Obesity: Pathophysiology and Clinical Management

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Abstract: Obesity is a serious socioeconomic, and also increasingly clinical problem. Between ¼-½ of population in the developed countries can be classified as obese. Four major etiological factors for development of obesity are genetic determinants, environmental factors, food intake and exercise. Obesity increases the risk of the development of various pathologic conditions including: insulin-resistant diabetes mellitus, cardiovascular disease, non-alcoholic fatty liver disease, endocrine problems, and certain forms of cancer. Thus, obesity is a negative prognostic factor for longevity. In this review we provide broad overview of pathophysiology of obesity we also discuss various a available, and experimental therapeutic methods. We also highlight functions of adipocytes including fat storing capacity and secretory activity resulting in numerous endocrine effects like leptin, IL-6, adiponectin, and resistin. The anti-obesity drugs are classified according to their primary action on energy balance. Major classes of these drugs are: appetite suppressants, inhibitors of fat absorption (i.e. orlistat), stimulators of thermogenesis and stimulators of fat mobilization. The appetite suppressants are further divided into noradrenergic agents, (i.e. phentermine, phenidimetrazine, benzphetamine, diethylpropion), serotoninergic agents (i.e. dexfenfluramine), and mixed noradrenergic-serotoninergic agents (i.e. sibutramine). Thus, we highlight recent advances in the understanding of the central neural control of energy balance, current treatment strategies for obesity and the most promising targets for the development of novel anti-obesity drugs.

Keywords: BMI, BVT.933, growth hormone, TNF, PRDM16.

INTRODUCTION

Obesity is a chronic disease that is increasing in prevalence since 1980 in the United States and other parts of the Western World. It poses a serious risk for the development of diabetes mellitus along with insulin resistance, cardiovascular disease, non-cholesterol fatty liver disease, and certain forms of cancer, modestly increasing the risk of overall mortality. Obesity varies by age and sex, and by race-ethnic group. In 2003-2004, 32.9% of adults 20-74 years old were obese and more than 17% of teenagers (age, 12-19 years) of North America were overweight [1].

The most widely used formula for relating the height and weight of an individual is body mass index (BMI). BMI is defined as a ratio of weight (kilograms) and height² (square meters) [2]. A BMI between 20-25 kg/m² is normal and associated with low mortality, whereas a BMI of 25-30 kg/m² is considered overweight. In adults a BMI above 30-40 kg/m² is defined as obesity and BMI above 40 kg/m² is severe obesity. Among the children and adolescent population with a BMI above the 95th percentile for age belong to the obese group [3]. However, BMI does not discriminate between muscle and adipose tissue and does not directly assess regional adiposity [4]. S tall, BMI primarily due to its simplicity often serves a guide in treatment selection.

Regional fat distribution has profound influence on health risks. In general, measures of fat distribution such as waist to hip ratio suggests a predisposition to developing some of these forms of obesity. A ratio above 1.0 in male subjects and a bove 0.6 in women suggests a higher risk. BMI in children and adolescents is influenced by body age and sex, and the offspring of two parents of normal weight. In addition, obesity is strongly conditioned by available food and sedentary lifestyle [6,7].

Male (android) or visceral obesity is closely associated with metabolic complications such as hypertension, insulin resistance, hyperuricemia, and dyslipoproteinemia. The t ypical female or gynoid obesity, with fat deposited in hips, femoral and gluteal regions, has much less effect on health outcomes. The waist-to-hip ratio is higher in obese individuals. Generally, 1.0 in male and 0.8 in female is considered a normal waist-to-hip ratio. BMI over 30 is defined as obesity, BMI over 40 kg/m² is severe obesity. Among the children and adolescent population with a BMI above the 95th percentile for age belong to the obese group [3]. However, BMI does not discriminate between muscle and adipose tissue and does not directly assess regional adiposity [4]. Therefore, BMI primarily due to its simplicity often serves as a guide in treatment selection.

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Treatment of obesity should be undertaken with a clear understanding of the realities of the problem and its outcomes. B oth, obese sity and hi gh vi sceral fa t increase he alth risks e ven whe n t otal body we ight and fa t are not sig nifi- cantly elevated. Weight regain is c ommon in obe sity upon discontinuation of any treatment. Failure of diet and exercise in the long-term treatment of obesity is quick frequent and creates an obvious need for pharma therapy [8]. The regulation of energy uptake and expenditure are controlled by complex systems, thus an improved understanding of pathophysiology is a prerequisite for selection of treatment options of obesity.

ENERGY BALANCE IN THE BODY

Fat accounts for 21-37% of the body weight of middle-aged men and women. In case of obese individual more calories are consumed than expended and appetite does not
subsequently reduced to compensate for the increase in energy stores (Fig. 1). The amount of adipose tissue is tightly regulated through neural and humoral signals transmitted to the brain. Failure of fat cells to send adequate signals or failure of the brain to respond to appropriate signals causes obesity [9]. An effective system for the regulation of energy balance requires sensors of energy stores in adipose tissue, mechanisms of relay of information to central control sites (hypothalamus) for subsequent integration, which in turn will determine food intake and energy expenditure [10].

Genetic experiments on animal models helped to understand the regulation of fat metabolism. Mice become obese due to mutations of at least 5 identified genes – the ob (obesity) gene encoding leptin [11], the db (diabetes) gene, agouti yellow, tubby, and fat genes. Homozygosity for mutant forms of ob or db genes produces the following phenotype: these mice eat excessively and have low energy expenditure, they become grossly fat and suffer from numerous metabolic abnormalities, including hyperglycemia, hyperinsulinemia, hypothermia, decreased thyroid hormone and reduced reproductive function.

Leptin is a peptide hormone that provides signals to the brain about the amount of fat stores and is secreted mainly by the adipose tissue [12]. Leptin is found in the blood of normal mice but not of genetically obese ob/ob mice. If recombinant leptin is injected into the third or the lateral ventricle of the ob/ob mouse, it reduces food intake and weight gain, acting on neural networks of the brain involved in the control of food intake and energy expenditure. In addition, leptin increases the level of activity in the recipient mice, normalizes body temperature and restores reproductive function (Fig. 2). Leptin mRNA is expressed exclusively in fat cells. The concentration of leptin in the circulation is proportional to fat stores and BMI in normal subjects, and its secretion is pulsatile and inversely related to hydrocortisone levels [13]. The generation of leptin is enhanced by glucocorticoids, estrogens and insulin and is reduced by β-adrenergic agonists [14]. From fat storage sites leptin reaches the brain and enters by saturable transport to hypothalamus.

In contrast to leptin, the leptin receptor is found in several forms. The leptin receptor, OB-R, is the product of the ob gene and it belongs to the class I cytokine receptor family. At least six OB-R splice variants have been identified. The most abundant one has the longest cytoplasmic tail, and it interacts with the Jak/Stat (Janus Kinase – Signal Transducer and Activator of Transcription) signaling pathway. The long form leptin receptor belongs to the cytokine receptor superfamily. This pathway is essential for the regulation of energy homeostasis by leptin but not for the leptin-dependent control of reproductive function and glucose homeostasis [15]. Activation of PI3-K/Akt pathway as well as the downstream mTOR pathway as well as downstream mTOR pathway is involved in the control of a substrate and weight loss by leptin [16, 17]. The shortest variant of the receptor encodes a soluble form that lacks the intracellular and trans-membrane domains [12]. Weight gain is not suppressed in a db/db mouse by parabiosis with a lean mouse or by leptin injections; this suggests that these mice are defective in the response to leptin as a result of mutation in the leptin receptor [18].

Mutations in leptin and in leptin receptor have been described at least in some obese patients. Since large populations of obese individuals have normal leptin and OB-R

![Fig. (1). Energy balance and etiology of obesity.](image-url)
genes, likely obesity has multiple causes, including environmental factors and a association of alleles of various genes implicated in the regulation of energy metabolism [12].

Among other targets, in the brain, leptin acts on neurons within arcuate nucleus of hypothalamus and signals them to reduce neuropeptide Y (NPY) production [19]. Food deprivation enhances production of NPY by the hypothalamus. NPY stimulates food intake and decreases sympathetic outflow, and through these ways lowers energy expenditure. It also promotes storage and synthesis of fat by an action on lipoprotein lipase in adipose tissue [14]. Although NPY is an important component of the response, its absence can be compensated by other mechanisms.

Leptin acts on other important targets: it increases gene expression of corticotropin-releasing factor (CRF) in the hypothalamus, which reduces food intake [18]. The action of melanocortin-stimulating hormone (MSH) may also be necessary for the response to leptin [11]. Orexins and other mediators produce ed in the hypothalamus act in central feedback mechanisms that regulate feeding behavior [20]. Food intake and energy expenditure will finally determine the weight of an individual.

Food intake is regulated by at least four processes: olfactory and gustatory factors, gastrointestinal distension, release of gastrointestinal hormones such as insulin, cholecystokinin (CCK) and gastrin-releasing peptide and activation of sympathetic components of the efferent sympathetic nervous system (SNS) [20, 21]. Most important hormones related to obesity are insulin and cholecystokinin. Serum insulin level is proportional to the mass of adipose tissue. It stimulates leptin release from fat cells and working centrally decreases food intake by affecting actions of CCK and NPY. However, the main action of insulin is to increase food uptake by decreasing blood glucose. CCK is a peptide secreted by duodenal in the presence of food. When it acts on CCK-A receptor in the gastrointestinal tract, it decreases food intake. Circulating CCK does not cross the blood-brain barrier, but the peptide synthesized in the brain acts on CCK-B receptors and functions as a satiety factor.

The appetite-inducing hormone ‘ghrelin’ is derived from its prohormone proghrelin by posttranslational processing. The presence of another peptide hormone called ‘obestatin’ was initially pre dicted on basis of the bioinformatics data and later isolated from rat stomach. Ghrelin is a ligand for growth hormone secretagogue receptor and it is synthesized in stomach [22, 23]. Interestingly, both ghrelin and obestatin are biosynthesized from the same precursor protein but possess opposing biological properties [24]. For instance injections of ghrelin stimulate feeding in mice, whereas injections of obestatin inhibit it. Similarly, ghrelin increases gastric emptying but obestatin slows it down. Ghrelin regulates the pituitary hormone axis, metabolism of carbohydrates and different functions of the kidney, heart, adipose tissue, pancreas, and gonads as well [25]. Chronic ghrelin administration increases food intake in addition to decrease in energy expenditure. These effects lead to weight gain and possible development of obesity. In contrast obestatin seems to work as a norexie hormone and thus prevent weight gain [26]. Ghrelin and obestatin differ in their effects on growth hormone axis. This fact underscores the importance of their posttranslational modification [24].
Energy expenditure is determined by physical activity, metabolic rate, and thermogenesis. Tissue fat metabolism includes carbohydrate-respiratory work, the maintenance of ions on gradients, and other enzymatic activities. Physical activity increases energy expenditure by working skeletal muscle in a dition to all a bove-mentioned factors. The SNS affects only skeletal muscle and cardiovascular system but also thermogenesis [27]. Brown fat is specialized in adaptive thermogenesis. Its thermogenic capacity is possible through the expression of the uncoupling protein-1 (UCP-1), which uncouples oxidative phosphorylation from electron transport through mitochon drial respiratory chain [28]. Brown fat cells are rich in mitochondria, and produce more heat and less ATP than white fat cells. UCP-2 occurs in both brown and white fat and is upregulated if mice are fed a high-fat diet. In humans, fat cells express the product of a gene similar to the mouse gene for UCP-2. Infants and children have much more brown fat than adults, it has extensive sympathetic innervation. It is at ists produced through the action of norepinephrine. Insulin signaling in the adipocytes, 

ADIPOSE TISSUE AND ITS PHYSIOLOGY

Physiological Features of White Adipose Tissue Innervations

The fat cell is under multiple influences that include the action of norepinephrine (F. Fig. 2). In the white fat cell, a decrease in sympathetic nerve terminals, whereas adrenal medulla secretes adrenaline. The major pathways regulating lipolysis are adrenergic. In human fat, both β1 and β2 stimulate cAMP production by activation of protein kinase A (PKA) leading to phosphorylation of perilipin and hormone-sensitive lipase (HSL), and promotion of lipolysis [29]. In human fat cells, large numbers of β2 adrenergic receptors, their stimulation inhibits cAMP production and lipolysis. Rodents possess β2 adrenergic receptors in the white fat cells, whereas in human fat cells, the role of β3 ARs is unclear.

Differences exist in the adrenergic regulation of lipolysis in adipose tissues from different subjects in normal-weight subjects and in obese subjects. The lipolytic response of isolated fat cells to β2 adrenergic agonists is waker in subcutaneous (abdominal/femoral) than in visceral adipose tissue [30]. One possible explanation includes desensitization of β2 adrenergic receptors with β2 reduced, or β2 A R s or β2 on increased α2 A R s and β2 AR s. Alterations in expression and function of HS L or other interacting proteins like adipocyte lipid-binding protein (ALBP) may also explain these site-related regional differences in lipolysis [31].

Reduced lipid mobilization occurs during exercise in subcutaneous fat of obese subjects [32]. Functional changes in α2, β1, and β2 adrenergic receptors balance with the extent of the fat mass and are related to fat cell hypertrophy. Hypertrophic subcutaneous fat cells (abdominal, femoral) are least responsive to the lipolytic action of catecholamins, they exhibit the highest amount of α1 AR s and the lowest amount of β1 and β2 AR s. Inc reased expression of T he form er w ith concomitant decrease of T he latter i n hypertrophied fat cells could be a physiological adaptation leading to a reduction of the lipolytic responsiveness of the hypertrophied adipocytes [33]. Limitation of basal and SNS-dependent lipolysis avoids excessive non-e sterified fatty acids (NEFA) release from m some fat depots.

The “buffering” effect of NEFA by adipose tissue is an important phenomenon. When NEFA buffering capacity is inadequate, other stressors are exposed to elevated NEFA concentrations [34]. Profound unresponsiveness of the subcutaneous adipose tissue to lipolysis by norepinephrine has been described in obese subjects [35]. β2 adrenergic -mediated increases in thermogenesis and lipid oxidation are impaired in obese individuals [36]. Oophorizations in n the coding and non-coding sequences in the human β3-AR gene could be of major importance for obesity, exercise expenditure, and β3-AR regulation of lipolysis. Full β3-AR-mediated lipolytic response disturbs the normal functional balance between β3-AR and β2-AR. A β3-adrenergic defect could be sufficient to alter normal β-adrenergic responsiveness. Besides, in humans, fat cell, a new redunction in β2-AR mediated lipolytic response disturbs the normal functional balance between β2-AR and β3-AR. A β2-adrenergic defect is sufficient to alter normal β-adrenergic responsiveness. Be sides, in human fat cell, a ny re duction in β2-AR mediated lipolytic response disturbs the normal functional balance between β2-AR and β3-AR. A β2-adrenergic defect is sufficient to alter normal β-adrenergic responsiveness. 

Insulin Signaling in the Adipocytes

Insulin plays a major role in the regulation of adipose tissue development and function. Insulin signaling in the adipocytes is an important phenomenon. When NEFA buffering capacity is inadequate, other stressors are exposed to elevated NEFA concentrations [34]. Profound unresponsiveness of the subcutaneous adipose tissue to lipolysis by norepinephrine has been described in obese subjects [35]. β2 adrenergic -mediated increases in thermogenesis and lipid oxidation are impaired in obese individuals [36]. Oophorizations in n the coding and non-coding sequences in the human β3-AR gene could be of major importance for obesity, exercise expenditure, and β3-AR regulation of lipolysis. Full β3-AR-mediated lipolytic response disturbs the normal functional balance between β3-AR and β2-AR. A β3-adrenergic defect is sufficient to alter normal β-adrenergic responsiveness. Besides, in humans, fat cell, a new reduction in β2-AR mediated lipolytic response disturbs the normal functional balance between β2-AR and β3-AR. A β2-adrenergic defect is sufficient to alter normal β-adrenergic responsiveness. Be sides, in human fat cell, a ny re duction in β2-AR mediated lipolytic response disturbs the normal functional balance between β2-AR and β3-AR. A β2-adrenergic defect is sufficient to alter normal β-adrenergic responsiveness. 

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species such as NO-/NO' ha ve been propos ed as poten tial regulators of insulin deprivation in rodent and human fat t cells [41]. Cachexia-inducing tumors produce a lipid-mobilizing factor (LMF), and induction of Lipoysis by L. MF w as a s sociated with increased levels of in tracellular cAMP [42]. Z AG is a new a dipose ti ssue that meditates in sulin-sensitizing ef fect o f exercise, s ome an ti-acid oxidation during m uscle contraction and represses ke y phosphate activated prot ein ki nase (A MPK) that increases fa tty nemia is closely linked to impaired vasoreactivity and endo- modulation of lipoysis in adipocytes. Z inc-α2-glycoprotein (ZAG) an d tu mor r elated L MF w ere d e etected in m ajor f at deposits i n m ice. Z AG e xpression a nd r elated w a s a l so found in h um an fat c e lls [42]. Various horm ones and a uta- coids are known to negatively control adenyl cyclase acti vity and inhibit cAMP production and lipolysis in fat cells. In addition, the simulation of 1st eptin s excretion was observed with va rio us a gonists (A1-adenosine, α2-AR, a nd NP Y-Y1 receptor agonists) [33].

**Functional Roles of Adipocytes**

Adipocytes allow surplus energy to be stored as triacyl- glycerol (TAG) during caloric abundance for retrieval during periods of food shortage or calorie debt. NEFAs appear as a result of lipolysis of TAG stores; they are released into circulation and are oxidized in skeletal muscle to provide energy. Under normal conditions, there is fine-tuning between TAG's synthesis and lipolysis. A number of adipocytes c could limit an abnormal increase in plasma NEFAs that is considered an important etiological factor in the initiation of insulin resistance in skeletal muscle. NEFAs are elevated in obese and represent a risk factor for the development of type 2 diabetes [43].

Another important function of adipocytes is their complex secretory activity. A number of peptide hormones and pro-inflammatory cytokines (adipokines) are secreted by the adipocytes exerting numerous endocrine effects. Among them is the previously mentioned leptin, which derives from subcutaneous fat depots. Adipocytes size and anatomical location appear to be the major determinants of leptin mRNA expression. *In vivo*, overfeeding and obesity, glucocorticoids treatment, glucose, and insulin administration increase circulating leptin levels. Therefore, the adipose tissue is a site of leptin secretion and leptin receptor dysfunction in mice, it was thought that this cytokine might be involved in the development of type 2 diabetes [44].

An important secretory product of the adipocytes is Interleukin-6 (IL-6). Plasma IL-6 concentration is increased in obese subjects and correlates with fat mass and BMI. High levels of IL-6 are found in type 2 diabetes and correlate with fasting insulin levels. In obese subjects, adipose tissue IL-6 secretion is decreased in obese subjects. A post-treatment lipid-mobilizing contribution of the cytokine [45].

Adiponectin is a new adipocyte-derived insulin-sensitizing hormone, which is secreted in high concentrations in the serum. Adiponectin concentrations are reduced in a variety of obesity and insulin-resistant states [46]. Hypoadiponecti nemia is closely linked to impaired vasoreactivity and endothelial dysfunction in humans. Adiponectin may play a protective role against atherosclerosis and insulin resistance [47]. Adiponectin effects are mediated by a denosine monophosphate activated protein kinase (AMPK) that augments fatty acid oxidation during muscle contraction and represses key enzymes of gluconeogenesis in the liver. AMPK also mediates in insulin-sensitizing effects of exercise, ome an ti-diabetic actions of metformin, and leptin action on skeletal muscle [48]. Unlikely, the role of adiponectin in mouse models of obesity and decreased after peroxisome proliferator-activated receptor γ (PPARγ) treatment. Whit a dipose tissue re-sistine mRNA expression and serum protein levels dropped during fasting and increased during re-feeding [49]. The role of resistin in human insulin resistance remains quite controversial [33].

Resistin is a 10-kDa adipocyte-secreted protein that possesses hormonal properties that have been claimed to represent an important link between obesity and insulin resistance [33]. In mice, resistin administration caused glucose intolerance and increased insulin resistance. In adaption, resistin levels of resistin were higher in mouse models of obesity and decreased after peroxisome proliferator-activated receptor γ (PPARγ) treatment. Whit a dipose tissue re-sistine mRNA and serum protein levels dropped during fasting and increased during re-feeding [49]. The role of resistin in human insulin resistance remains quite controversial [33].

Adipocyte tissue of the obese secretes several pro-inflammatory protei ins such as TNF α and β1, IL-1, IL-6, inducible nitric oxide synthase (iNOS), monocyte chemotactic prote in (MCP-1), proc ougulant plasminogen activator inhibitor-1 (PAI-1), fa ctor Va nd t issue f actor a nd acute phase (s erm amyloid 3, 1-γ-glycoprotein, a nd ni pocain 24p3). TNF α is increased in fa t c e lls in obese subjects and β-adrenergic stimulation is a positive regulator of TNF expression, whereas GH and PPARγ activators suppress its expression. Regulators of TNF production in adipocytes might modulate insulin sensitivity via this cytokine [33].

Two recent studies have led to a major breakthrough in the understanding of the origin and the role of TNF and other cytokines in obesity [50, 51]. They have shown that macrophages accumulate in the adipose tissue of obese subjects and human adipose tissue. Macrophage accumulation occurs in proportion to adipocyte size and it increases the catabolic capacity for production of pro-inflammatory and acute phase molecules that contribute to obesity-related disorders. Thus, the adipose tissue secretes macrophages and could be largely responsible for the major part of adipose tissue TNF, IL-1, IL-6, MCP-1, and iNOS expression. Release of macrophage TNF and IL-6 may contribute to the chronic increase in insulin sensitivity of fat cells and to all other re-lated disturbances [52].

**PATHOGENESIS AND ETIOLOGY OF OBESITY**

**Obesity as a Disorder of the Homeostatic Control of Energy Balance**

Although it is known that a disturbance of the homeostatic mechanisms controlling energy balance causes obesity, it is less clear how the balance is disturbed, since the mechanisms are very complex and involve numerous systems in the body. Soon after the first demonstration of leptin deficiency and leptin receptor dysfunction in mice, it was thought that alterations in leptin kinetics might provide a simple explanation of how energy balance was disturbed in obese subjects. But most of the information on leptin was derived from rodent experiments. Plasma leptin is higher in obese subjects compared with normal weight individuals. In fact, leptin concentrations are proportional to body fat mass in both obese and lean subjects [53]. Thus, obesity is not due to the deficiency
in circulating leptin. Resistance to leptin might be one of factors in development of obe sity. Such resistance could be at the level of carriage of leptin in the circulation or its transport into the central nervous system (CNS) [54]. Defects in the leptin receptor (as in ob/ob mice) or in the transducing system – decreased expression of CRF or overexpression of NPY – could re-present the hereditary susceptibility. The gene for UCP in white adipose tissue is responsible for the obesity in the "db/db" mouse, which is phenotypically similar to the "ob/ob" mouse. The gene effect called tub is expressed in skeletal muscle and has a synergistic action with another transcription factor C/EBPα to promote conversion of pre-adipocytes to adipocytes. The gene for UCP3 is preferentially expressed in adipose tissue and has a synergistic action with another transcription factor C/EBPα to promote conversion of pre-adipocytes to adipocytes. The gene for UCP3 is preferentially expressed in adipose tissue and has a synergistic action with another transcription factor C/EBPα to promote conversion of pre-adipocytes to adipocytes.

**Genetics and Obesity**

Genetic determinants can either play a major role in the pathogenesis of obesity or enhance susceptibility to it. The dysmorphic forms of obesity in which genetic factors are responsible for the obesity in the "db/db" mouse. The gene is phenotypically similar to the "ob/ob" mouse. The gene effect called tub is expressed in skeletal muscle and has a synergistic action with another transcription factor C/EBPα to promote conversion of pre-adipocytes to adipocytes. The gene for UCP3 is preferentially expressed in adipose tissue and has a synergistic action with another transcription factor C/EBPα to promote conversion of pre-adipocytes to adipocytes.

**Environmental Factors and Obesity**

Environmental factors interact with genetic susceptibility in the pathogenesis of obesity. For example, hypothalamic injury from trauma or surgery and destructive lesions in the region of the ventromedial or the paraventricular nuclei can produce obesity. The two major factors in human obesity are hyperphagia and a disturbance in the ANS activity. One explanation for this is the increased secretion of NP Y, which is produced in the arcuate nucleus and stimulates eating [62]. Other possible explanations are impaired reproductivity of dopamine, decreased release of 5-HT, and increased or decreased sensitivity of the NPY system.

**Food Intake and Obesity**

A typical obese subject has usually put on 20 kg over 10 years. This means that there has been a daily excess of energy input over output of 30-40 kcal initially, increasing gradually to maintain the increased body weight. The type of food eaten can play a role in disturbing the energy balance. Fat has more calories per gram compared to carbohydrates or proteins. In the obese, there are 9 calories per gram of fat, whereas the leptin-releasing hormone (CRF) has no caloric value of carbohydrates and proteins is only 4 calories. It is possible that the mechanisms regulating appetite are more sensitive to fat than to protein and carbohydate, so satiety systems come into the picture too late. Increase in density of foods, port ion size, better palatability of food, so satiety systems come into the picture too late. Increase in density of foods, portion size, better palatability of food, so satiety systems come into the picture too late.

**Physical Activity and Obesity**

Physical activity can be broadly divided into exercise and non-exercise activities. Non-exercise activities include employment-related work and the activity of daily living. It is difficult to measure the energy expended in non-exercise activity. In general, an increase in sedentary behavior, and a decrease in activity of daily living and employment physical activity promotes obesity [68]. It is now recognized that increased energy expenditure by physical activity has a more positive effect on energy balance.
positive role in reducing fat stores and adjusting energy balance in the obese, especially when combined with modification of the diet. Native population study gives an example. Many years ago, a tribe of Pima Indians was divided into two groups: one of them settled in Mexico and continued with simple life, eating frugally and spending most of the time in hard physical work. They are usually lean and have low incidence of NIDDM. Another group moved to the USA—an environment with easy access to calorie rich food and less need for hard physical work. They are on average 57 pounds heavier than the Mexican group and have a higher incidence of early onset NIDDM [69, 70].

PHARMACOTHERAPY OF OBESITY

Obesity results from an imbalance between energy uptake and energy expenditure [7, 66, 68]. Obesity is a particularly challenging medical condition because of its complex etiology (Fig. 3). The environmental factors can be modulated through behavioral changes such as healthy eating and physical activity, whereas biological components are much more difficult to address [71]. The history of treatment of obesity is marked by limited but long lasting success, rebound recovery of weight after cessation of treatment, and some therapeutic disasters. Cure of obesity is rare and obesity is not a single entity. Still, palliation of obesity related disorders remain a realistic clinical goal. Overweight patients exhibit symptoms of the metabolic syndrome that includes type 2 diabetes, hypertension, and dyslipidaemias [33]. Failure of diet and exercise in the long-term treatment of obesity is common and creates an obvious need for concomitant pharmacotherapy. Drug treatment is recommended for subjects with a BMI more than 30 kg/m² and thus at medical risk from obesity, and if given at all, should be used only as an adjunct behavioral and lifestyle changes. Characterization of obesity—associated genes revealed new biochemical pathways and molecular targets for pharmacological intervention, which will likely lead to new treatments [71].

Anti-obesity drugs can be classified according to their primary mechanism of action on energy balance. There are four general classes of anti-obesity drugs. The first group comprises drugs, which suppress appetite through reducing hunger perception, increasing the feeling of satiety, and reducing food intake by acting in the CNS. As a result these drugs facilitate compliance of the patient with caloric restriction. The second group—inhibitors of fat absorption—reduce energy intake through a peripheral gastrointestinal mechanism of action. The third group of drugs also acting peripherally increases thermogenesis without planned physical activity. The last group of drugs stimulates fat mobilization acting peripherally to decrease triglyceride synthesis without planned increases in physical activity or decrease in food intake. Importantly, the benefit of all four groups can be overcome by decreased voluntarily

<table>
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<tr>
<th>Strategy in the Treatment of Obesity</th>
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<tr>
<td><strong>Nonpharmacological treatment ≥ 6 months</strong></td>
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<tr>
<td>Satisfactory response</td>
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<tr>
<td>Continue</td>
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<tr>
<td>Consider pharmacotherapy</td>
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<td>≥ 2 kg/first 4 weeks</td>
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<td>Good response</td>
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<td>Maintain weight with pharmacotherapy, diet and exercise</td>
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Fig. (3). Various approaches to treat obesity. Obesity is one of the more difficult to treat clinical conditions. The details of this flow-chart are discussed in details in the text.
physical activity or increased consumption of calorie dense food [71].

Nowadays the only drugs approved for use are a small set of centrally acting appetite suppressors that reduce food intake by modulating concentrations of monoamines norepinephrine (serotonin and/or norepinephrine) and norepinephrine in the central nervous system. Amphetamines are no longer recommended and not approved for use because of the addictive potential of these agents. Benzphetamine and phendimetrazine belong to Schedule III according to the Drug Enforcement Administration (DEA). This means that these agents have moderate abuse and dependence potential compared to Schedule IV agents, which have low addictive potential. Both Schedule III and Schedule IV agents need prescription due to their addictive properties [72, 73]. Studies concerning safety and efficacy of these drugs show a consistent but moderate difference in weight loss in comparison with placebo. Side effects of medications that inhibit reuptake of norepinephrine include insomnia, euphoria, dry mouth, constipation, palpitations, and hypertension [74, 75]. These medications are contraindicated in individuals with hypertension, advanced cardiovascular disease, obesity, or those who have a history of cardiac valve dysfunction [78]. It is approved by the FDA for weight loss in adults with a history of abdominal obesity and maintenance of weight loss in adults with type 2 diabetes. However, these drugs have a small number of dropouts in both the study and control group, and generalization is problematic [79].

Appetite Suppressants

Noradrenergic Agents

Noradrenergic drugs available in the USA include phenetermine, phendimetrazine, benzphetamine, and diethylpropion. They inhibit norepinephrine reuptake in the central nervous system. Amphetamines are no longer recommended and not approved for use because of the addictive potential of these agents. Benzphetamine and phendimetrazine belong to Schedule III according to the Drug Enforcement Administration (DEA). This means that these agents have moderate abuse and dependence potential compared to Schedule IV agents, which have low addictive potential. Both Schedule III and Schedule IV agents need prescription due to their addictive properties [72, 73]. Studies concerning safety and efficacy of these drugs show a consistent but moderate difference in weight loss in comparison with placebo. Side effects of medications that inhibit reuptake of norepinephrine include insomnia, euphoria, dry mouth, constipation, palpitations, and hypertension [74, 75]. These medications are contraindicated in individuals with hypertension, advanced cardiovascular disease, obesity, or those who have a history of cardiac valve dysfunction [78]. It is approved by the FDA for weight loss in adults with a history of abdominal obesity and maintenance of weight loss in adults with type 2 diabetes. However, these drugs have a small number of dropouts in both the study and control group, and generalization is problematic [79].

Serotonergic Agents

Serotonergic agents act by inhibiting reuptake of serotonin, stimulating its release or both. One of these drugs, dexfenfluramine, was approved by the FDA in 1996 on the basis of its low risk/benefit ratio and extensive clinical experience in Europe, although some concerns had been previously raised about the possible risk of pri mary pulmonary hypertension and loss of serotoninergic neurons. Their efficacy was close to the efficacy of noradrenergic drugs [76]. But it was reported that dexfenfluramine alone or in combination with other generation drug fenfluramine or phentermine were associated with heart valvular disease and pulmonary hypertension. Both fenfluramine and dexfenfluramine were withdrawn from the global market in 1997 [72]. Selective serotonin-reuptake inhibitors are approved for indications other than obesity, such as obsessive-compulsive disorders and depression but showed lack of long-term efficacy [77].

Mixed Noradrenergic-Serotonergic Agents

Sibutramine, an inhibitor of both serotonin and norepinephrine reuptake, also weakly inhibits dopamine reuptake [72]. Sibutramine, phentermine, fenfluramine, and several others (Fig. 4) are derivatives of L(-) ephedrine. Unlike fenfluramine and dexfenfluramine it does not cause release of serotonin and has not been associated with development of cardiac valve dysfunction [78]. It is approved by the FDA for weight loss in adults with a history of abdominal obesity and maintenance of weight loss in adults with type 2 diabetes. However, these drugs have a small number of dropouts in both the study and control group, and generalization is problematic [79]. Clinical trials up to two years have been completed and they show that although weight loss was regained during the second year of treatment and follow-up, weight loss was significantly greater in individuals treated with tianeptine compared to placebo. Side effects of sibutramine include increased blood pressure and tachycardia, dry mouth, insomnia, and ad libitum eating. Sibutramine is contraindicated in cases of uncontrolled hypertension, coronary artery disease, congestive heart failure, arrhythmia, or stroke, severe renal or hepatic dysfunction, neuralgia, and drug abuse [72].

Fig. (4). Chemical structures of ephedrine derivatives, that have been tested as appetite suppressors. Ephedrine, an alkaloid originally extracted from Ephedra vulgaris, is a sympathomimetic amine. Its principal mechanism of action is release of norepinephrine and indirect actions on the noradrenergic receptor system, a part of the sympathetic nervous system. The use of its derivatives, especially sibutramine is discussed in the text.
**Cannabinoid Receptor Antagonists**

Cannabinoids have been studied for their appetite-suppressant effect. Their effect on central and peripheral receptors is well characterized. Cannabinoid receptors are found in the brain as well as many peripheral tissues, and CB2 receptors are primarily found in immune system cells. Cannabinoid receptor antagonists block the action of endocannabinoids at their receptors, reducing appetite and weight gain [88, 89].

**Inhibitors of Fat Absorption**

Given the central role of dietary fat in obesity, a logical approach to weight loss is to decrease the amount of fat available to be metabolized. Orlistat is the only FDA approved medication used for treatment of obesity that reduces nutrient absorption. Orlistat belongs to a class of anti-obesity drugs that acts directly and specifically at the site of fat breakdown in the small intestine. Preventing hydrolysis of triglycerides (dietary fat) into absorbable mono-acylglycerols and free fatty acids (FFAs) is the goal of orlistat (Fig. 5). Orlistat inhibits the activity of lipase, the enzyme that mediates fat breakdown in the lumen of the small intestine [80, 83].

The medication taken up to one hour after meal will result in inhibition of lipase enzymes in the gut lumen, resulting in a reduction of dietary fat absorption. Orlistat is the only FDA approved medication used for treatment of obesity that reduces nutrient absorption. Orlistat acts by binding to gastrointestinal lipases in the lumen of the small intestine, preventing hydrolysis of triglycerides (dietary fat) into absorbable mono-acylglycerols and free fatty acids (FFAs) [80, 82].

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Other steps required for the absorption of dietary fat, which involves pro-teins, might represent a valid new strategy in the treatment of obesity. However, lack of DGAT in mice does not show that weight loss following orlistat treatment is due to a sustained weight loss [81].

**Stimulators of Thermogenesis**

Adaptive thermogenesis is observed in cold (non-shivering thermogenesis) and overfeeding (diet-induced thermogenesis). The bioenergetics of mitochondria and the induction of pros in tissues that control the efficiency of oxidative phosphorylation are the key cellular processes of a thermogenic response. Thyroid hormone is not a viable pharmacological anti-obesity approach, since it causes action of orlistat [88, 89]. Although absolute concentrations of vitamins D, E, and β-carotene decrease during orlistat treatment, the co-concentrations remain within the normal range and on a few individuals with low values need supplementation [83]. The latter side effect can be counteracted by administration of a multivitamin at least two hours before or after the dose of orlistat. These results support the potential of orlistat for long-term management of obese patients in combination with an appropriate diet [86].
loss of lean body mass and mobilizes calcium from the bone [93, 94]. In contrast, β3 selective adrenergic agonists have anti-obesity and anti-diabetic effects in rodents and induce brown adipose tissue hypertrophy also in dogs and monkeys [95, 96]. However, it is still controversial whether β3 AR agonists will have a relevant impact on energy expenditure in humans. Highly selective, orally bioavailable β3 AR agonists are now in clinical trials (Table 1) [97, 98].

In adult humans, the major thermogenic tissue is skeletal muscle that, in non-obese individuals, comprises about 40 percent of body weight and accounts for 20-30 percent of the total oxygen consumption at rest. UCP-1 is unique among uncoupling proteins; it has a primary role in norepinephrine-dependent adaptive non-shivering thermogenesis and consequent metabolic inefficiency. Its expression is increased in cold exposure as well as overfeeding and decreased in fasting and states of genetic obesity [99]. Proteins highly similar to UCP-1 have been recently identified. These proteins are also expressed in tissues other than brown fat. UCP-2 is ubiquitously distributed in the body, so because of high likelihood for undesirable side effects, it is not an appropriate target for anti-obesity drug. UCP-3 is primarily expressed in skeletal muscle in humans, its expression is co related with

Table 1. The Pharmacologic Options of Obesity Treatment

<table>
<thead>
<tr>
<th>Groups</th>
<th>Mechanism of Action</th>
<th>Examples</th>
<th>Indications</th>
<th>Contraindications</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appetite Suppressors</td>
<td>Inhibit norepinephrine release in CNS</td>
<td>Benzphetamine, Phendimetazine</td>
<td>Obesity, weight maintenance</td>
<td>Hypertension, hyperthyroidism, advance cardiovascular disease, glaucoma, agitated states, history of drug abuse [69]</td>
<td>Insomnia, euphoria, dry mouth, constipation, palpitations, hypertension, moderate addictive potential [70-72]</td>
</tr>
<tr>
<td></td>
<td>Inhibit reuptake of serotonin and/or its release</td>
<td>Dexfenfluramine, Fenfluramine</td>
<td>Obesity, weight maintenance, obsessive-compulsive disorder, depression [74]</td>
<td>Heart valvular disease, pulmonary hypertension [69, 74]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Inhibit norepinephrine and serotonin reuptake in CNS</td>
<td>Sibutramine (Meridia, Reductil)</td>
<td>Obesity, weight maintenance [69]</td>
<td>Uncontrolled hypertension, coronary artery disease, congestive heart failure, arrhythmia, stroke, severe renal/hepatic dysfunction, glaucoma, history of drug abuse [69]</td>
<td>Hypertension, tachycardia, dry mouth, insomnia, constipation [77, 138]</td>
</tr>
<tr>
<td>Inhibitors of fat absorption</td>
<td>Bind gastrointestinal lipases</td>
<td>Orlistat (Xenical)</td>
<td>Obesity, weight maintenance [81]</td>
<td>Gastrointestinal side effects, decreased absorption of fat-soluble vitamins [80, 83-86]</td>
<td></td>
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<tr>
<td>New and investigational drugs</td>
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<tr>
<td>Stimulators of thermogenesis</td>
<td>β3 AR agonists</td>
<td>SWR-0342SA [92-94]</td>
<td>Obesity and diabetes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stimulators of fat mobilization</td>
<td>Stimulate the formation of brown adipose tissue</td>
<td>PPARγ ligands, PCG1 [128]</td>
<td>Obesity and diabetes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cannabinoid receptor 1 antagonists</td>
<td>Suppress appetite, increase thermogenesis</td>
<td>Rimonabant (Acomplia), Taranabant</td>
<td>Obesity</td>
<td>Severe psychiatric mood related disorders [77-79]</td>
<td></td>
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<tr>
<td>Other drugs</td>
<td>Increase energy expenditure</td>
<td>Selective inhibitors of PTP1B [124, 125]</td>
<td>Obesity and diabetes</td>
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<tr>
<td></td>
<td>Activate 2C serotonin receptor</td>
<td>BVT 933 [8]</td>
<td>Obesity</td>
<td></td>
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<tr>
<td></td>
<td>Specifically inhibits fatty acid synthase</td>
<td>C75 [8]</td>
<td>Obesity</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Activates leptin pathway, inhibits activity of acetyl coenzyme A carboxylase</td>
<td>Axokine (Ciliary Neurotrophic Factor) [102]</td>
<td>Obesity</td>
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</table>
energy expenditure in Pima Indians, and mutations in gene encoding UCP-3 were identified in some individuals with severe obesity and NIDDM [100]. So its stimulation could provide a safer mechanism to increase thermogenesis in the whole body. Therefore, a phenomenon stimulating UCP-3 activity could result in beneficial effects against obesity and NIDDM [101].

**Stimulators of Fat Mobilization, Modulators of Fat Storage**

Another pos sible anti-obesity approach could be the stimulation of brown adipose tissue formation, either by de novo recruitment from pre-adipocytes or by inter-conversion of white adipocytes. P PARγ li gands are very effective in inducing of U CP1 expression in brown but not i n white adipocytes, which indicates the existence of a brown adipose tissue specific factor. Such a cofactor, P PARγ co-activator-1 (PGC-1) is strongly induced by cold [102]. PGC-1 allows P PARγ to function in the specific context of thermogenesis by allowing the expression of UCP1 and by favoring multiplication of mitochondria. PGC-1 could promote the development of the brown adipocyte phenotype. Thus, it seems that PGC-1 plays a key role in transcriptional programs of a dynamic thermogenesis and this finding could stimulate development of novel anti-obesity drugs [102].

**Calorie Restriction Mimetics**

Perhaps the most studied caloric restriction mimetics (CRM) is resveratrol, a plant-derived polyphenol produced in response to attacking pathogens. The important source of this compound is: roots of Japanese knotweed (Fallopia japonica), skin of red grapes, red wine, peanuts, and mulberry. This polyphenol has been shown to retard the aging process in yeast, nematodes and fruit flies by 70%. The molecular pathway mediating caloric restriction in yeast requires a specific signal transduction. It is believed that resveratrol is a stimulator of SIRTs involved in the regulation of fat metabolism. In particular, the discovery and cloning of the adipocyte-derived hormone leptin and its receptor PPARγ proved to be a major breakthrough. Leptin reflects the lipid content of the total body of a non-fasting person. In disease states such as obesity, insulin resistance, and diabetes, leptin levels are reduced but its sensitivity to insulin is increased [107]. Recent studies have shown that increased dose of resveratrol allowed obese mice to remain on high-calorie diet [108]. Moreover, resveratrol intake protects against radiation-induced development of cancer and cardiovascular diseases [110]. As well as is utilized in treatment of metabolic disorders such as diabetes 2 [111]. Besides the red wine, resveratrol is easily accessible in a supplement form.

Another very important group of CRM are insulin sensitizers wit h metformin at the forefront. This drug is very widely used against pre dominantly obesity-driven type 2 diabetes and cardiovascular diseases [112, 113]. Metformin increases sensitivity of muscle and fat cells but does not increase secretion of insulin. Additionally, metformin is implicated in suppression of endogenous glucose production [116] and its inhibitory effect depends on the AMP-activated protein kinase (AMPK) [117]. Moreover, it has been shown that 2 months treatment with metformin has a significant impact on mi cing the outcome of long-term calorie restriction in mice [118].

Another group of CRM used in treatment of obesity and type 2 diabetes is thiazolinediones that includes rosiglitazone and pioglitazone [119]. These two drugs increase the sensitivity of the cell to insulin by activation of the nuclear receptor PPARγ (see a lso pioglitazone [120]. However, recent studies link thiazolinediones with increased risk of death from cardiovascular causes [120].

Fourth CRM involved in glucose metabolism is 2-deoxy-D-glucose. This molecule is able to keep certain level of blood glucose with e ffects on insulin sensitivity. It was originally developed for the treatment of muscle and fat cells but does not increase secretion of insulin. Problems related to formulation were pain and lipoatrophy at injection sites. Ongoing studies are evaluating the potential for use in treating obesity and diabetes. This drug is used in the treatment of type 2 diabetes and is effective in lowering visceral fat [122].

**Other Investigational and New Drugs**

The major leaps towards the development of more effective anti-obesity drugs have actually led into a better understanding of fat metabolism. In particular, the discovery and cloning of the adipocyte-derived hormone leptin and its receptor PPARγ proved to be major breakthroughs. Leptin reflects the lip e content of the total body of a non-fasting person. In a few children, severe, early-onset obesity has been associated with the inability to produce functional leptin. Therapy of a leptin-deficient girl with recombinant human leptin resulted in a dramatic reduction in body weight (16.4 kg) and changes in body composition [124]. In case of treatment of a dults who have normal levels of leptin and are leptin resistant. Problems related to formulation were pain and lipoatrophy at injection sites. Ongoing studies are evaluating the potential for use in treating obesity and diabetes. This drug is used in the treatment of type 2 diabetes and is effective in lowering visceral fat [122].

A new drug, which is now in phase I clinical trials, is ‘Axokine’. This is an engineered version of ciliary neurotrophic factor. It was originally developed for the treatment of amyotrophic lateral sclerosis. Axokine activates leptin pathway, in addition it does not cause rebound weight gain even in leptin resistant model of obesity because it bypasses compensatory adjustments ensuring the maintenance of body fat homeostasis. A s a r e sult th e e patient is s atisfied w ith l ess food, s o t h e p e rson w ill be p ractically d ieting. A xokine works by hyper-activating the leptin pathway, and turning on
satiety signal. It was demonstrated that leptin, in addition to its role as a satiety factor, also inhibits activity of acetyl coenzyme A carboxylase, thus preventing accumulation of lipids in non-a-dipeose tissues and uptake of fatty acids and uptake of glucose [126].

The protein-tyrosine phosphatase (PTP1B) is another interesting target for obesity drugs. Recent research showed that PTP1B regulates leptin signal transduction, in a way that lowered levels of PTP1B increase energy expenditure and vice versa. In addition it negatively regulates insulin signaling [127]. The problem has been in designing a molecule that specifically inhibits PTP1B. One research group developed an antisense oligonucleotide to selectively block PTP1B expression. This antisense oligonucleotide normalized serum triglyceride and cholesterol concentrations [128]. Antisense technology has an advantage of being able to block the production of protein rather than just inhibiting it once it is produced.

PTP-935 is a selective serotonin reuptake inhibitor (SSRI), which is now in phase II clinical trials. It activates specifically only one, the 2C serotonin receptor. Patients treated with PTP-935 showed statistically a nadc linearly significant weight loss compared with those on placebo. Atty a cidual synthase has also recently received serious attention as a new target of anti-obesity treatment [8]. Specific inhibitor of fatty acid synthase, C75, in obese mice suppresses food intake, reduces body weight, and normalizes obesity-associated hyperglycemia and hyperinsulinemia.

PPAR_2 and PPAR_y receptors (which are expressed widely in tissues and cell types) constitute multiple therapeutic targets for treatment of diabetes and obesity. Ideally, drugs preferentially block the PPAR_y agonist potent actions rather than the PPAR_2 actions. Antisense technology has the potential to induce aneuploidy and tumorigenic dedifferentiation of normal cells.

In view of the multiple metabolic and vascular effects of adiponectin, its expression in adipocytes is associated with its role as a satiety factor, and its potential to induce aneuploidy and tumorigenic deregression of normal cells.

**STRATEGIES FOR USE OF MEDICATIONS IN THE TREATMENT OF OBESITY**

Obesity is a chronic condition, so pharmacotherapy should be initiated with the knowledge that long-term use of pharmacological agents will be most likely needed (Fig. 3). Therefore, the possible risks of long-term medical therapy must be weighed against potential improvements in the patient’s risk of obesity-related disease. In general, the pharmacotherapy should be initiated only in patients whose BMI is at least 30 in the absence of obesity-related medical conditions or BMI of at least 27 and the presence of such conditions. Since efficacy of approved drugs is similar in different groups of anti-obesity drugs, usually the choice is empirical and is based on consideration of underlying medical conditions and contraindications. Non-pharmacological treatment should be considered for obese children and adolescents if their BMI is in the 95th percentile or higher; in these individuals, pharmacotherapy can be instituted for enhancement of weight loss during the period of active weight loss or to prevent weight regain [78]. At present, combinations of anti-obesity drugs are not recommended outside clinical trials [74]. Treatment in children and adolescents can be considered in those patients with BMI in the 95th percentile or higher or if they suffer from obesity-related conditions, which can be treated by weight reduction or use of weight-loss agents. A treatment that is effective and well tolerated in the short term may result in significant weight loss for the first four to six months following initiation of treatment, adherence to the regimen, diet, and exercise can be reassessed and possibly the dose should be adjusted. If there continues to be minimal response to the medication, the clinician should consider discontinuing another medication. Major areas of promise for pharmacotherapy are in enhancing weight maintenance in those who have lost weight. Behavioral modifications combined with pharmacological approach may result in better outcome. In patients without weight loss of at least 2 kg during the first four weeks of treatment, adherence to the regimen, diet, and exercise should be reassessed and possibly the dose should be increased. If there continues to be minimal response to the medication, the clinician should consider discontinuing another medication. The safety and efficacy of orlistat and sibutramine are not determined for children and adolescents, since no standardized clinical trials have been conducted so far for this population [132]. Further studies are needed to evaluate the safety and efficacy of zonisamide in adolescents, since no standardized clinical trials have been conducted so far for this population.

**CLOSING REMARKS**

Obesity can be viewed as a disturbance of complex homeostatic mechanisms controlling energy balance in the body. The very high complexity and multi-pathway regulation of body mass on one side, and the effects of obesity on fertility, (auto)immunity, cardiovascular disease, non-alcoholic fatty liver disease, endocrine problems, cancer development, diabetes, and other diseases show the inter-connected nature of various body functions. For example, the P13-K/Akt pathway that is implicated in cell survival and proliferation, branches through the mTOR-signaling cascade into metabolism regulation [133-136]. The mTOR pathway is activated by growth factors and hormones, and the response to growth factors can be blocked by many different agents, including mTOR inhibitors. The use of these agents in the treatment of cancer is currently under investigation.
Currently approved prescription medications, even moderate in their efficacy, can help carefully selected obese patients to lose weight or to reduce the rate of regain. The safety and efficacy of many anti-obesity drugs beyond two years have not yet been established and long-term effects on morbidity and mortality are still determined. Recent advances in stem cell research at least theoretically open new possibilities for obesity treatment, like for example switching (brown) fat cells into muscle cells [137]. Still, primary means in treatment of obesity are behavioral interventions, which include appropriate diet and physical activity. Finally, it should be emphasized that the ultimate therapeutic goal in the treatment of obesity is not weight loss, but rather a reduction in morbidity and mortality from associated complications. Such considerations would favor new anti-obesity drugs that not only affect weight control but also improve metabolic and cardiovascular function.

ACKNOWLEDGEMENTS

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ABBREVIATIONS

AR = Adrenergic Receptor
ALBP = Adipocytes Lipid Binding Protein
ANP = Atrial Natriuretic Peptide
AMPK = Adenosine M onophosphate Activated Protein Kinase
ANS = Autonomic Nervous System
BMI = Body Mass Index
cAMP = Cyclic Adenosine Monophosphate
CB1 = Cannabinoid receptor 1
CCK = Cholecystokinin
cGMP = Cyclic Guanosine Monophosphate
CNS = Central Nervous System
CRF = Corticotropin Releasing Factor
CRM = calorie restriction mimetics
DEA = Drug Enforcement Administration
DGAT = Diacylglycerol Acyl Transferase
FDA = Food & Drug Administration
FATP = Free Fatty Acid Transporter
FABPs = Fatty Acid Binding Proteins
GH = Growth Hormone
HSL = Hormone Sensitive Lipase
IL = Interleukin
iNOS = Inducible Nitric Oxide Synthase
Jak/Stat = Janus Ki nase-Signal Transducer a nd Activator of Transcription
LMF = Lipid Mobilizing Factor
MSH = Melanocyte Stimulating Hormone
MCP-1 = Monocyte Chemotactic Protein-1
mTOR = Mammalian target of rapamycin
NP4 = Neuropeptide 4
NEFA = Non-Esterified Fatty Acid
NO = Nitric Oxide
NIDDM = Non-Insulin Dependent Diabetes Mellitus
OB-R = Leptin Receptor
PDE-3B = Type 3b Phosphodiesterase
PKA = Protein Kinase A
PKB = Protein Kinase B
PAI-1 = Plasminogen Activator Inhibitor 1
PPARα & γ = Peroxisome P roliferator Ac tivated Receptor α & γ
PGC-1 = Peroxisome P roliferator Ac tivated Receptor-Co-Activator-1
PTP1B = Protein-Tyrosine Phosphatase-1B
SNS = Sympathetic Nervous System
SSRI = Selective Serotonin Reuptake Inhibitor
TAG = Triacyl-Glycerol
TNF = Tumor Necrosis Factor α
UPC-1, = Uncoupling Proteins
ZAG = Zinc-α2-Glycoprotein.

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