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Current knowledge in the neurophysiologic modulation of obesity

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Abstract

Obesity is today one of the commonest of life-threatening diseases in developed countries and generally results from an imbalance between energy intake and energy expenditure. Although there is increasing evidence for a genetic basis of obesity in some clinical syndromes, this seems to be the cause only in a limited number of patients and obesity is far from being considered as a gene-related disease. Eating is a complex and multifactorial process involving autonomous pathways that transfer sensory and motor information between the entire length of the digestive tract and the central nervous system. Modulation of the amount of energy that we take in as food involves several mechanisms and networks that connect the brain with the gut, this process being key to the regulation of body weight over time, as well as to the modification of long-term eating behaviors. Furthermore, this axis is closely coupled to other systems that are involved in energy homeostasis, namely, food preference, energy expenditure, and lifestyle. The identification of several neuropeptides that modulate eating behavior in various ways, along with studies performed in animal models, have focused attention on the role of these molecules and their clinical implications in the development of obesity in humans.

1. Introduction

There is growing concern over the increasing prevalence of obesity worldwide. In the United States, according to the large-scale Behavioural Risk Factor Surveillance System, prevalence of obesity has risen to 19.8% of the total population, representing an approximately 50% increase over obesity levels in the early 1990s (12%). Simultaneously, the incidence of diabetes among adults has increased from 5% to 7.3% within the past decade [1]. Prevalence of obesity is increasing at an alarming rate not only in the United States but also in many Western countries as well as in the third-world countries (>17% in Baltic Republics [2], in excess of 50% of adult population in Mexico [3]). There is a growing body of evidence that the prevalence of overweight and obesity also increases in areas where tremendous socioeconomic changes have taken place, such as in East Germany [4].This is also the case in countries with historically low incidence of obesity [5] (ie, an increase of up to 9.5% in overweight population was reported in China [6]).

Even more alarmingly, the parallel increases of obesity and diabetes prevalence in adults are progressively extending to ever younger age groups, affecting even 9- and 10-year olds, in whom obesity, as in older age groups, is directly linked with an increase in the risk of impaired glucose tolerance [7] and type 2 diabetes mellitus [8]. Moreover, obesity in children (>3 years old) presents an increasingly important predictor of adult obesity [9].

Existing evidence appears to point to a high prevalence of obesity among Greek adults and children [10]. For example, it has recently been reported that prevalence of overweight and obesity among children in northern Greece is 22.2% and 4.1%, respectively, and has been rising in the last few decades, especially among boys [11]. It is well known that obesity creates a survival disadvantage in the long term. This disadvantage takes the form of augmentation in endocrine dysfunction and metabolic disease, particularly type 2 diabetes and cardiovascular disease. In addition, increased cancer rates, psychological and psychiatric dysfunctions, and orthopedic diseases have been demonstrated. There is also evidence that obesity is linked via multiple pathways with gonadal dysfunction, such as hyperinsulinemia, and increased androgen and estrogen production [12]. Current measurements used to determine excess mortality risk from obesity are based on the body mass index (BMI), which is

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calculated by dividing the body weight in kilograms by the square of the height in meters. In nonselected populations, BMI correlates with the percentage of body fat, and this relationship is independently influenced by sex, age, and race [13]. It is noteworthy that the anatomic distribution of fat is of critical importance, with visceral obesity portending a much greater risk of disease [14-16].

Accumulated data have established the function of adipose tissue as an endocrine organ. In this regard, it is now recognized that neuropeptides in the hypothalamus also play a fundamental role in the regulation of energy balance.

A number of neuropeptides are thought to increase feeding, including neuropeptide Y (NPY), agouti-related protein (AGRP), and melanin-concentrating hormone (MCH). On the other hand, several peptides are known todecrease food intake, including leptin, corticotropin-releasing factor, cholecystokinin (CCK), cocaine- and amphetamine-regulated transcript (CART), and glucagon.

A more in-depth understanding of the pathogenesis of human obesity should ultimately guide treatment of affected individuals. Thus, the purpose of this review is to highlight the current knowledge about the pathophysiology of obesity and trace potential interactive pathways, which could serve as the basis for new therapeutic approaches.

2. Peripheral regulation

2.1. Insulin

Insulin acts primarily as an anabolic hormone but is also the key regulator of extracellular glucose concentrations. Although glucose provides the primary stimulus, production and secretion of insulin is a multifaceted process including several other molecules, such as free fatty acids, amino acids, keto acids, as well as a number of hormones, neuromodulators, and receptors, such as glucagon-like peptide 1 (GLP-1) and specific G protein–coupled receptors [17]. Insulin is believed to function as one of the adiposity signals to the brain for modulation of energy balance. It is generally known that circulating levels of insulin are proportional to the fat stores [18,19]. In particular, the visceral compartment has been identified as an important contributor to hyperinsulinemia, and its related syndrome, the metabolic syndrome, is the clinical paradigm of that close correlation [20]. Furthermore, many therapeutic schemes that regulate either glucose or lipid metabolism (metformin, thiazolidinediones [TZDs], and corticosteroids) have substantial effects on each other in multiple tissues (liver, skeletal muscle, and adipose tissue). Likewise, syndromes of adipose tissue deficiency, such as lipodystrophies, are known to cause severe insulin resistance [21].

The first report of insulin's crucial impact on the brain in the modulation of food intake was obtained in baboons [22]. A more recent study has shown that a selective decrease in hypothalamic insulin receptors causes hyperphagia and insulin resistance in rats [23]. Oral and intracerebroventricular administration of an insulin mimetic resulted in a dose-dependent reduction of food intake and body weight in rats. The biological action of these molecules is limited to the hypothalamic insulin receptors. Thus, insulin mimetics have a unique advantage over insulin in the control of body weight and promise a novel antiobesity treatment [24].

2.2. Adipose tissue

Adipocytes are involved in a variety of functions, including glucose homeostasis, inflammation, energy balance, lipid metabolism, and the fibrinolytic-hemostatic system (Fig. 1). It has been shown that adipocytes secrete several proteins and chemical messengers, including leptin, tumor necrosis factor α (TNF-α), resistin, adiponectin, interleukin (IL) 6, and angiotensinogen [21]. Because several of these so-called adipocytokines profoundly influence insulin sensitivity and glucose metabolism, they could well provide a molecular link between increased adiposity and impaired insulin sensitivity [25,26]. The connection between adipose tissue and hormonal secretion is also not disputed. Increased cortisol levels in Cushing syndrome as well as after corticosteroid treatment are typically followed by an increase in the visceral adipose tissue volume. Such conditions of hypercortisolemia are seen in stress-induced activation of the hypothalamus-pituitary-adrenal axis [27,28].

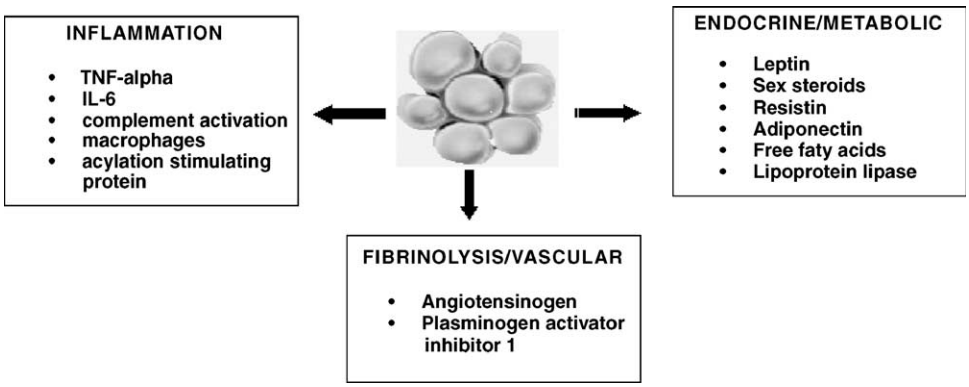

Fig. 1. Major products of adipose tissue.

2.3. White and brown adipose tissue

The uncontrolled expansion of white adipose tissue (WAT) seen in obesity predisposes affected individuals to health complications. Another type of fat, brown adipose tissue (BAT) has the opposite function, allowing dissipation rather than storage of energy. Recent studies on the transcriptional control of adipocyte differentiation offer a new perspective on conversion between brown and white adipocytes.

Brown adipose tissue is specialized in adaptive thermogenesis, the aspect of energy expenditure induced by cold exposure or diet [29], and is present throughout the life span in rodents but not in humans. Production of the uncoupling protein 1 (UCP1), which is involved in adenosine triphosphate synthesis, and the large number of mitochondria in brown adipose cells is regarded as the main activators promoting energy dissipation as heat. The oxidation of fatty acids in mitochondria produces a gradient of protons between the mitochondrial compartments separated by the internal membrane, and this gradient of protons is mainly used to produce ATP via ATP synthase. The presence of UCP1 in the internal membrane of BAT mitochondria induces the loss of the proton gradient, heat production representing the final result of the burned fatty acids.

In contrast, UCP1 messenger RNA (mRNA) is expressed only at low levels in WAT [30] and is rarely induced in some endocrinologic disorders (eg, phaeochromocytoma and primary aldosteronism). Uncoupling protein 1 knockout mice were generated and it was found that they were unable to maintain their body temperature upon cold exposure but they did not become obese [31], thus, proving that these rodents can maintain body mass by an alternative mechanism, independent of the UCP1 pathway.

When the BAT sympathetic nervous system activity is increased by cold exposure or overfeeding, the stimulatory effect on UCP1 activity and expression is mediated essentially by the β3-adrenoceptor [32]. This third subtype of the family of the β-adrenoceptors was found to be the predominant β subtype in rodent BAT and WAT [32,33]. The β3-adrenoceptor was found to be downregulated in the BAT and WAT of both the obese *fa/fa* Zucker rat (a genetic model with a default in the leptin receptor) [32] and the *ob/ob* mouse (genetically obese mice lacking leptin), compared with lean animals [34]. These obese animals have been successfully treated with β3-adrenoceptor agonists and the reduction of their body mass was accompanied by the appearance of BAT in white depots [35]. In β 3-adrenoceptor knockout mice, the capacity to adapt to a cold environment was fully preserved, but there was an increase in fat deposit under basal conditions and in response to a high-fat diet [36]. It has been shown in rodents that a cold-induced increase in UCP1 expression occurs in the WAT [37], although this is not obtained in β 3-adrenoceptor knockout mice. These mice lack the 3 known β-adrenoceptors (β-less mice) and on a high-fat diet, in contrast to wild-type mice, they developed massive obesity, entirely due to a failure of diet-induced thermogenesis [38]. These lines of data suggest that the β3-adrenoceptor–UCP1 axis plays a key role in thermogenesis and might be a promising new target for antiobesity drugs. However, in a study concerning 14 healthy young lean male volunteers who were treated with a highly selective β3-adrenoceptor agonist (CL 316,243), Weyer et al [39] failed to detect any effect on thermogenesis and plasma leptin concentration. Furthermore, treatment failed to produce any measurable reduction of fat mass after 8 weeks.

Particular interest is being focused on the peroxisome proliferator–activated receptors (PPAR), especially PPARγ2, which are thought to be key regulators in the differentiation of adipocyte. The recently identified PPARγ coactivator 1a (PGC-1a), which is expressed at higher levels in BAT than in WAT [40], seems to be essential to the understanding of the different biological function of the 2 types of adipose tissue. PGC-1a coactivates the PPARγ-RXRa heterodimer to stimulate the UCP1 promoter. It has been shown that PGC-1a transduction to human white adipocytes can alter their metabolic function and increase their fat oxidation capacity [41]. Conversely, adipocyte may also transdifferentiate into white adipocyte. In warm acclimated animals, where there is no adrenergical stimulation, BAT gradually loses its characteristics and converts into a tissue composed of uniocular cells with mitochondria similar to that seen in white adipocytes [42].

Alteration in energy balance, through a conversion of WAT to BAT, may introduce an alternative topic for new therapeutic strategies in the treatment of obesity [43].

2.4. Adipose tissue and inflammation

Although adipose tissue and adipocytes have been widely examined in the search for the mechanisms underlying obesity and associated diseases, little is understood about their role in inflammation. Adipocytes and diverse types of immune cells, such as T cells and macrophages, possess similar roles in pathways, such as complement activation and inflammatory cytokine production. Adipose tissue macrophage numbers increase in obesity and participate in inflammatory pathways that are activated in the adipose tissue of obese individuals. Among the 100 most significantly obesity-correlated genes, 30% encode proteins that are characteristic of macrophages. Expression analysis of macrophage and nonmacrophage cell populations isolated from adipose tissue demonstrated that adipose tissue macrophages are responsible for almost all adipose tissue TNF-α expression and significant amounts of IL-6 expression [44]. Growing evidence has pointed to a correlative and causative relationship between inflammation and insulin resistance, especially via the actions of adipose-derived proinflammatory cytokine TNF-α [45]. It has been demonstrated that TNF-α mediates insulin resistance as a result of obesity in many rodent obesity models and is

overexpressed in WAT in obese and insulin-resistant states. Corroborating the crucial role of inflammation in the pathophysiology of obesity, mice with genetically disturbed TNF receptor were partially protected from obesity-induced insulin resistance [46]. Administration of TNF-α antibodies improved insulin sensitivity in obese rodents [47].

In humans, IL-6 circulating levels are correlated with BMI and are inversely related to insulin sensitivity [48,49]. Interleukin 6 signals via a heterodimeric receptor complex consisting of a soluble IL-6α subunit (IL-6 receptor [IL-6R]) and a signal transducing subunit (gp130). The IL-6R gene maps to an important candidate locus for type 2 diabetes on chromosome 1q21. An Asp358Ala polymorphism of the IL-6R has been reported to associate with obesity in Pima Indians and type 2 diabetes in Danish whites [26].

This connection is also established in animals, but the exact correlation and its clinical outcome remain unknown. Mice genetically lacking IL-6 developed mature-onset obesity [50]. Furthermore, intracerebroventricular administration of IL-6 decreases body fat in rats [51]. Recently, a marked improvement in insulin resistance, endothelial function, and low-grade inflammation were observed in the weight-losing morbid obese patients after bariatric surgery but circulating levels of TNF-α, IL-6, and its soluble receptors did not change, indicating their unique role in insulin sensitivity [25].

2.5. Leptin

Leptin plays a major role in the family of cytokines. Reduction of visceral fat activates a complex procedure, involving various neuronal signals, peptides, and cytokines, which ultimately lead to increase of appetite and decrease of energy expenditure.

Leptin (from the Greek word *leptos*, meaning thin) is primarily produced by adipocytes, is secreted into the peripheral circulation, and must cross the blood-brain barrier before it can have any effects on the hypothalamus [52]. Leptin seems to alter the efficacy with which a number of meal-related signals modulate food intake. Leptin receptors are abundantly expressed in the arcuate and the dorsomedial nuclei of the hypothalamus [53]. Leptin interacts with 2 different cell types within the arcuate: medial neurons that contain the orexigenic peptides NPY and agouti-related peptide, and lateral neurons that express proopiomelanocortin (POMC), the precursor for the anorexigenic melanocyte-stimulating hormone (α-MSH). Elevation of leptin levels results in a decrease of orexigenic NPY and agouti-related peptide expression, and an increase in the expression of anorexigenic POMC. Experimentally, the effects of intracerebroventricular injection of leptin were achieved without any change in peripheral leptin levels, supporting the hypothesis of leptin's central action [54].

The role of leptin and its receptors in the regulation of energy balance is well illustrated by observations that rodents which have mutations in either their signaling leptin receptors (*db/db* mice or *fa/fa* Zucker rats) [55] or in leptin production (*ob/ob* mice) [56] are extremely obese. In obese mice (because of leptin deficiency), increased appetite, reduced metabolic rate, and a variety of endocrine abnormalities (hyperglycemia, hyperinsulinemia, hypercortizolemia, and infertility) have been observed [57]. Experiments in rodents have demonstrated that forebrain administration of leptin and NPY have opposing effects on the neurophysiologic responses of the nucleus tractus solitarius (NTS) to gastric loads [58]. There is evidence that the effect of leptin on gastrointestinal motility is not limited to the modification of various centrally acting neuropeptides, but also acts directly on the vagal nerve, and through its afferent branch, modulates the NTS function. However, because gut vagal afferent responses to the same range of gastric loads were unchanged by central administration of either leptin or NPY, a potentional alternative pathway might be involved.

The isolation of leptin and its relevant gene in humans aroused great enthusiasm and, initially, leptin was thought to be the "magic bullet" weight-control hormone. However, further investigations showed that, in both animals and humans, leptin levels are increased in obesity, thus supporting the theory of "leptin resistance," similar to that of insulin resistance. In addition, exogenous leptin administration as a potential therapy in obese individuals seems to be ineffective either in reducing body weight or in maintaining such a result when achieved. Subjects who are heterozygous for leptin mutations are partially deficient in leptin, and this can directly influence the laying down of fat tissue [59], suggesting that these individuals might benefit from exogenous leptin supplementation.

Leptin treatment of transgenic mice with BAT deficiency is unable to prevent obesity [60], signifying that the increase in energy expenditure caused by leptin is closely associated with BAT [61]. However, most of the reductions in body weight achieved with leptin treatment are due to reduced energy intake rather than increased energy expenditure. Leptin appears to gain access to the cerebrospinal fluid via a saturable transport mechanism similar to that described for insulin; however, leptin receptors demonstrate notable structural and functional differences by comparison with those of insulin [62].

Current data on leptin resistance point to a postreceptor defect [63]. It is likely that leptin resistance is related to the function of a suppressive factor of the cytokines (suppressor of cytokine signaling–3), which inhibits the phosphorylation of specific intracellular peptides (signal transduction and transcription, STAT peptides) from janus kinases [64]. Although leptin is more effective and long-lasting than insulin, they both appear to act as long-term hormonal adiposity signals to the brain proportionally to body fat storage. Interestingly, studies have demonstrated, both in experimental animals and in human subjects, that the association between insulin and leptin resistance may be independent of body fat mass [65,66]. Schwartz et al [67] found that the relationship between plasma leptin levels and

BMI did not differ significantly among subjects with type 2 diabetes mellitus from that observed in nondiabetic subjects, indicating that obesity associated with type 2 diabetes mellitus is unlikely to result from impaired leptin secretion. Furthermore, according to their findings, insulin sensitivity contributes to the association between body adiposity and plasma levels of insulin, but not leptin, suggesting that the mechanisms underlying the association between body adiposity and circulating levels of these 2 hormones appear to be different.

The use of leptin-related synthetic peptides on body weight and food intake has been evaluated in vivo [68] with encouraging results, showing that the active region of leptin's molecule is located in domains between 106 and 140 of the amino acid sequence. This finding heightens expectations for the development of smaller and potent leptin analogs. An effective use of another cytokine as a substitute for leptin has been reported, introducing new sites for therapeutic intervention in the leptin signaling pathway [69].

2.6. Resistin

A new adipocyte hormone—resistin—was recently identified in mice [70] while screening for genes that were induced during the differentiation of adipocytes but were down-regulated in mature adipocytes exposed to rosiglitazone. Mouse resistin consists of 114 amino acids and circulates as a homodimer of 2 peptides joined by a disulfide bridge [71]. Resistin is more highly expressed in visceral white fat than in subcutaneous fat [70]. In obese mice, serum levels of resistin are strikingly increased and administration of TZDs (insulin sensitizers) seems to decrease resistin levels. These observations point to resistin as a mediator of insulin resistance.

In addition, neutralization of resistin activity with the use of resistin-specific antibodies decreases glucose levels and improves insulin sensitivity in mice, whereas the injection of resistin has the opposite effects. In humans, a significant positive correlation between resistin and BMI was recently reported [72]; however, according to the same study, serum resistin was not a significant predictor of insulin resistance. In a small group of patients, evidence was provided that resistin levels correlate with insulin resistance in nondiabetic subjects, but this association is less marked than that seen for leptin and insulin resistance [73].

In contrast to the previously mentioned reports, a recent study concerning 123 middle-aged women and 120 healthy young subjects found that serum resistin levels did not correlate with markers of adiposity (including BMI, waist-to-hip ratio, insulin resistance, lipid profile, and serum leptin levels). It is of particular interest that females had higher resistin levels than males [73,74]. In addition, no difference in serum resistin levels between lean healthy and obese insulin-resistant nondiabetic and type 2 diabetic adolescents was documented. In another study, although cross-sectional analysis in obese subjects demonstrated no correlation between serum resistin and parameters related to adiposity or insulin resistance, longitudinal analysis revealed change in serum resistin to be positively correlated with changes in BMI, body fat, fat mass, visceral fat area, and mean glucose and insulin in obese patients before and after weight loss through diet [75].

These findings suggest that insulin modulates its own activity through the regulation of resistin, but the potential role of mutations in the resistin gene and their contribution to insulin resistance in humans remain to be investigated. However, the fact that resistin inhibits adipocyte differentiation and may function as a feedback regulator of adipogenesis, although in parallel might decrease insulin sensitivity, confirms the necessity for weight reduction and exercise in managing obese subjects with hyperinsulinemia [76].

2.7. Adiponectin

In the mid-1990s, an adipose-secreted protein with homology and complement factor C1q was cloned independently by different groups and was named *adipoQ*, *Acrp 30*, or adiponectin. Adiponectin is an adipocyte-specific secreted protein that sensitizes the liver and muscle to the action of insulin [77]. Adiponectin decreases the postprandial rise of plasma free fatty acids and improves postabsorptive insulin-mediated suppression of hepatic glucose output. It also acts as an anti-inflammatory and anti-atherogenic plasma protein [78]. In vitro findings have suggested a new role for adiponectin, as a regulator of blood cell formation and lymphopoiesis [79].

In humans, adiponectin levels are inversely related to the degree of adiposity. It has been reported that adiponectin levels are reduced in obesity, even in young subjects [80-84]. Adiponectin levels were found to be higher in women compared with men [81,82], despite the negative association between estradiol and adiponectin [85]. Predominantly central fat distribution is an independent negative predictor of serum adiponectin [85]. In a recent small clinical study, serum adiponectin was inversely associated with bone mineral density and visceral fat volume, indicating that adiponectin may play a role in the protective effects of visceral fat on bone mineral density [86]. Although women have more subcutaneous fat and men have more visceral fat, previous studies have found that the sex difference in adiponectin levels is independent of total body fat or fat redistribution [82].

It was recently demonstrated that a genetically inherited decrease in adiponectin levels predisposes subjects to insulin resistance and type 2 diabetes [87]. Secretion of adiponectin exhibits ultradian pulsatility as well as a diurnal variation, with a significant decline at night and a nadir in the early morning. The 24-hour variations are identical to those of cortisol and leptin-binding protein, suggesting that the latter may have a direct inhibitory effect on adiponectin secretion. However, neither a 48-hour fast nor leptin administration was shown to regulate serum adiponectin in healthy men and women [85].

Described mutation in the relevant gene contributed to the development of severe obesity in humans [88]. Adiponectin expression and levels in the circulation are up-regulated by the PPARγ agonist rosiglitazone [89], suggesting the correlation between adiponectin, adipocyte function, and obesity. Roglitazone belongs to the TZDs, which are insulin-sensitizing drugs that ameliorate insulin resistance and lower plasma levels of both glucose and insulin in several genetic models of obesity.

From the data previously mentioned, it could be concluded that a close correlation exists between adiponectin levels and insulin resistance; however, a recent study challenged this conception [73]. Furthermore, in this clinical study, no significant correlation was established between adiponectin levels and the homeostasis model assessment ratio or fasting insulin. The in vivo effects of adiponectin injections in mice were investigated by several groups producing promising results as regards insulin sensitization and stimulation of fatty acids β-oxidation [90]. Recently, a study reported the cloning of human and mouse adiponectin receptors that mediate antidiabetic metabolic effects [91]. The 2 receptors, designated AdipoR1 and AdipoR2, are abundantly expressed in skeletal muscle and liver, respectively, and are structurally very different from G protein–coupled receptors. The gene for the human AdipoR1 receptor is located on chromosome 1p36.13-q41, and the gene for AdipoR2 on 12p13.31. Expression or suppression of receptor activity by small-interfering RNA supports the conclusion that they serve as receptors for both globular and full-length adiponectin, and that they mediate increased AMP kinase and PPARα activity, giving rise to increased fatty-acid oxidation and glucose uptake, which accounts for increased insulin sensitivity mediated by this adipocytokine. In conclusion, activation of the adiponectin pathway may provide novel therapeutic strategies for obesity-linked disorders.

3. The nervous system

3.1. Hypothalamic neuropeptides

3.1.1. Neuropeptide Y/agouti-related protein

Neuropeptide Y is a 36–amino acid hypothalamic orexigenic neuropeptide secreted in the arcuate nucleus. Five Y receptors are known, which arbitrate the action of NPY and its other family members, peptide YY, and pancreatic polypeptide PP [92]. Neuropeptide Y receptors have been identified in a variety of tissues, including brain, spleen, small intestine, kidney, testis, placenta, and aortic smooth muscle [92]. In addition, Y1 receptors have been associated with vascular smooth muscle contraction by regulating the action of noradrenaline [92].

Administration of leptin suppresses the expression of NPY, whereas leptin paucity has the opposite effect [93]. Animal studies have identified hypothalamic neuropeptides pathways involved in regulating feeding and metabolism [94,95], such as NPY/AGRP neurons, activated by the fall in plasma leptin during starvation. Hyperphagia observed in insulin-depleted diabetic rats is correlated with the increase of NPY production, which is mentionally marginally normalized if insulin is administered [96]. Hypothalamic NPY and AGRP overactivity in rodents leads to obesity and neuroendocrine abnormalities [94,97]; however, transgenic NPY knockout mice do not have altered feeding behavior, thus, arousing questions concerning the physiological role of NPY [98]. With respect to this report, mice with genetic depletion of the Y5 receptor (Y5R) developed mild late-onset obesity; however, feeding attitude was unaffected in younger Y5R-null mice, demonstrating that although the Y5R contributes to feeding, it is not the critical receptor in mice [99]. Consequently, human NPY Y1 receptor, a gene encoded in 1993 [100], has attracted interest. It is assumed that under normal circumstances, lack of NPY can be overlapped from the other orexiogenic peptides.

Agouti-related protein is an endogenous α-MSH antagonist at the melanocortin-4 receptor (MC4R), colocalized with NPY in arcuate nucleus neurons [94], called the infundibular nucleus in humans. The pathophysiology of food intake under particular clinical circumstances, such as stress, obesity in Prader-Willi syndrome (PWS), and illness-associated anorexia, appears to lie in downstream or separate circuits and might involve many of the known neuropeptides. Recent experiments reported that stress-induced cortisol secretion was followed by elevated NPY secretion [101]. Prader-Willi syndrome is the most common genetic cause of marked obesity [102] and is associated with life-threatening hyperphagia, as well as growth hormone (GH) deficiency and hypothalamic hypogonadism. Until recently, investigators believed that increased activity of hypothalamic NPY/AGRP neurons might be responsible for hyperphagia in these subjects [103]. On the other hand, anorexia associated with severe illness may be mediated by disturbances in the normal physiological response of hypothalamic pathways, perhaps via circulating cytokines or endotoxins [104]. However, Goldstone et al [105] did not find increased activity of NPY/AGRP neurons either in obese PWS adults or in severe illness. Thus, obesity in PWS is likely to be multifactorial and the exact origin of the neuroendocrine abnormalities is currently unresolved [106]. Craniopharyngioma is the commonest structural cause of hypothalamic obesity [107]. In these patients, the preoperative percentage of obese patients was reported to be elevated after surgical treatment [108], indicating the vital importance of the hypothalamus in food consumption.

Intracerebroventricular and oral administration of a selective and potent antagonist for the Y1 receptor (J-104870) significantly suppressed spontaneous food intake in Zucker fatty rats [99]. Several strategies have been proposed in treating hyperphagia in PWS (behavioral approaches, fenfluramine, fluoxetine, biliopancreatic diversion, and vertical banded gastroplasty), although the available data for their efficacy are controversial [106].

Growth hormone replacement in children with PWS was also reported to improve muscle mass and to contribute to weight loss [108], although GH deficiency is rarely the main cause of severe obesity. However, in cases where GH deficiency is confirmed, exogenous supplementation is crucial to provide adequate muscle strength needed to induce mobility, exercise, and increase energy expenditure.

3.1.2. Melanin-concentrating hormone

Melanin-concentrating hormone is synthesized in the magnocellular neurons in the lateral hypothalamus and the zona incerta. To date, 2 receptors for MCH in humans have been identified, namely, MCH-R1 and MCH-R2. As an orexigenic peptide, MCH interacts with other neuropeptides that influence feeding behavior. Animals treated with MCH developed hyperphagia and obesity, whereas ablation of the rodent MCH receptor leads to a lean phenotype [109,110]. Melanin-concentrating hormone is overexpressed in the leptin-deficient (*ob/ob*) mouse, whereas further ablation of MCH in this animal (double-null mice lacking both leptin and MCH) led to attenuation of obesity. It is of great interest that no decrease in hyperphagia was observed [111]. Hence, the role of MCH mainly concerns the regulation of energy expenditure. Consistent with this proposition, activation of MCH neuronal pathways stimulated adiposity, partially resulting from increased lipogenesis in the liver and WAT and reduced energy expenditure in BAT [112]. In addition to its orexigenic action, MCH seems to be involved in the activation of the stress axis, specifically due to the significant expression of the MCH-R1 receptor in the amygdala and hippocampus [113]. Although this notion exceeds the scope of the present review, studies in behavioral animal models, using MCH-R1 antagonists, provided evidence for a potential role of MCH in the regulation of mood and emotion [114]. Central administration of a MCH-R1 antagonist resulted in sustained reductions in food intake, introducing a new potential approach for the treatment of obesity [115] as well as anxiety and depressive syndromes [113].

3.1.3. α-Melanocyte–stimulating hormone

α-Melanocyte–stimulating hormone is a product of the POMC gene and inhibits food intake by its action via the melanocortin receptors in the hypothalamus [116]. Melanocyte-stimulating hormone interacts with at least 5 receptors, 2 of which (MC3R and MC4R) are expressed in the brain. MC3Rs are mainly indicated in the hypothalamus and limbic system whereas MC4Rs are widely expressed (cortex, hippocampus, thalamus, hypothalamus, spinal cord, and peripheral sympathetic nervous system) [117]. As mentioned previously, α-MSH competes with AGRP, which acts as an endogenous antagonist on MC receptors [97]. It has been demonstrated that melanocortin system action is not limited to specific receptors but is also implicated in the modulation of insulin production and its peripheral action. Animals genetically rendered unable to produce POMC, as well as rodents lacking MC receptors, express obese phenotype [118,119]. It has been suggested that prevalence of such gene lesions in humans accounts for approximately 5% of obese children [33].

Consistent with the inhibitory role of MSH, food deprivation results in decreased expression of POMC in the arcuate nucleus [120]. Proopiomelanocortin mRNA abundance is low in *ob/ob* mice but increased through long-term leptin treatment [120]. The anorexigenic and thermogenous effects of leptin were reduced in animals with inhibited MC receptor [121], indicating that leptin's efficacy is somehow dependent on the impact of the POMC pathway. Seasonal cycles in food intake and energy metabolism as well as the influence of daylight (known to be related to POMC secretion) were investigated by Reddy et al in 1999. Their results clearly demonstrated that male Siberian hamsters show profound decreases in food intake and body weight when exposed to short days; however, these photoperiodically regulated long-term metabolic responses are not associated with major changes in mRNA expression of the 3 investigated hypothalamic peptides (orexin, NPY, and POMC) [122].

3.1.4. Orexin

Orexin (also known as hypocretin) is a peptide localized in neuronal cell bodies of the lateral hypothalamic area [123] and its adjacent area, which contribute to the regulation of food intake and energy balance. It has been identified as a ligand for an orphan G protein–coupled receptor [124]. In rats, orexin-containing neurons project to numerous hypothalamic and extra-hypothalamic sites, including the cerebral cortex, circumventricular organs, and brainstem [125]. Hence, orexin is likely to be involved in regulating various functions, such as emotion, arousal, feeding, and drinking [126,127]. It has been shown in rats that centrally administered orexin increases food intake. The effect of orexin on anorexia induced by CCK was recently investigated and it was reported that orexin significantly reversed the CCK-induced loss of appetite [128]. Owing to the hypothesis that CCK increase is possibly associated with IL-1 [129] and also related to anorexia nervosa [130], the role of orexin has attracted considerable scientific interest. Although these experimental studies were performed on rats, preliminary findings indicate that orexin might be a promising target for pharmacologic intervention in the treatment of anorexia and cachexia induced by various diseases.

3.1.5. Cocaine- and amphetamine-related transcript

Cocaine- and amphetamine-related transcript peptides are neuropeptides involved in feeding, which are widely distributed in the brain, gut, pituitary, adrenals, and pancreas [131]. In the arcuate nucleus, CART colocalizes within the majority of POMC-containing neurons, and in the lateral hypothalamus it colocalizes with MCH. This anatomic finding shows that CART plays a crucial as well as a complicated role in orexins. Indeed, it has recently

been noted that a centrally injected CART fragment (55-102) resulted in increased food intake in rats [132]. In addition, genetic disruption of cannabinoid receptor type 1 in mice causes hypophagia and leanness, indicating that the cannabinoid system interferes with the orexigenic mechanism [133].

By contrast, other studies have reported that short-term administration of CART peptide into the ventricular system in rats led to a dose-dependent decrease in food intake [134,135]. The discrepancies previously mentioned might partly relate to photoperiodic differences in CART expression as well as the circadian regulation of the colocalized POMC. However, the observation that CART mRNA remains unchanged in seasonally fat vs lean hamsters is consistent with the view that CART-producing cells in the arcuate are involved mainly in energy homeostasis rather than long-term seasonal regulation of body weight [136].

3.1.6. Prolactin-releasing peptide

Prolactin-releasing peptide (PrRP) is a poor prolactin secretagogue produced in the hypothalamus. Prolactin-releasing peptide is mainly secreted in the NTS and in the ventrolateral medulla, whereas PrRP receptor is expressed primarily in the hypothalamus, the thalamus, and the border of the NTS-area postremal [137]. This tissue distribution suggests an alternative function of PrRP to its purported hypophysiotropic function. Although paraventricular nucleus injection of PRL-releasing peptide did not alter food intake, both intraventricular and intrahypothalamic injections of the peptide decrease food intake and alter the release of several hypothalamic neuropeptides (α-MSH, cocaine- and amphetamine- regulated transcript, neurotensin) [138]. Prolactin-releasing peptide is down-regulated by fasting. Co-administration of PrRP and leptin has additional effects on appetite, body weight, and energy expenditure [139]. Some authors have shown that more than 90% of PrRP neurons in all regions where PrRP is expressed contain leptin receptors. Prolactin-releasing peptide neurons are also activated by CCK, and it has been suggested that PrRP may mediate some of the satiating actions of CCK on higher brain centers [140]. Thus, it seems that PrRP neurons are involved in the regulation of food intake and energy homeostasis mainly by affecting the leptin-sensitive brain circuitry and the central function of CCK.

3.2. Brain stem

Despite the acknowledged supremacy of the hypothalamus in collecting the peripheral signals and in initiating relevant responses, the brainstem is coupled to other systems that modulate energy requirements and food intake. Meals are terminated by feedback from the digestive tract to the brainstem and this does not depend on nutrients or energy absorbed from the food. Release of CCK postprandially activates receptors on the afferent sensory fibers of the vagus and, through their axons, stimulates cell bodies which are located predominantly in the NTS of the brainstem [141]. The NTS is a key brainstem region that involves many autonomic functions. Indirect modulation by other factors, such as diet preferences, availability of food, and hypercatabolic circumstances, indicates that the brainstem-gut axis communicates with other brain locations as described previously. Indeed, NTS probably lacks an effective blood-brain barrier and its neurons are open to modulation by circulating factors, such as leptin. The leptin-receptor messenger is expressed in brainstem serotonergic neurons, suggesting that they are direct targets of leptin action and mediate some of the effects of leptin on feeding [142]. Leptin and serotonergic neurons act within a common pathway to gonadotrophin-releasing hormone neurons, possibly through a subtype of serotonin receptor (5HT receptor) [143]. It seems that the brainstem has a role in the control of individual meal size whereas the hypothalamus is fundamental to long-term energy homeostasis.

3.3. Peripheral nervous system

The noradrenergic tone increases in WAT during fasting [144,145]. There are 2 types of adipocytes existing in WAT with different roles: those where β2-adrenoceptors (that couple negatively with adenyl cyclase) are prevalent, and those where β1- and β3-adrenoceptors (coupling positively with adenyl cyclase) are prevalent.

The β-receptor–rich adipocytes are reached directly by noradrenergic fibers and react with intense lipolysis. The β-receptor–rich adipocytes would not react to guarantee a reservoir to refill the slimmed adipocytes rapidly [146]. It has been proposed that the increase in parasympathetic tone, which occurs at night, promotes the nocturnal deposition of fat [147]. It seems logical to assume that the greater parasympathetic nervous system activity in the visceral WAT might result in greater accumulation of fat in this area compared with subcutaneous adipose tissue. Peculiar patterns of fat distribution seen in patients with lipodystrophy, HIV infection, Cushing syndrome, and in the elderly may be associated with altered parasympathetic activity. It is has also been shown that decreased activation of the parasympathetic nervous system (which occurs in patients with obesity and type 2 diabetes mellitus) increases lipolysis and raises plasma free fatty acid levels, leading to insulin resistance in skeletal muscle and the liver [147]. Thus, decreases in free fatty acid levels induced by increased parasympathetic nervous system activity as a result weight loss or by pharmacologic means may deter the development of atherosclerosis and improve insulin sensitivity [148].

4. Gut peripheral signals

4.1. Ghrelin

Ghrelin is a 28–amino acid peptide mainly secreted by gastric endocrine cells into the systemic circulation [149], but under particular circumstances, ghrelin is also derived from other tissues including the pancreas [150]. It is an

endogenous ligand for the GH secretagogue receptor, and it has structural and functional similarities to the gut hormone motilin [151]. Fasting increases, whereas feeding decreases, circulating ghrelin concentrations. The mean levels of circulating ghrelin are decreased in obese subjects [152]. Administration of ghrelin in both animals and humans resulted in a remarkable increase in appetite via the activation of the orexiogenic the NPY/AGRP pathway in the arcuate nucleus [153,154]. Conversely, ghrelin serum concentration is negatively correlated to leptin and insulin [155]. In obese Zucker *fa/fa* rats, plasma ghrelin concentrations were significantly increased, regardless of the feeding status of the animals, substantiating a part for ghrelin in the advance of obesity in the absence of the leptin signal [156]. Obese patients treated surgically (gastric bypass) had diminished levels of circulating ghrelin despite weight loss; in contrast, dietary-achieved weight loss was linked with elevated serum ghrelin [152,157]. Alterations in hormonal milieu because of surgical management [158] and long-term effects on food intake and satiety are currently under investigation [159].

The most potent inhibitor of ghrelin secretion is somatostatin and its natural analog cortistatin, which concurrently reduce the secretion of beta cells. According to this concept, the pancreas might play a role in appetite regulation. Synthetic compounds endowed with antagonistic activity could beneficially lessen appetite and contribute to the maintenance of the reduced body weight. However, a recent study in ghrelin-deficient mice (ghrelin-null mice) failed to record any difference regarding growth, fertility, appetite, bone density, and adipose tissue distribution in these rodents [160], dampening the initial optimism of investigators. Ghrelin receptor agonists, with potent activity after oral administration, are already available [161], and their potential anabolic role in conditions where appetite and GH are diminished (eg, cachexia) is a topic for further investigation [104,162].

Recent studies have found that fasting levels of ghrelin are grossly elevated in PWS, which could contribute to their hyperphagia. Thus, gastric bypass and ghrelin antagonists may play a leading role in a new strategy in treating obesity in these patients [163].

4.2. Peptide YY

Peptide YY (PYY_{3-36}) is a new and promising peptide with intermediate action, belonging to the "family" of neuropeptides P. It is secreted from the intestine and colon postprandially and its circulating concentrations remain elevated during meals [164,165]. Endogenous PYY levels are low in obese subjects, suggesting that PYY deficiency may contribute to the pathogenesis of obesity [166]. Consistent with this in morbidly obese patients who were treated surgically (vertical banded gastroplasty), the low preoperative PYY concentration gradually rises to the control levels postoperatively [167]. Treatment with PYY in both animals and humans certainly suppressed appetite for an interval of 12 to 24 hours and reduced plasma levels of ghrelin [166].

It is noteworthy that PYY effect is different from that of fast-acting ghrelin and the long-term effects of insulin and leptin [167]. Clinical use of PYY is currently under investigation [166]. PYY reduces food intake by modulating appetite circuits in the arcuate nucleus of the hypothalamus [165], notably by antagonizing orexiogenic NPY at the level of its receptor and, in addition, by ameliorating the activity of POMC neurons [166]. A recent study showed that repeated administrations of pancreatic polypeptide (another member of the same "P" family) decreased body weight gain and ameliorated insulin resistance and hyperlipidemia in *ob/ob* [168].

4.3. Cholecystokinin

Cholecystokinin is mainly produced by neuroendocrine secretory cells lining the intestinal lumen. Cholecystokinin peptides exert their action on 2 distinct receptor subtypes: CCK-A (alimentary), now called the CCK1R, which is mostly expressed peripherally; and CCK-B (brain), renamed the CCK2R, which is primarily present in the brain. Cholecystokinin reduces food intake via the parasympathetic nervous system during food ingestion [169] and increases absorption by retarding stomach emptiness. That is achieved through the reduction of the stomach's mobility and the contortion of the gallbladder. Under normal circumstances, CCK triggers the pancreas during the intestinal phase of pancreatic secretion. As demonstrated in animals, CCK central action is catalyzed by serotonin and is associated with the paraventricular nucleus, suggesting that CCK interacts with other food intake modulators. This procedure is followed by a reduction of dopamine and acetylcholine in accumbens as a part of the final feeling of satiety [170]. Elevation of circulating CCK induces an immediate decrease of ghrelin and increase of leptin levels [171].

Although CCK does not cross the blood-brain barrier, central administration of CCK results in a feeling of satiety, indicating that its role is not limited to the peripheral nervous signaling. Recently, it was hypothesized that the activity of CCK in the central nervous system may not be restricted to the increase of IL-1β production in the brain [172]. Animals treated with CCK receptor antagonists had increased levels of serum leptin as well as of the cerebrospinal fluid–plasma leptin ratio, suggesting that CCK might facilitate the passage of leptin through the blood-brain barrier [173].

4.4. Glucose-dependent insulinotropic polypeptide/GLP-1

Glucose-dependent insulinotropic polypeptide (GIP, or gastric inhibitory polypeptide) and GLP-1 are known as the duodenal incretin hormones, possessing insulinotropic activity [174]. Wild-type mice fed with a high-fat diet exhibited both hypersecretion of GIP and extreme visceral and subcutaneous fat deposition with insulin resistance [175]. In contrast, mice lacking the GIP receptor fed with a

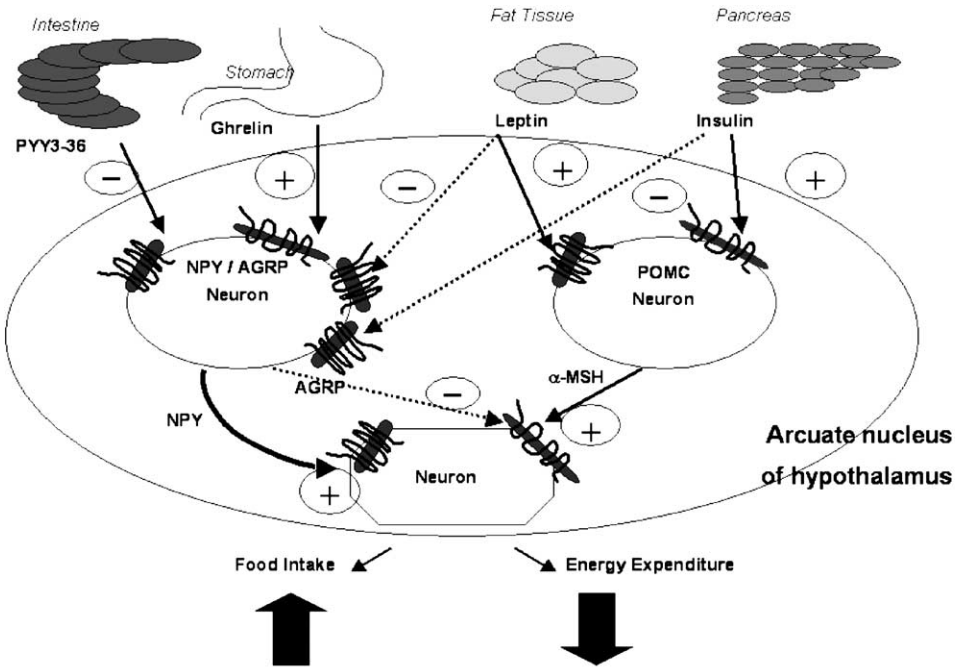

Fig. 2. Hormones and peptides involved in energy homeostasis and their action in hypothalamus. Solid lines indicate net stimulatory effect; dashed lines, net inhibitory effect.

high-fat diet were clearly protected from both the obesity and the insulin resistance. Thus, secretion of GIP by the duodenum, although not impairing the appetite, certainly links overnutrition to obesity [175].

Although glucose is the main regulator of GIP secretion, GIP-producing cells are modified by various secretagogue factors by means of a complicated mechanism [176]. A recent study reported that significantly enhanced incretin responses occurred in all examined subjects during a large meal test vs a small meal, irrespective of their glucose metabolism and body weight [177], suggesting that large meals could probably improve the beta-cell sensitivity to glucose in obese subjects and possibly also in type 2 diabetic patients. Glucose-dependent insulinotropic polypeptide is released postprandially into the circulation in response to feeding, stimulating insulin secretion; however, its short biological half-life detracts from GIP's suitability as a potential therapeutic agent for the treatment of type 2 diabetes.

It has been reported that GLP-1 responses were highest after a meal rich in olive oil in patients with type 2 diabetes, which may indicate a relation between fatty acid composition, incretin responses, and triacylglycerol metabolism postprandially [178]. Remarkable elevation of postprandial GLP-1 concentration was described in obese type 2 diabetic subjects after therapy with a second-generation α-glucosidase inhibitor (miglitol) [179]. This fact indicates that GLP-1 might play a role in mediating satiety and thus stabilizing body weight in obese type 2 diabetic patients. Of note, central intracerebroventricular injection of GLP-1 powerfully inhibits feeding in rodents [174].

Current scientific interest is focused on the construction of stable GIP analogs to circumvent the rapid degradation caused by the ubiquitous enzyme dipeptidylpeptidase IV, and preliminary results are promising [180-182].

5. Discussion

Several authors have excellently reviewed the environmental and cognitive factors that overpower homeostatic regulation [183] whereas others have focused on the hypothalamic neuropeptides involved in the food intake and body weight regulation [184]. In the present review, we try to summarize the role of several anorexigenic and orexigenic (both central and peripheral) neuropeptides on food intake and their integration with the homeostatic regulatory system.

Although experimental findings concerning several neuropeptides within the last decade are indisputably a great step forward in the understanding of the pathophysiology of obesity, many pieces of the puzzle are still missing

Table 1
Currently available antiobesity drugs

Drug name	Mechanism of action	Side effects
Orlistat	Decrease in fat absorption due to the inhibition of pancreatic lipase	Decrease in absorption of fat-soluble vitamins, soft stools, increase defecation, oily discharge
Sibutramine	Inhibition of norepinephrine, dopamine, and serotonin reuptake	Increase in heart rate and blood pressure, insomnia, headache

Table 2
Potential targets for the development of antiobesity drugs in the future

Agonists	Antagonists
GLP-1	Endocannabinoid receptor
Insulin mimetics and sensitizers	Fatty acid synthesis inhibitors
Leptin analogues and sensitizers	Ghrelin
MC4R agonists	MCH receptor
Dopaminergic, noradrenergic, serotonergic agents	NPY receptor

Data are limited primarily to the pathways described in the text.

(Fig. 2). The great variety of transgenic manipulations that alter energy balance suggests that there are many potential targets for antiobesity drugs. The difficulty is to determine which of these are most likely to lead to useful therapies. Although important data have been added to our knowledge from experiments in transgenic mice, no antiobesity drug that was rationally targeted to a specific protein has ever reached the marketplace. To date, only 2 medications—sibutramine and orlistat—have been approved for long-term use in the treatment of obesity; however, these currently available treatment approaches are inadequate and show little potential for future management of obesity (Table 1). As with research in other chronic diseases, progress in obesity research has mainly resulted from empiric observations, and the most effective treatment is surgical. Initial treatment should focus on lifestyle modifications—dietary interventions and increased physical activity—with behavioral modification strategies used adjunctively. For severely obese patients with significant medical comorbidities or physical conditions, 2 surgical procedures may be considered: vertical banded gastroplasty and gastric bypass.

Anorectic drugs (which enhance serotonergic and noradrenergic transmission) may work mainly through hypothalamic actions, as does recombinant leptin; therefore, it is possible that these drugs would not act to full effect in the presence of hypothalamic damage. Lipase inhibitors require dietary adherence and are therefore unlikely to have a useful role in the presence of hyperphagia or behavioral disturbance, unless the patient is under constant supervision. Several other drugs currently approved for other uses show promise in their ability to cause weight loss. If the medications presently available for the treatment of obesity are not optimal, the ideal obesity medication needs to be defined. Because visceral obesity and its close association with diabetes, hypertension, and hyperlipidemia carries a greater mortality risk than generalized increases in body fat, the ideal obesity medication would reduce body fat with a preferential loss of visceral fat, while preserving lean tissue, and would be well tolerated. This ideal drug should work through a downstream regulator of the physiological mechanisms controlling body weight by altering eating habits (ie, hyperphagia) but without altering the other behavioral characteristics of each individual.

There are few reports describing significant linkage of BMI with markers on the X chromosome, but the clinical extent of this potential association and the biological mechanism underlying it need to be clarified. The sex-specific component in the predisposition to obesity and genetic heterogeneity are the main factors inhibiting identification of a susceptibility gene for obesity [185]. Current investigational direction is focused on the effort to isolate more genes that can predispose people to obesity, offering new targets for drug intervention in the future. Although each new signaling pathway discovered in the hypothalamus is a potential target for drug development in the treatment of obesity, the growing number of such signaling molecules indicates a highly complex process that controls food intake (Table 2). Dramatic increase in our knowledge regarding gene-related obesity is mainly based on experimental studies. The identification of potential gene-to-gene interactions in this field seems to be one of the greatest scientific challenges at present. However, steps may be slow because this process will be even more difficult in humans who have greater genetic variability. Consequently, we believe that research should focus on deciphering the molecular basis of the system, and that could be followed by application of this understanding to treatment targets. Because research in obesity tends to move toward physiological observations and molecular approaches and away from the present reliance on empiric observations, defining advanced clinical end points (eg, measurement of visceral fat or assessment, or energy expenditure) will become ever more important.

Conclusively, lessons from “knockout” models demonstrate that some individuals may have a different genetic predisposition to obesity and become overweight without remarkable hyperphagia mainly due to a decrease in metabolic rate. However, the standard in the majority of obese subjects is the imbalance between energy intake and energy expenditure, closely correlated with psychosocial factors (lifestyle).

Behavioral modification to improve diet and increase physical activity continues to be the cornerstone of obesity treatment. It seems essential to view weight loss as a basic modality for improvement in health, and the optimal goal of obesity treatment should be reduction in comorbidity rather than merely cosmetic management.

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