (D2), the enzyme involved in the intracellular production of the active form of the thyroid hormone, T3 (see Sect. 11.2.2). A synergic effect between T3-dependent and cAMP-dependent actions, which includes the increase in fatty acid oxidation associated with mitochondria uncoupling, results in energy dissipation in the form of heat.

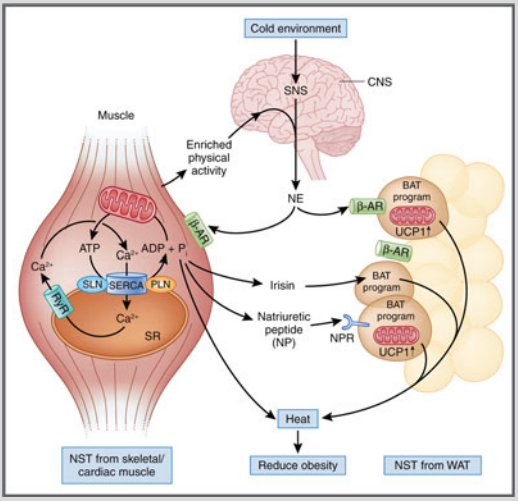
For many years, the role of BAT in the thermogenic response in humans has been considered to be relevant only in newborns due to the insignificant amounts of brown fat found in adults. However, in the last few years, a number of new findings revealed that in addition to the classical BAT, there is an inducible thermogenic adipose tissue, also referred to as beige adipocytes, which are interspersed in white fat depots in adult humans. The origin of the beige adipocytes is not completely clear, but it seems that they have a complete different origin than that of the classical brown fat cells. Conversely, strong evidence supports a common origin for classical BAT and skeletal muscle cells. Interestingly, muscle cells recently also appear as potential players in the cold- and diet-induced thermogenic responses, with a mechanism involving a controlled cycling of calcium (see Box 11.5).

Box 11.5

Exposure to cold induces norepinephrine (NE) release by the sympathetic nerve terminals within the skeletal muscle. NE binding to β-adrenergic receptors in muscle cells mediates the activation of the sarcoplasmic reticulum calcium ATPase (SERCA). Two proteins are known to associate to SERCA in muscle, phospholamban and a recently identified protein named sarcolipin. Sarcolipin uncouples SERCA-mediated ATP hydrolysis from Ca^{2+} pumping, resulting in the dissipation of energy in the form of heat. Simultaneously, NE induces the "browning" of the adipose tissue in a combined action with at least two other muscle-derived peptides: irisin and natriuretic peptide, which are secreted by skeletal and cardiac muscles, respectively. One of the main responses that lead to the "browning" of the adipocytes is the expression of UCP1 in the mitochondria, which induces heat production (see Sect. 6.2.5).

(continued)

Box 11.5 (continued)



Schematic representation of the thermogenic responses in the muscle and in the adipose tissue. *CSN* central nervous system; *SNS* sympathetic nervous system; *NE* norepinephrine; *β-AR* β-adrenergic receptor; *SERCA* sarcoplasmic reticulum Ca^{2+}-ATPase; *PLN* phospholamban; *SLN* sarcolipin; *RyR* ryanodine receptor; *SR* sarcoplasmic reticulum; *BAT* brown adipose tissue. Figure reproduced by permission from Macmillan Publishers Ltd. from Kozac LP & Young ME. Nat. Med. 18:1458–1459, 2012

11.2.1.2 Diet-Induced Thermogenesis

Adaptive thermogenesis also occurs in response to diet. The diet-induced thermogenesis can be defined as the increase in energy expenditure above the basal fasting level as a response to food intake. This phenomenon is illustrated in Fig. 11.15a, which represents the mean pattern of the diet-induced thermogenesis throughout a day. Indeed, feeding increases the metabolic rate by 25–40 %, while starvation reduces it to up to 40 %, and these compensatory changes in metabolism may be the explanation for the low efficacy of treatments for obesity. This can be exemplified by a study in which the energy expenditure was measured in obese and nonobese volunteers submitted to overfeeding or underfeeding diets that resulted in controlled gain or loss of weight, respectively. The results of this study, shown in Fig. 11.15b, revealed that a 10 % increase or 10 % decrease in body weight was associated to compensatory changes in energy expenditure in both the obese and the nonobese groups of individuals.

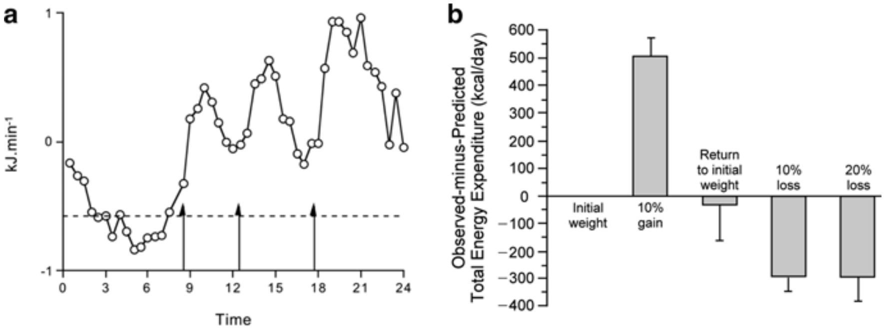


Fig. 11.15 (**a**) Mean pattern of diet-induced thermogenesis measured throughout the day in 37 subjects. The *dashed line* indicates the level of basal metabolic rate and the *arrows* indicate the time of the meals (Reproduced from Westerterp Nutr. Metab. 1:5, 2004). (**b**) Changes in the 24-h energy expenditure of 41 subjects subjected to controlled diets that resulted in 10 % weight gain or 10 % or 20 % weight loss, as well as when they returned to their original weights (Reproduced with permission from Leibel et al., N. Engl. J. Med. 332:621–628, 1995)

The mechanisms through which food intake affects the metabolic rate are not completely clear, but they seem to involve the "browning" of the adipose tissue (see previous topic) and the melanocortin system described in Sect. 11.1.5.

11.2.2 *Role of Thyroid Hormones*

The thyroid hormones thyroxine (T4) and triiodothyronine (T3) are iodinated hormones produced in the thyroid gland that play a major role in the control of energy expenditure by mediating the increase in the metabolic rate. This can be clearly illustrated by the fact that patients with hyperthyroidism show up to a 50 % increase in the total body energy expenditure, while in severe hypothyroidism it can fall by as much as 50 %.

The thyroid gland is a butterfly-shaped endocrine organ composed of two lobes, located on the anterior side of the neck (Fig. 11.16a). The name thyroid comes from the Greek word *thyreos*, which means shield, in a reference of its position around the larynx and trachea. Histological observation of the thyroid shows spherical follicles formed by a single layer of polarized epithelial follicular cells (Fig. 11.16b). The basolateral membrane of the follicular cells is in contact with the bloodstream from where iodide is uptaken through a sodium/iodide co-transporter (NIS, from Na^+/I^- symporter) (Fig. 11.16c). This mechanism makes the iodide concentration inside the thyroid to be 20- to 50-fold higher than in the blood. The follicular cells surround a region called follicular lumen, which is filled with a colloidal substance composed mainly by a large glycoprotein named thyroglobulin. Around the follicles, the parafollicular cells form the thyroid parenchyma, which produce the hormone calcitonin, involved in calcium homeostasis.

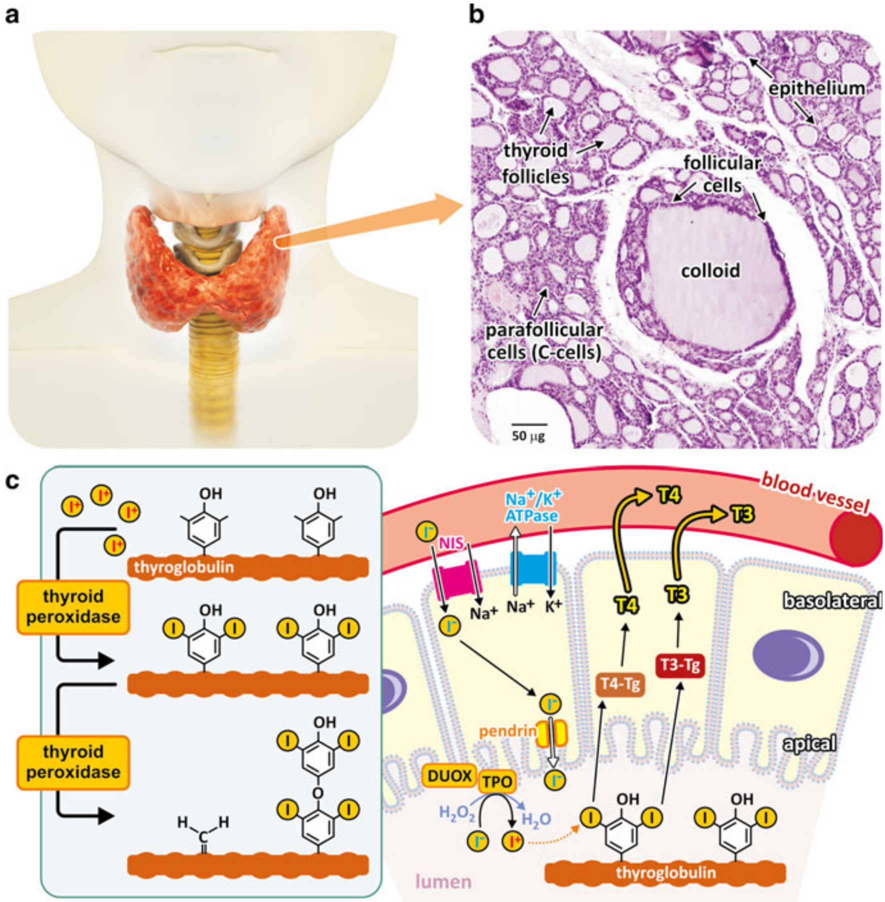


Fig. 11.16 (**a**) Anatomy of the thyroid gland. (**b**) Histological image of thyroid follicles showing the follicular cells, the colloid, and the parafollicular cells. (**c**) Iodine organification and the synthesis of thyroid hormones. The follicular cells uptake iodide from the blood through the transporter NIS (Na^+/I^- symporter) located on their basolateral membranes. The activity of the Na^+/K^+-ATPase on the follicular cell membrane maintains a low intracellular concentration of Na^+. At the apical membrane, the enzyme thyroperoxidase (TPO) oxidizes the iodide and incorporates the iodine to tyrosine residues of thyroglobulin in the lumen of the follicles. Iodinated tyrosines are conjugated forming T3 or T4 (*inset*)

The first step of thyroid hormone synthesis is called the "organification" of iodine, which consists in the iodide oxidation followed by its incorporation to tyrosine residues of the thyroglobulin (Fig. 11.16c). Thyroperoxidase (TPO), an enzyme located on the apical membrane of the follicular cells, catalyzes iodide oxidation using hydrogen peroxide as the oxidizing agent and the subsequent iodination of thyroglobulin, generating either a mono-iodinated tyrosine (MIT) or di-iodinated tyrosine (DIT). The next step in the synthesis of thyroid hormones is also catalyzed by TPO and consists of the coupling of two neighboring iodotyrosyl residues through the formation of an ether bond between the iodophenol part of a donor iodotyrosyl and the hydroxyl group of the acceptor iodotyrosyl residue (Fig. 11.16c). The cleavage of the iodophenol group of the tyrosyl donor forms an alanine side chain that remains in the thyroglobulin polypeptide chain as dehydroalanine. The coupling of two DIT generates T4, whereas when a DIT and a MIT are coupled, the product is T3.

The secretion of the thyroid hormones depends on the endocytosis of the iodinated thyroglobulin from the colloid, which is stimulated by the thyroid-stimulating hormone (TSH) released from the pituitary gland. Thyroglobulin is then digested by lysosomal proteases, and the thyroid hormones are released in the bloodstream, where they circulate bound to specific binding proteins, mainly the thyroxine-binding globulin (TBG) and transthyretin (formerly known as thyroxine-binding prealbumin), but also by albumin.

After transport into the cells, the thyroid hormones bind to nuclear receptors (THR) that belong to the large superfamily of the steroid receptors (Fig. 11.17). The affinity of T3 for THR is about 100-fold higher than that of T4. THR acts as a hormone-activated transcription factor that regulates gene expression through binding

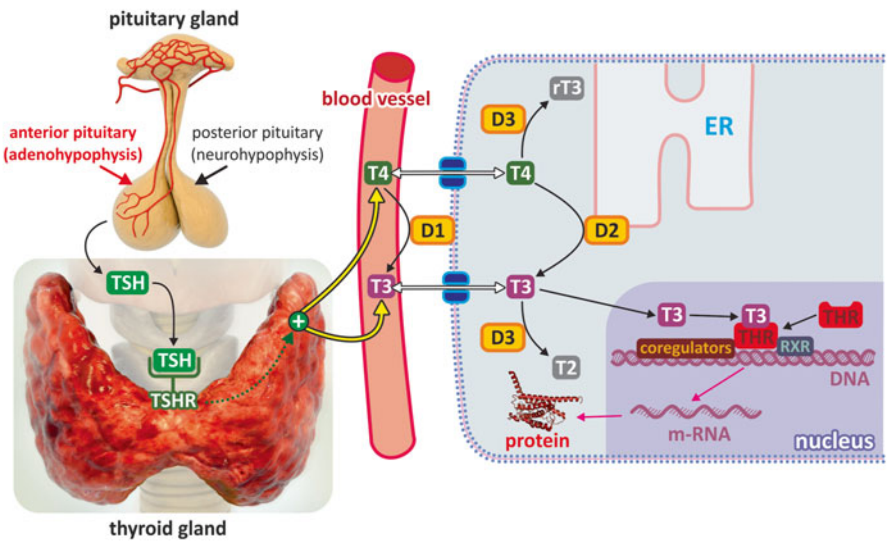


Fig. 11.17 Mechanism of action of thyroid hormones. The pituitary gland secretes the thyroid-stimulating hormone (TSH), which binds to the TSH receptor (TSHR) in the thyroid gland, stimulating the release of T4 (in higher amounts) and T3. Circulating T4 can be converted into T3 on the surface of some cells, especially liver and kidney cells, in a reaction catalyzed by the type 1 deiodinase (D1). T3 and T4 are transported into the cell. At the membrane of ER, T4 is converted to T3 through the action of the type 2 deiodinase (D2). Both T3 and T4 can also be inactivated by type 3 deiodinase (D3), which converts T4 to the inactive reverse T3 (rT3) or T3 to the inactive diiodothyronine (T2). T3 binds to the thyroid hormone receptors (THR) and the complex regulates the expression of specific genes by binding to DNA either as monomers, as homodimers, or as heterodimers with the retinoid X receptor (RXR)

to specific hormone-responsive elements in DNA (Fig. 11.17). THR can bind to DNA either as monomers, as homodimers, or as heterodimers with the retinoid X receptor (RXR), a nuclear receptor that binds 9-cis retinoic acid. The heterodimer seems to be the major functional form of the receptor. Additionally, in the absence of the hormone, the receptors function as transcription inhibitors, repressing the expression of some genes.

It is important to bear in mind that although T3 is more biologically active than T4 due to its higher affinity to THR, the major coupling reaction occurring inside the thyroid is the one that generates T4 (it is estimated that the thyroid gland secretes about 80 μg T4 and only 5 μg T3 each day). Thus, a critical step for the thyroid hormones action is the conversion of T4 into T3, which occurs mainly in the peripheral tissues. This reaction is catalyzed by the deiodinases, enzymes that remove one iodine atom from the outer ring of T4. There are three isoforms of deiodinases (Fig. 11.17). Type 1 deiodinase (D1) is expressed on the outer face of the plasma membrane of liver and kidney cells, being responsible for the production of T3 in the serum. Type 2 deiodinase (D2) is an intracellular isoform of the enzyme, expressed on the membrane of the endoplasmic reticulum, mainly in cardiac and skeletal muscles, adipose tissue, the central nervous system, and thyroid and pituitary glands. D2 is responsible for the control of cytoplasmic levels of T3. Type 3 deiodinase (D3) inactivates the thyroid hormones by catalyzing the removal of an iodine atom from the inner ring, which converts T4 to the inactive reverse T3 or T3 to inactive T2.

Thyroid hormones regulate a broad range of physiological processes including growth, development, and energy metabolism. The effects of thyroid hormones on energy metabolism can be clearly recognized in cases of hypo- or hyperthyroidism. Almost all patients with hyperthyroidism exhibit weight loss even under a high food intake diet, whereas weight gain is a very usual condition of hypothyroidism patients. This happens because the general effect of the thyroid hormones is to increase the metabolic rate by simultaneously activating, directly or indirectly, the metabolic pathways that consume and produce ATP. In this context, thyroid hormones are also critical for thermogenesis since the heat that is automatically released from the metabolic reactions is consequently increased.

The regulation of the metabolic rate by thyroid hormones occurs through different mechanisms depending on the tissue (Fig. 11.18). In muscle, their action includes the upregulation of the expression and the activity of Na^+/K^+-ATPase and sarcoplasmic reticulum Ca^{2+}-ATPase, increasing ATP consumption by these enzymes (see Sect. 10.3). Consequently, the cellular respiratory activity is increased to maintain the ATP levels. In BAT, thyroid hormones enhance noradrenaline signaling pathway as well as the expression of UCP1, sustaining the thermogenic effect mediated by the sympathetic nervous system (see Sect. 11.2.1).

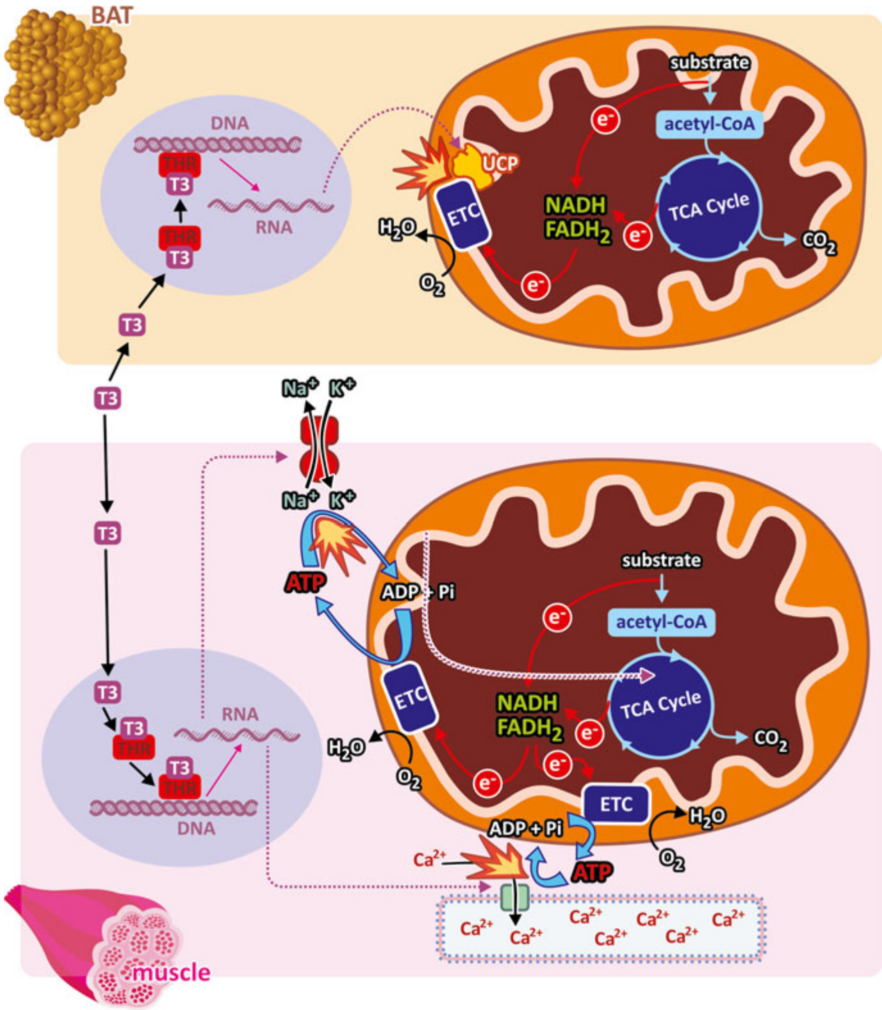


Fig. 11.18 Main metabolic effects of thyroid hormones in the peripheral tissues. Thyroid hormones induce the expression of UCP1 in BAT, increasing cellular respiratory activity, and of Na^+/K^+-ATPase and Ca^{2+}-ATPase in muscle, increasing ATP consumption by these enzymes. These effects accelerate the metabolic rate and lead to thermogenesis. The *dashed arrows* indicate the enzymes whose expression is induced by the thyroid hormones and the fire represents the thermogenic effect

Besides these actions on the peripheral tissues, it is now evident that the metabolic effects of the thyroid hormones are also mediated by their action on the central nervous system, specifically on hypothalamic areas such as ARC, VMH, and PVH (Fig. 11.19). In ARC, T3 upregulates the expression of the neuropeptides AgRP and NPY and downregulates the expression of POMC, leading to hyperphagia (see Sect. 11.1.5). Simultaneously, T3 inhibits AMPK in VMH, which activates the sympathetic nervous system leading to the enhancement of BAT thermogenic pro-

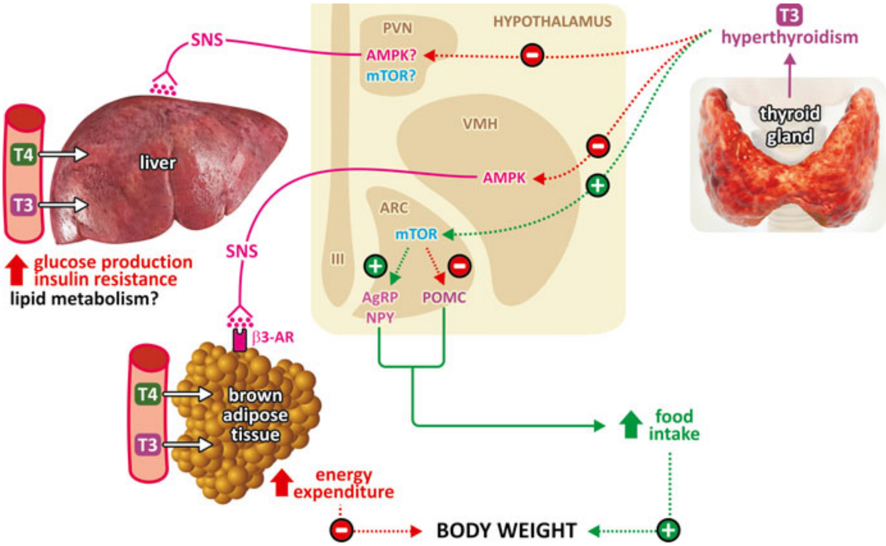


Fig. 11.19 Central actions of thyroid hormones. In ARC, T3 regulates feeding through mammalian target of rapamycin (mTOR), which upregulates the expression of AgRP and NPY and downregulates the expression of POMC, increasing food intake. In VMH, T3 inhibits AMPK, activating the sympathetic nervous system and the thermogenic program in BAT. Additionally, T3 action on PVH is probably involved in the control of hepatic glucose homeostasis

gram (see Sect. 11.2.1). Thus, these combined effects of thyroid hormones on hypothalamic regions promote an increase both in food intake and energy expenditure. Additionally, it is also evident that the central action of thyroid hormones also controls glucose metabolism in different tissues, although the mechanism through which this occurs are still unknown.

11.3 Obesity and the Metabolic Syndrome

Obesity is caused by a massive accumulation of adipose tissue, which is primarily a result of an imbalance between energy intake and energy expenditure. The increase in adipose mass is strongly associated to the development of insulin resistance and type 2 diabetes, which together with hyperlipidemia, glucose intolerance, and hypertension characterize a clinical entity sometimes referred to as metabolic syndrome.

A crucial clue for the understanding of the metabolic syndrome was the discovery that obesity itself causes an inflammatory state in the metabolic tissues, which in turn is tightly linked to the development of insulin resistance. In this section, we will discuss this metabolic-triggered inflammation, which has been recently termed metaflammation, a chronic, low-grade inflammatory response that seems to be initiated by the excess of nutrients.

11.3.1 Chronic Inflammation and Insulin Resistance in Obesity

Adipose tissue occupies a central position in the development of the obesity-induced inflammation. The first observation that clearly linked obesity and chronic inflammation was that the pro-inflammatory cytokine tumor necrosis factor-α (TNF) is overexpressed and secreted in higher levels by adipocytes of obese individuals (Fig. 11.20a). After this first discovery, it became clear that besides TNF, several other cytokines and inflammatory mediators were produced in high levels by adipose and also by other metabolic tissues from obese individuals, generating a chronic inflammatory state. Additionally, immune cells such as macrophages are recruited to and infiltrate these inflamed tissues, amplifying the inflammatory response.

The connection between the chronic inflammatory state in obesity and the development of insulin resistance became apparent from the discovery that the signaling pathway triggered by TNF (and by other overexpressed cytokines) blocks insulin action downstream of the activation of its receptor (Fig. 11.20b). In summary, what occurs is the following. In response to the inflammatory signals, intracellular kinases, mainly JNK (c-jun N-terminal kinase) and IKK-β (inhibitor of nuclear factor-κB (NF-κB) kinase-β), are activated. These kinases have as one of their substrates IRS (the insulin receptor substrate), which is phosphorylated by them in Ser residues instead of the Tyr residues that are phosphorylated in response to the insulin signaling pathway (see details of the insulin signaling pathway in Sect. 8.4.2).

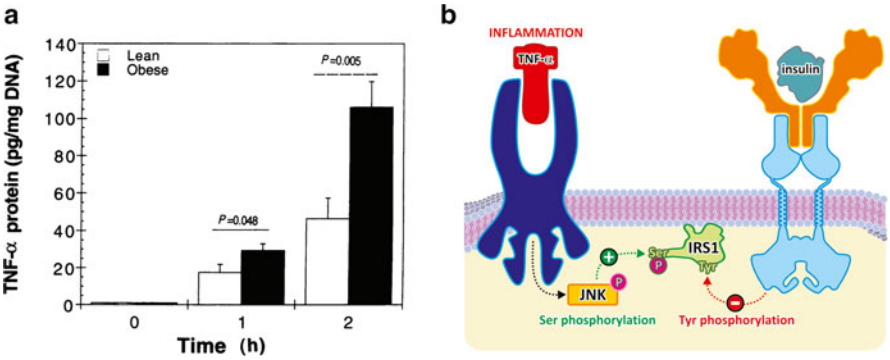


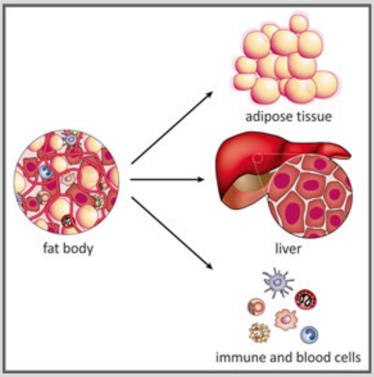
Fig. 11.20 (**a**) Comparison of TNF secretion during 2 h by the same amount of adipocytes explanted from the adipose tissue from 18 lean and 19 obese female subjects (Reproduced with permission from Hotamisligil et al., J. Clin. Invest. 95:2409–2415, 1995). (**b**) Integration of inflammation and insulin signaling pathways. Binding of TNF to its cellular receptor triggers the activation of the kinases JNK and IKK-β, which catalyze the Ser phosphorylation of IRS. IRS phosphorylation in Ser residues blocks its phosphorylation in Tyr residues by the insulin receptor, inhibiting insulin action

IRS phosphorylation in Ser residues impairs its phosphorylation in Tyr by the insulin receptor, leading to the inhibition of insulin-mediated cellular responses.

At a first glance, it is intriguing that the control of metabolism would be so tightly linked to the inflammatory process. Under an evolutionary perspective, one can understand the development of the immune and the metabolic responses as basic requirements for survival. The efficient use of the available nutrients and the ability to successfully eliminate the pathogens are essential features from the time of primitive organisms. Clues sustaining the coevolution of these processes can be found in nature, for example, in the case of the insects, in which the control of metabolic homeostasis and the immune responses are carried out by the same organ, the fat body (Box 11.6).

Box 11.6 Coevolution of Immune and Metabolic Responses

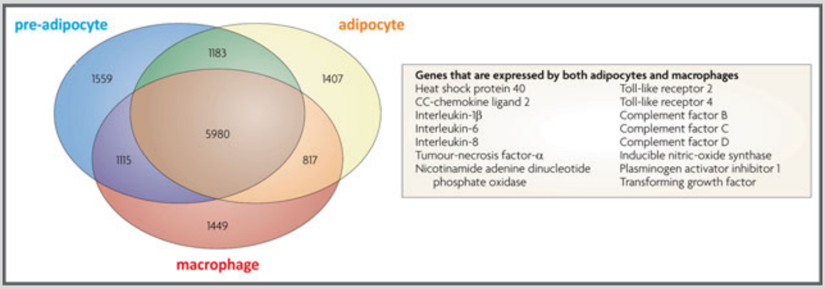
In insects, a single organ, the fat body, accumulates the functions that are carried out in mammals by the liver, the adipose tissue, and the immune cells. The fat body is the largest organ in the insect body cavity, and it is the major site of intermediate metabolism in these organisms. It metabolizes and stores lipids, carbohydrates, and proteins; it is the target for the majority of the insect hormones and also synthesizes the hemolymph proteins. Additionally, the fat body cells express the innate immune receptors, proteins that recognize molecular patterns specific of pathogens, in high levels. Through the activation of these receptors, the fat body produces and secretes a number of antimicrobial agents and regulators of cellular immune response. It is interesting to note that the metabolic organs of the more complex organisms contain resident immune cells, such as the Kupffer cells in the liver and the macrophages in the adipose tissue.



Organization of the metabolic and immune cells in insect and mammals (Reproduced with permission from Hotamisligil, Nature 444:860–867, 2006)

(continued)

Box 11.6 (continued)
Another remarkable evidence of the common evolutionary origin of the metabolic and immune responses is the fact that macrophages and adipocytes show an extensive genetic and functional overlap, with several genes expressed preferentially or approximately equally by pre-adipocytes, adipocytes, and macrophages, including many inflammatory genes (see figure below).



Transcriptional profile overlapping in pre-adipocytes, adipocytes, and macrophages (*left*) and the list of the inflammatory genes expressed in both adipocytes and macrophages (*right*) (Reproduced with permission from Hotamisligil & Erbay, Nat. Rev. Immunol. 8:923–934, 2008)

11.3.2 Origin of Inflammation in Obesity

The discovery that obesity is linked to a chronic inflammatory state raises the question of which are the triggers of inflammation in this case. This issue is now under intense investigation but the obesity-related factors that initiate the inflammatory process have not been identified so far.

The classical inflammatory response is driven by the contact of the host cells with molecular components specifically present in pathogens (known as pathogen-associated molecular patterns, PAMPs) or exposed during tissue injury (the damage-associated molecular patterns, DAMPs). These molecules are recognized by cellular receptors, known as pattern recognition receptors (PRR), which have a central role in the innate immune response. PRR can be membrane-bound receptors, such as the Toll-like receptors (TLRs), which are located on the plasma or endosomal membranes, or cytoplasmic receptors, such as the NOD-like receptors (NLRs) and the RIG-I-like receptors (RLRs). The binding of PAMPs or DAMPs to the PRR triggers a chain of signaling events that result in the activation of a number of transcription factors, which induce the expression of several pro-inflammatory cytokines, including TNF-α, and antimicrobial molecules, such as interferons (Fig. 11.21).

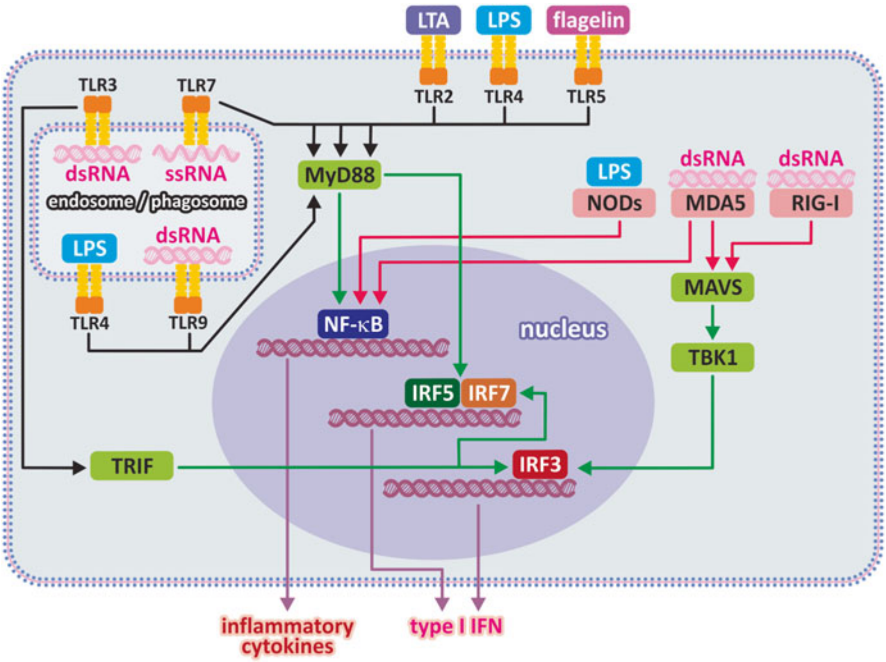


Fig. 11.21 Sensing microbial molecular patterns by host innate immune system. Toll-like receptors (TLRs), NOD-like receptors (NLRs), RIG-like receptors (RLRs), and C-type lectin receptors (CLRs) are pattern recognition receptors (PRR) expressed on cellular membranes or in the cytoplasm of a variety of cells in host tissues. Ligand binding to PRR triggers different signaling pathways that culminate with the activation of transcription factors, such as the IRFs, AP-1, and NF-κB, inducing the expression of interferons α and β (IFNα, β) and several pro-inflammatory cytokines. They recognize different microbial components, such as cell walls, microbial (and modified host) nucleic acids, bacterial motor flagellin, or stress (danger)-induced molecules. The information of ligand binding to PRR is transmitted to the transcription factors through some adaptor proteins, including MyD88, TRAM, TRIF or MAVS. Additionally, some NLRs can activate caspase-1, which cleaves the pro-IL-1β and pro-IL-18 in the active IL-1β and IL-18 that are released from the cell

The starting signal for the inflammatory response caused by overfeeding is still unclear. One hypothesis is that nutrients themselves would be recognized by innate immune system, although probably this occurs only when nutrient are in excess. This would happen if nutrients were not the preferential ligands of PRR, binding to these receptors with low affinity. During normal feeding the blood levels of nutrients are maintained low due to their rapid metabolization. Thus, very few nutrient molecules would bind PRR and trigger inflammation. Conversely, as nutrient concentration is maintained high enough to allow PRR occupation, the innate immune response is triggered, resulting in the establishment of the inflammatory state. Indeed, there is evidence that saturated fatty acids are recognized by one of the PRR, the Toll-like receptor 4 (TLR4), the PRR that usually recognizes the bacterial lipopolysaccharide (LPS). Alternatively, it is also speculated that the increase in the intestine permeability during feeding allows some pathogens or inflammatory molecules (such as LPS) to enter the organism together with the nutrients, triggering inflammation.

Another explanation for the inflammatory effect of overnutrition is related to a cellular response known as endoplasmic reticulum stress (ER stress). ER is the site of protein synthesis and the place where all the secretory and membrane proteins are assembled and folded. The accumulation of unfolded or misfolded proteins in this organelle triggers ER stress, a series of events that inhibit protein synthesis, increase protein degradation, and increase the expression of chaperone proteins, known as the unfolded protein response (UPR). Among the triggers of ER stress, we can cite the high concentrations of saturated fatty acids and glucose (characteristics of the high caloric diets) and hypoxia. UPR leads to the upregulation of the production of inflammatory mediators either directly through the activation of NF-κB or via JNK and IKK-β (Fig. 11.22). The inflammatory mediators themselves also activate JNK and IKK-β pathways, as discussed in the previous sections, amplifying inflammation and inhibiting the insulin signaling pathway.

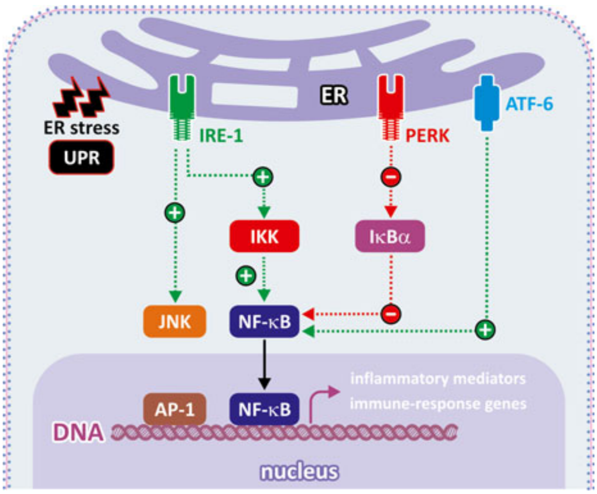


Fig. 11.22 ER stress pathways leading to inflammation. Three components of ER membrane are implicated in the inflammatory response, IRE-1, PERK, and ATF-6. IRE-1 acts either through its association with TRAF2, which activates JNK and IKK, and consequently AP-1 and NF-κB, or through the splicing of XBP1 mRNA. PERK inhibits the translation of IκBα, an inhibitor of NF-κB, thereby increasing NF-κB transcriptional activity. ATF-6 also increases NF-κB transcriptional activity

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