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Obesity: Pathophysiology and Clinical Management

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Abstract: Obesity is a serious socioeconomic, and also increasingly clinical problem. Between ¼ - 1/3 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 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, phendimetrazine, 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 Western World. It poses a serious risk for the development of diabetes mellitus along with insulin resistance, cardiovascular disease, non-alcoholic fatty liver disease, endocrine problems, 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 height^2 (square meters) [2]. A BMI between 20-25 kg/ m^2 is normal and associated with lowest mortality, whereas a BMI of 25-30 kg/m^2 is considered overweight. In adults a BMI above 30-40 kg/m^2 is defined as obesity and BMI above 40 kg/ m^2 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]. Still, BMI primarily due to its simplicity often serves a guide in treatment selection.

Regional fat distribution has a profound influence on health risks. In general, measures of fat distribution such as waist circumference and sagittal abdominal diameter are more highly correlated with cardiovascular disease risk factors and diabetes than BMI [4]. It appears that the typical male (android) or visceral obesity is closely associated with metabolic complications such as hypertension, insulin resistance, hyperuricemia, and dyslipoproteinemia. The typical female or gynecoid obesity, with fat deposited in hips, femoral and gluteal regions, has much less metabolic consequences. The waist-to-hip ratio has been used to determine these forms of obesity. A ratio above 1.0 in male subjects and above 0.6 in women suggests an undesirable obesity pattern [5].

Obesity could be viewed as a consequence of the interaction of environmental factors and the individual genetic predisposition. A child of two obese parents has about 80 % chance of becoming obese, whereas the risk is only 15% for the offspring of two parents of normal weight. In addition, obesity is strongly conditioned by available food and sedentary life style [6, 7].

Treatment of obesity should be undertaken with a clear understanding of the realities of the problem and its outcome. Both, obesity and high visceral fat increase health risks even when total body weight and fat are not significantly elevated. Weight regain is common in obesity upon discontinuation of any treatment. Failure of diet and exercise in the long-term treatment of obesity is quite frequent and creates an obvious need for pharmacotherapy [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

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subsequently reduced to compensate for the increase in energy stores (Fig. **1**). The amount of the 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, hyperinsulinaemia, 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, leptin receptor is found in several forms. The leptin receptor, OB-R, is the product of the *db* 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 is also involved in the control of appetite 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

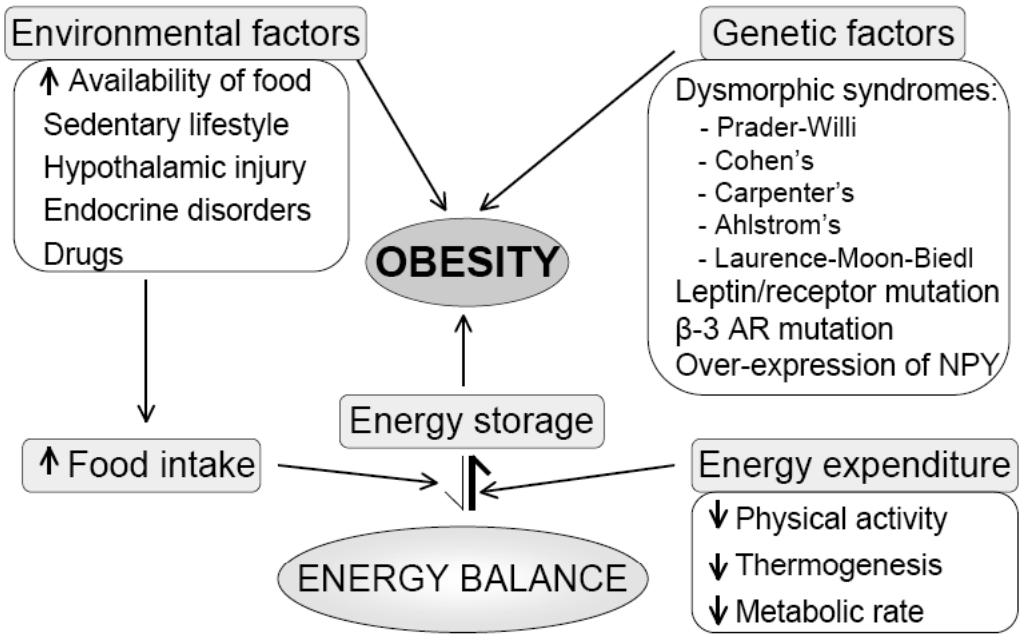

Fig. (1). Energy balance and etiology of obesity. Energy balance is determined by the interplay between food intake, energy expenditure and energy storage. Obesity is a multifactorial disorder resulting from combination of several environmental and genetic factors. Reduction in physical activity, metabolic rate and thermogenesis eventually decrease energy expenditure leading to increased energy storage and obesity. Availability of palatable food as well as hypothalamic injury and different drugs stimulate food intake. A growing list of genetic factors including dysmorphic syndromes, leptin/receptor mutation, β-3 AR mutation and overexpression of NPY contribute to development of obesity.

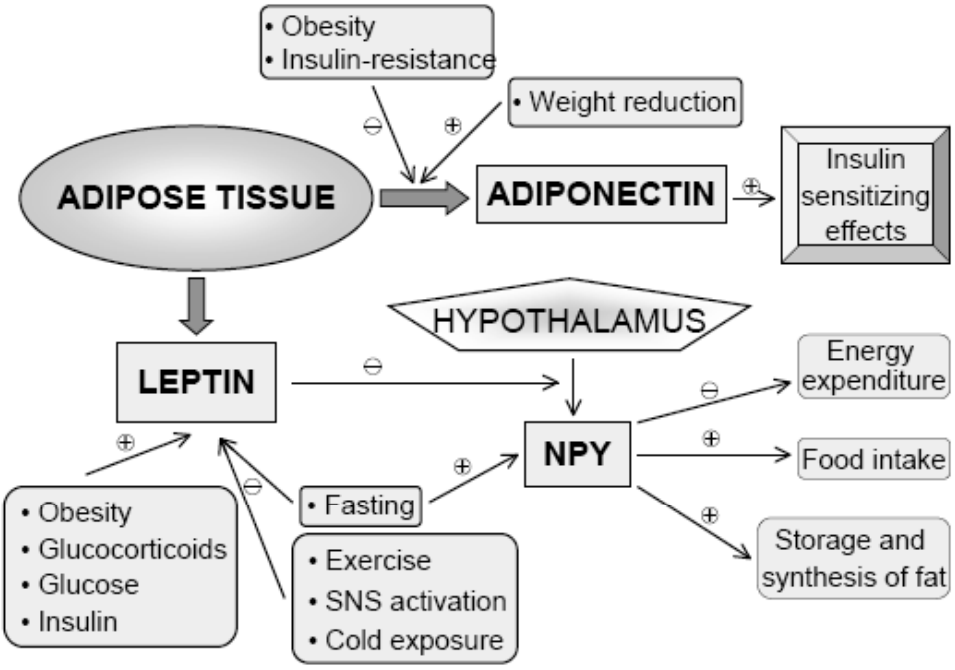

Fig. (2). Physiologic regulation and metabolic effects of leptin and adiponectin. Adipose tissue secretes leptin in states of food deprivation, SNS stimulation, exercise and cold exposure. Leptin secretion from adipose tissue is inhibited by obesity states, glucocorticoids, glucose and insulin. Leptin reaches hypothalamus, where in turn it inhibits secretion of NPY that normally reduces energy expenditure, enhances appetite and stimulates synthesis and storage of fat. Adiponectin normally sensitizes tissues for insulin effects. Obesity and insulin resistance negatively regulate adiponectin secretion from adipose tissue, whereas weight reduction enhances its secretion.

genes, likely obesity has multiple causes, including environmental factors and 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 melanocyte-stimulating hormone (MSH) may also be necessary for the response to leptin [11]. Orexins and other mediators produced 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 thermogenic 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 duodenum 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 predicted 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 norexic hormone and thus prevent weight gain [26]. Ghrelin and obestatin differ in their effects on growth hormone, obestatin does not seem to have any effect on growth hormone axis. This fact undermines the importance of their posttranslational modification [24].

Energy expenditure is determined by physical activity, metabolic rate and thermogenesis. The metabolic side of energy expenditure includes cardio-respiratory work, the maintenance of ion gradients and various enzymatic activities. Physical activity increases energy expenditure by work of the skeletal muscle in addition to all above-mentioned factors. The SNS affects not 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 mitochondrial 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 innervations. Heat is produced through the action of noradrenalin on β ARs (mainly β_3) in brown fat. Activation of β ARs increases lipolysis and fatty acid oxidation. Interestingly, in genetically obese mice the expression of β_3 ARs is decreased [27].

ADIPOSE TISSUE AND ITS PHYSIOLOGY

Physiological Features of White Adipose Tissue Innervations

The fat cell is under multiple influences, including that of autonomous nervous system (Fig. **2**), local blood flow changes and various hormones and factors delivered from plasma or produced locally. Following SNS stimulation, noradrenaline and NPY are released from sympathetic nerve terminals, whereas adrenal medulla secretes adrenaline. The major pathways regulating lipolysis are adrenergic. In human fat cells, both β_1 & β_2 adrenergic receptors (ARs) initiate activation of lipolytic cascade by stimulation of cyclic adenosine monophosphate (cAMP) production, activation of cAMP-dependent protein kinase A (PKA) leading to phosphorylation of perilipin and hormone-sensitive lipase (HSL), and promotion of lipolysis *in vitro* [29]. Human fat cells express large number of α_2 adrenergic receptors, their stimulation inhibits cAMP production and lipolysis. Rodents possess β_3 adrenergic receptors in the white fat cells, whereas in human fat cells the role of the β_3 ARs is unclear.

Differences exist in the adrenergic regulation of lipolysis in adipose tissues from different sites in normal-weight subjects and in obese subjects. The lipolytic response of isolated fat cells to the catecholamines is weaker in subcutaneous (abdominal/femoral) than in visceral adipose tissue [30]. One possible explanation includes defective signaling pathways such as reduced β_1 or β_2 ARs or increased α_2 AR responsiveness. Alterations in expression and function of HSL 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 $\alpha_2/\beta_1\&\beta_2$ adrenergic receptors balance appear 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 α_2 ARs and the lowest amount of β_1 & β_2 ARs. Increased expression of the former with concomitant decrease of the latter in hypertrophied fat cell 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-esterified fatty acids (NEFA) release from some fat deposits.

The "buffering" effect of NEFA by adipose tissue is an important phenomenon. When NEFA buffering capacity is inadequate, other tissues are exposed to elevated NEFA concentrations [34]. Profound unresponsiveness of the subcutaneous adipose tissue to lipolysis by neural stimulation has been described in obese subjects [35]. β_2 adrenergic – mediated increases in thermogenesis and lipid oxidation are impaired in obese individuals [36]. Polymorphisms in the coding and non-coding sequences in the human β_2-AR gene could be of major importance for obesity, energy expenditure, and β_2-AR dependant lipolytic function. Full β-adrenergic activation of the human fat cell usually requires synergistic activation of β_1 and β_2-ARs. A β_2-adrenergic defect could be sufficient enough to alter normal β-adrenergic responsiveness. Besides, in human fat cell, any reduction in β_2-AR mediated lipolytic response disturbs the normal functional balance existing between α_2 and β-AR mediated affects and amplifies reduction of the lipolytic responsiveness initiated by the physiological amines in stressful situations [33].

Insulin Signaling in the Adipocytes

Insulin plays a major role in the control of adipose tissue development and function. Insulin not only regulates lipogenesis but also the rate of lipolysis and NEFA efflux. Insulin controls glucose uptake and causes fatty acid transport protein translocation and enhanced fatty acid uptake in adipocytes [37]. Insulin inhibits basal and catecholamine-stimulated lipolysis through phosphorylation *via* the Ser/Thr protein kinase B (PKB) -dependent action and activation of type 3B phosphodiesterase (PDE-3B), leading to a decreased cAMP level, that prevents HSL activation. Insulin-induced antilipolysis and activation of NEFA re-esterification are blunted in omental compared to subcutaneous fat cells. Various functional differences have been identified at the receptor level and the post-receptor level of insulin signaling cascade [38].

Other substances possibly playing a role in lipolytic pathways are atrial natriuretic peptide (ANP), growth hormone (GH), and miscellaneous agents such as nitric oxide (NO). ANP stimulation of human fat cells activates cyclic GMP (cGMP)-dependent protein kinase (cGK-I type), which phosphorylates perilipin and HSL, thus explaining lipolytic action [39]. Although GH treatments in adults reduce visceral obesity and affect insulin sensitivity, the physiological contribution of GH to the control of human adipose tissue lipid mobilization remains elusive [33]. GH dependent modification of the relationships between adenylyl cyclase and $Gi\alpha_2$ protein removes inhibition of cAMP production and consequently increases lipolysis [40]. NO or related redox

species such as NO^+/NO^- have been proposed as potential regulators of lipolysis in rodent and human fat cells [41]. Cachexia-inducing tumors produce a lipid-mobilizing factor (LMF), and induction of lipolysis by LMF was associated with increased levels of intracellular cAMP [42]. ZAG is a new adipose tissue protein that may be involved in the modulation of lipolysis in adipocytes. Zinc-α_2-glycoprotein (ZAG) and tumor related LMF were detected in major fat deposits in mice. ZAG expression and protein was also found in human fat cells [42]. Various hormones and autacoids are known to negatively control adenylyl cyclase activity and inhibit cAMP production and lipolysis in fat cells. In addition, the stimulation of leptin secretion was observed with various agonists (A_1-adenosine, α_2-AR, and NPY-Y_1 receptor agonists) [33].

Functional Roles of Adipocytes

Adipocytes allow surplus energy to be stored as triacylglycerol (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 mainly oxidized in skeletal muscle to provide energy. Under normal conditions there is fine-tuning between TAG synthesis and lipolysis. So adipocytes could limit an abnormal increase in plasma NEFAs that is considered as an important etiological factor in the initiation of insulin resistance and metabolic syndrome in the obese. 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) secreted by the adipocytes exert 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 treatments, glucose, and insulin administration increase circulating leptin levels, whereas fasting, sustained exercise, cold exposure, and SNS activation reduce leptin levels [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 subcutaneous adipose tissue IL-6 secretion increases following exercise with concomitant increase in NEFA output, which suggests a post-exercise lipid-mobilizing contribution of the cytokine [45].

Adiponectin is an adipocytes-derived insulin-sensitizing hormone, which is secreted in high concentrations in the serum. Adiponectin concentrations are reduced in a variety of obese and insulin-resistant states [46]. Hypoadiponectinemia is closely linked to impaired vasoreactivity and endothelial dysfunction in humans. Adiponectin may play a protective role against atherosclerotic vascular changes [47]. Adiponectin effects are mediated by adenosine monophosphate activated protein kinase (AMPK) that increases fatty acid oxidation during muscle contraction and represses key enzymes of gluconeogenesis in he patocytes. AMPK also mediates in sulin-sensitizing effect of exercise, some anti-diabetic actions of metformin, and leptin action on skeletal muscle [48]. Unlike other adipokines adiponectin is decreased in obesity and increased in weight reduction. The mechanisms that determine inter-individual variability of adiponectin secretion, hence affecting body fatness, remain to be clarified [33].

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

Adipose tissue of the obese expresses several pro-inflammatory proteins such as TNF α and β1, IL-1, IL-6, inducible nitric oxide synthase (iNOS), monocyte chemotactic protein (MCP-1), procoagulant plasminogen activator inhibitor-1 (PAI-1), factor V and tissue factor and acute phase (serum amyloid 3, α-1-glycoprotein, and lipocain 24p3). TNF is increased in fat cells in obesity 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 mouse strains and in human adipose tissue. Macrophage accumulation occurs in proportion to adipocyte size and it increases the capacity for production of pro-inflammatory and acute phase molecules that contribute to obesity - related disorders. Thus, the adipose tissue macrophages 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 local decrease in insulin sensitivity of fat cells and to all other related 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 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 obesity. 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 *db/db* mice) or in the transducing system – decreased expression of CRF or overexpression of NPY could represent other disturbances in leptin system [55].

Dysfunctions of mediators other than leptin are implicated in obesity. TNF, another cytokine that relays information from fat to brain, is increased in the adipose tissue of insulin-resistant obese individuals [56]. It has been suggested that UCP-2, a protein uncoupling oxidative phosphorylation in white fat cells is dysfunctional in obese individuals [21]. Alterations in PPAR transcription factors α, β and γ may have a role in obesity. These transcription factors promote lipogenesis and regulate gene expression of enzymes associated with lipid and glucose homeostasis. PPARγ 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 UCP in white adipose tissue has regulatory sites for PPARγ and C/EBP-α [57].

Genetics and Obesity

Genetic determinants can either play a major role in the pathogenesis of obesity or enhance susceptibility to its development. The dysmorphic forms of obesity in which genetics play a major role include the Prader-Willi syndrome, Ahlstrom's syndrome, the Laurence-Moon-Biedl syndrome, Cohen's syndrome, and Carpenter's syndrome [7]. Reportedly, 244 genes, when mutated in the mouse, result in an obese phenotype. A growing number of studies indicate associations between DNA sequence variation in specific genes and the occurrence of obesity. Interestingly, the involvement of 22 such genes was reported in at least five separate studies. The obesity gene map shows putative loci on all chromosomes except Y [58].

In the *ob/ob* mice both copies of the leptin gene are defective resulting in truncated protein. Unlike in humans, treatment of obese mice with leptin reduces both food intake and body fat. Splicing defects on the leptin receptor are responsible for the obesity in the *db/db* mouse, which is phenotypically similar to the *ob/ob* mouse. The gene defect called *tub* results in a defective phosphatase and causes retinitis pigmentosa and obesity in mice, making it similar to the Laurence-Moon-Biedl syndrome in humans [7].

Linkage of human obesity to other factors related to energy balance has been reported. For instance, the Trp/64/Arg mutation of the human β_3-adrenergic receptor (β_3-AR) gene is associated with an earlier age of onset of NIDDM and characteristics of insulin resistance as well as weight gain in patients with morbid obesity. However, such findings have not been consistent in different ethnic populations [59]. It has been reported that plasma IL-8 levels are increased in obese subjects. IL-8 is related to fat mass and TNF system. Elevated circulating IL-8 could be one of the factors that link obesity to greater cardiovascular risks [60]. Most of genomic studies in humans, demonstrated substantial genetic heterogeneity influencing BMI regulation [61].

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 hypothalamic obesity are hyperphagia and a disturbance in the ANS activity. One explanation for this is altered secretion of NPY, which is produced in arcuate nucleus and stimulates eating [62]. Other possible explanations are impairment in reproductive function, decrease in sympathetic and increase in parasympathetic activity – other key features of hypothalamic obesity [63]. Endocrine disorders such as Cushing's disease, polycystic ovary syndrome and administration of some drugs (phenothiazines; such as chlorpromazine, antidepressants; amitriptyline, antiepileptics; valproate, steroids; glucocorticoids, antihypertensive agents; terazosin) may be associated with obesity [64, 65].

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. There are 9 calories per gram of dietary fat, whereas caloric value of carbohydrates and proteins is only 4 calories. It is possible that the mechanisms regulating appetite react more slowly to fat than to protein and carbohydrate, so satiety systems come into the picture too late. Increase in density of foods, portion size, better palatability of food, increase in availability and low cost promote obesity [66]. Obese people try to diet to lose weight. But when a subject reduces calorie intake, there is a shift into negative energy balance. An individual loses weight but, in parallel, the resting metabolic rate decreases, and there is a concomitant reduction in energy expenditure. Probably, the system is trying to return the body weight to the "set-point", which implies maintenance of energy balance is dependent on numerous metabolic feedback loops that are tuned by an individual's susceptibility genes. Thus, an individual who was previously obese and is now of normal weight, generally needs fewer calories for maintaining that weight than a an individual who has never been obese. The decrease in energy expenditure appears to be largely due to an alteration in the conversion efficiency of chemical energy to mechanical work in skeletal muscle. This adaptation to the caloric restriction contributes to the difficulty of maintaining weight loss by diet [67].

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 role in reducing fat stores and adjusting energy balance in the obese, especially when it is 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 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/m^2 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 gene products has 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 reduce fat mass and/or 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

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 monoamine neurotransmitters (serotonin and/or noradrenaline) in the brain. The modulation can occur at the level of neurotransmitter release and/or reuptake. Currently research focuses on identification of specific subtypes of serotonin receptors that are involved in the regulation of food intake. Appetite suppressant medications generally produce an average weight loss of about 10 % of initial body weight [71].

Appetite Suppressants

Noradrenergic Agents

Noradrenergic drugs available in the USA include phentermine, phendimetrazine, benzphetamine, and diethylpropion. They inhibit noradrenaline reuptake in the central nervous system. Amphetamines are no longer recommended and not approved for use because of the addicting 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 dependency 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 noradrenaline include insomnia, euphoria, dry mouth, constipation, palpitations, and hypertension [74, 75]. These medications are contraindicated in individuals with hypertension, advanced cardiovascular disease, hyperthyroidism, glaucoma, agitated states and history of drug abuse [72].

Serotoninergic Agents

Serotoninergic 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 primary 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 older 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-Serotoninergic 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 and weight maintenance in conjunction with a reduced - calorie diet [72]. It is given in a dose of 5-15 mg daily. Individuals receiving sibutramine over 6 months period and following a reduced-calorie diet usually lose 5-8 percent of their pretreatment weight. Sibutramine-induced weight loss is typically maintained for one-year period. Clinical trials up to two years have been completed and they show that although weight was regained during the second year of treatment and follow-up, weight loss attained was significantly greater in individuals treated for two complete years. Importantly, other metabolic factors related to weight loss also improve. These include improvement in lipid profile and hyperuricemia, as well as glycemic control and plasma insulin levels in patients with type 2 diabetes. However, because of big number of dropouts in both the study and the control group, generalization is problematic [79]. Side effects of sibutramine include increases in blood pressure and tachycardia, dry mouth, insomnia, headache, and constipation [80]. Sibutramine is contraindicated in cases of uncontrolled hypertension, coronary artery disease, congestive heart failure, arrhythmia, or stroke, severe renal or hepatic dysfunction, narrow-angle glaucoma, and history of drug abuse [72].

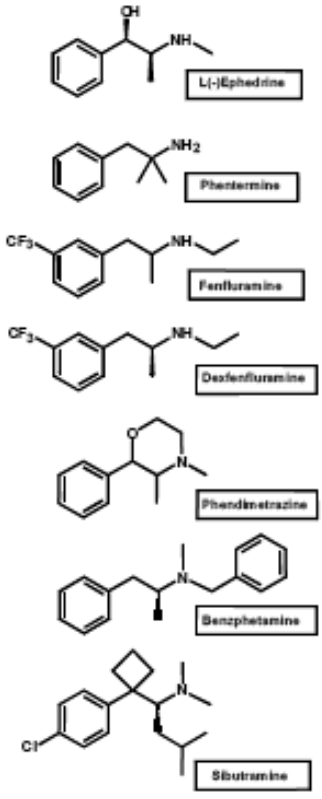

Fig. (4). Chemical structures of ephedrine derivatives, that have been tested as appetite suppressors. Ephedrine, an alkaloid originally extracted from *Ephedra vulgaris*, is a sympathomimetic amine. Its principal mechanism of action relies on its direct and indirect actions on the adrenergic receptor 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 stimulatory effect on appetite. Thus cannabinoid receptor became new drug target for obesity treatment. Cannabinoids act on central and peripheral receptors: cannabinoid receptors 1 (CB1) which are located in the brain as well as many peripheral tissues, and CB2 receptors which are primarily found in immune system cells. Cannabinoid receptor antagonists reduce food intake by blocking central CB1 receptors. They probably also act peripherally by increasing thermogenesis and thus energy expenditure. One of cannabinoid receptor antagonists rimonabant demonstrated clinical efficacy in the treatment of obesity and also improved cardiovascular and metabolic risk factors [81]. It appears that rimonabant reduces adipose mass through enhanced lipolysis, induction of enzymes of the beta-oxidation and TCA cycle, and increased energy expenditure. In addition to a transient reduction of food consumption, increases of both fatty acid oxidation and energy expenditure induced by the molecule summate leading to a sustained weight loss [82]. Despite these promising mechanisms of action, it was shown that weight loss following rimonabant and taranabant treatment did not exceed that attained with other currently approved anti-obesity medications. In addition, potentially severe psychiatric adverse effects limit their clinical use [80, 81].

Inhibitors of Fat Absorption

Given the central role of dietary fat in obesity, a logical way to achieve and maintain 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 belong to a class of anti-obesity drugs that acts directly and specifically at the site of fat breakdown in the lumen of small intestine [80, 83]. It acts by binding to gastrointestinal lipases in the lumen of bowel, preventing hydrolysis of triglycerides (dietary fat) into absorbable mono-acylglycerols and free fatty acids (Fig. **5**). The medication taken up to one hour after meal will result in excretion in the stool of one third of dietary fat ingested. In double blind, placebo-controlled study, orlistat had moderate efficacy for weight loss in adults (reduction by 9 percent of pre-intervention weight in comparison to 5.8 percent among those who took placebo) [84]. Orlistat slowed the rate of weight regain during a second year of use. Orlistat has additional beneficial effects, such as moderate decrease in diastolic blood pressure, in insulin level, reduction in total cholesterol and low-density lipoprotein levels, improvement in glycosylated hemoglobin and decreased need for sulfonylurea drugs in patients with type 2 diabetes [85]. Systemic absorption of orlistat is negligible and the potential for systemic adverse events thus seems to be small. Side effects include flatulence with discharge, fecal urgency, fecal incontinence, steatorrhoea, oily spotting, and increased frequency defecation [83]. Orlistat also decreases absorption of fat-soluble vitamins, mainly vitamin D and vitamin K [86]. As vitamin K absorption may be decreased, warfarin anticoagulation may be potentiated during orlistat therapy [87]. Therefore, patients receiving warfarin who start Orlistat need close monitoring of their INR. Reduction in the absorption of amiodarone and cyclosporine is another potential drug interaction of orlistat [88, 89]. Although absolute concentrations of vitamins D, E, and β-carotene decreased during orlistat treatment, the concentrations remained within the normal range and only 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].

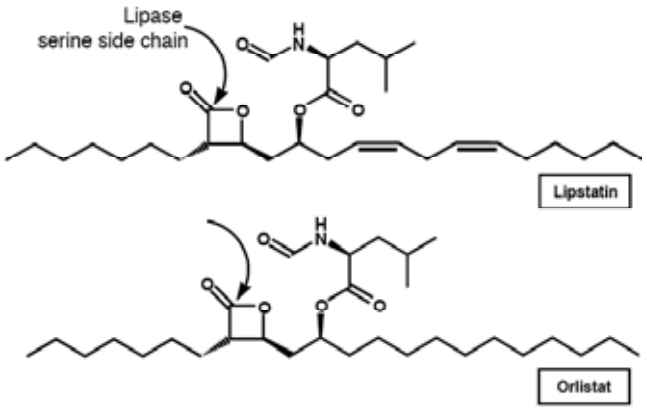

Fig. (5). Lipase inhibitors lipstatin and orlistat. Orlistat (Tetrahydrolipstatin) is a stable derivative of the microbial product lipstatin (isolated from *Streptomyces toxytricini*). Orlistat and Lipstatin act by covalent attachment to a serine side chain. The site of attachment (the lactame ring of Orlistat or Lipstatin) is indicated by an arrow. The covalent attachment results in the inhibition of the lipase.

Other steps required for absorption of dietary fat, which involves proteins, might represent promising drug targets. After hydrolysis, free fatty acids cross the membrane of the epithelial cell lining the intestinal wall. FATP4, a newly discovered free fatty acid transporter, might have a major role in this process. But its therapeutic value could be limited if free fatty acids are mainly transported passively [90]. Inside epithelial cell free fatty acids are transferred to the endoplasmic reticulum fatty-acid-binding proteins (FABPs). Possible inhibition of FABPs is questionable since the highest concentration of FABPs is in the enterocyte cytosol. Acyl-CoA is then transferred to 2-monoacylglycerol to re-synthesize triglycerides. Acyl-CoA: diacylglycerol acyltransferase (DGAT) is the key enzyme in triglyceride re-synthesis and its inhibition could represent a valid new strategy in the treatment of obesity. However, lack of DGAT in mice does not prevent fat absorption, thus other pathways for triglyceride synthesis must exist [91].

Stimulators of Thermogenesis

Adaptive thermogenesis confers the ability to adapt to prolonged exposure to cold (non-shivering thermogenesis) and overfeeding (diet-induced thermogenesis). The biogenesis of mitochondria and the induction of specific mitochondrial proteins that control the efficiency of oxidative phosphorylation are the key cellular processes of adaptive thermogenesis [92]. Thyroid hormone and noradrenaline released from sympathetic nerve endings have a profound impact on adaptive thermogenesis. Thyroid hormone is not a viable pharmacological anti-obesity approach, since it causes

loss of lean body mass and mobilizes calcium from the bone [93, 94]. In contrary, β_3 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 β_3 AR agonists will have a relevant impact on energy expenditure in humans. Highly selective, orally bio-available β_3 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 primary role in nora drenaline 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 correlated with

Table 1. The Pharmacologic Options of Obesity Treatment

Groups	Mechanism of Action	Examples I	ndications	Contraindications	Adverse Effects
Appetite Suppressors	Inhibit norepinephrine release in CNS	Benzphetamine Phendimetazine	Obesity, weight maintenance	Hypertension, hyperthyroidism, advance cardiovascular disease, glaucoma, agitated states, history of drug abuse [69]	Insomnia, euphoria, dry mouth, constipation, palpitations, hypertension, moderate addictive potential [70-72]
	Inhibit reuptake of serotonin and/or its release	Dexfenfluramine Fenfluramine	Obesity, weight maintenance, obsessive-compulsive disorder, depression [74]		Heart valvular disease, pulmonary hypertension [69, 74]
	Inhibit norepinephrine and serotonin reuptake in CNS	Sibutramine (Meridia, Reductil)	Obesity, weight maintenance [69]	Uncontrolled hypertension, coronary artery disease, congestive heart failure, arrhythmia, stroke, severe renal/hepatic dysfunction, glaucoma, history of drug abuse [69]	Hypertension, tachycardia, dry mouth, insomnia, headache, constipation [77, 138]
Inhibitors of fat absorption	Bind gastrointestinal lipases	Orlistat (Xenical)	Obesity, weight maintenance [81]		Gastrointestinal side effects, decreased absorption of fat-soluble vitamins [80, 83-86]
New and investigational drugs					
Stimulators of thermogenesis	β_3 AR agonists	SWR-0342SA [92-94]	Obesity and diabetes		
Stimulators of fat mobilization	Stimulate the formation of brown adipose tissue	PPARγligands PCG1 [128]	Obesity and diabetes [99]		
Cannabinoid receptor 1 antagonists	Suppress appetite, increase thermogenesis	Rimonabant (Acomplia) Taranabant	Obesity		Severe psychiatric mood related disorders [77-79]
Other drugs	Increase energy expenditure	Selective inhibitors of PTP1B [124, 125]	Obesity and diabetes		
	Activate 2C serotonin receptor	BVT 933 [8]	Obesity		
	Specifically inhibits fatty acid synthase	C75 [8]	Obesity		
	Activates leptin pathway, inhibits activity of acetyl coenzyme A carboxylase	Axokine (Ciliary Neurotrophic Factor) [102]	Obesity		

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 safer mechanism to increase thermogenesis in the whole body. Therefore, a pharmacological stimulation of UCP-3 activity could result in beneficial effects against obesity and NIDDM [101].

Stimulators of Fat Mobilization, Modulators of Fat Storage

Another possible 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. PPARγ ligands are very effective in inducing of UCP 1 expression in brown but not in white adipocytes, which indicates the existence of a brown adipose tissue specific co factor. Such a cofactor, PPARγ co-activator-1 (PGC-1) is strongly induced by cold [102]. PCG-1 allows PPARγ to function in the specific context of thermogenesis by allowing the expression of UCP 1 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 program of adaptive thermogenesis and this finding could stimulate development of novel anti-obesity drugs [102].

Calorie Restriction Mimetics

Perhaps the most studied calorie restriction mimetics (CRM) is resveratrol, a plant-derived polyphenol produced in a response to attacking pathogen. The important source of this compound is: root 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 calorie restriction in yeast requires activation of the silent information regulator 2 (Sir2) gene which is implicated in the lifespan extension [103, 104]. The mechanism of action of resveratrol in lifespan determination is based on the ability to mimic the calorie restriction in a Sir2-dependent manner. The mammalian homologs of Sir2 are SIRT1-7 and are expressed in different compartments of the cell such as cytoplasm, nucleus and mitochondria. It is believed that resveratrol-dependent activation of SIRTs in human results in regulation of various physiological pathways including fat mobilization [105], insulin secretion [106] gluconeogenesis [107]. Recent study has shown that increased dose of resveratrol allowed obese mice to remain on high-calorie diet without shortening lifespan [108]. Moreover, resveratrol intake protects against radiation [109], development of cancer, cardiovascular disorders [110-112] as well as is utilized in treatment of metabolic disorders such as diabetes 2 [113]. Besides the red wine, resveratrol is easily accessible in a supplement form.

Another very important group of CRM are insulin sensitizers with metformin at the fore front. This drug is very widely used against predominantly obesity-driven type 2 diabetes and cardiovascular diseases [114, 115]. Metformin increases sensitivity of insulin receptors on the surface 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 mimicking the outcome of long-term calorie restriction in mice [118].

Another group of CRM used in treatment of obesity and type 2 diabetes is thiazolidinediones 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 also previous paragraph). However, resent studies link thiazolidinediones 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 plasma glucose without reducing food consumption. Long intake of 2-deoxy-D-glucose has very little effect on body weight and consumption but can lower blood pressure significantly [119, 121].

Previously discussed leptin could also be included in the group of drugs regulating body weight and food intake. Leptin maintains its physiologic actions through effects on hypothalamic centers responsible for hunger and feeding [122]. However its long-term intake results in leptin resistance, of which mediator remains unknown. The way to solve this issue is direct leptin gene transfer into hypothalamus using recombinant adeno-associated virus. Such injection of recombinant adeno-associated virus-leptin is effective in lowering level of fat, insulin, triglycerides and prevents from weight gain [123].

Other Investigational and New Drugs

The major leaps towards the development of more effective anti-obesity drugs have actually lead into a better understanding of fat metabolism. In particular the discovery and cloning of the adipocyte-derived hormone leptin and its receptor proved to be major breakthroughs. Leptin reflects the lipid content of the total body of a non-fasting person. In a few children, severe, early-onset obesity has been associated with inability to produce functional leptin protein. Treatment of a leptin-deficient girl with recombinant human leptin induced a dramatic reduction in body weight (16.4 kg) and changes in body composition [124]. In case of treatment of adults who have normal leptin levels with recombinant leptin results were much less promising (loss of 7.1 to 8.5 kg). Actually, those patients have a lot of endogenous leptin and are leptin resistant. Problems related to formulation were pain and induration at injection site. Ongoing studies are evaluating the both different formulations of leptin and leptin-replacement therapy during low-calorie dieting [125].

A new drug, which is now in phase III 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. As a result the patient is satisfied with less food, so the person will be practically dieting. Axokine 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 co-enzyme A carboxylase, thus preventing accumulation of lipids in non-adipose tissues and stimulating oxidation of fatty acids and uptake of glucose [126].

The protein-tyrosine phosphatase (PTP1B) is another interesting target for anti-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 blood glucose level in diabetic and obese mice and lowered 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.

BVT.933 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 BVT.933 achieved statistically and clinically significant weight loss compared with placebo. Fatty acid synthase has also recently received recently 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 hyperinsulinaemia.

PPARα and PPARγ receptors (which are distributed widely in tissues and cell types) constitute multiple therapeutic targets for treatment of diabetes and obesity. Ideally, drugs possessing both PPARα/γ agonist potencies are expected to provide the best means to decrease multiple risk factors for morbidity and mortality existing in diabetic patients by acting on fat cells and liver. PPARγ is mainly expressed in adipose tissue; so metabolic effects are thought to result from direct action on the adipose tissue and secondary impact in liver and skeletal muscle. The beneficial effects of PPARγ agonists on muscle, liver, and vessels are mediated by their ability to improve insulin-mediated uptake and metabolism of glucose and NEFA in the adipocytes, to induce the production of adiponectin, and to reduce production of adipocyte-derived factors leading to insulin resistance (resistin, TNF and inflammatory molecules) [129, 130]. It has been also demonstrated that experimental drugs with dual activation of PPARα and γ have potential for use in the treatment of various aspects of metabolic dysfunction in type 2 diabetes that include dyslipidemia, hyperglycemia, and hyperinsulinaemia [131].

In view of the multiple metabolic and vascular effects of adiponectin, it is possible that improvement in metabolic disturbances of metabolic syndrome attributable to the effects of PPARγ agonists could be related to their action on adiponectin production and release by fat tissue [33]. Novel treatments are needed to help those millions of people suffering from obesity, especially the dramatically rising number of overweight children who are at risk of lifelong diabetes and the accompanying risk of heart disease and disability.

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 in the presence of such conditions. Since efficacy of approved drugs is similar in different groups of anti-obesity drugs, usually the choice is empirical with consideration of underlying medical conditions and contraindications. Non-pharmacological treatment should be tried for six months and weight-loss agents considered if reduction in weight is unsatisfactory. 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 medication, diet, and exercise should be reassessed and possibly the dose should be adjusted. If there continues to be minimal response to the medication, the clinician should consider discontinuing or substituting another medication. Major areas of promise for pharmacotherapy are in enhancing weight maintenance in those who have lost weight by variety of methods [74]. Since almost all non-surgical obesity treatments lead to weight loss for the first four to six months followed by regain, 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 if their BMI is in the 95th percentile or higher or if they suffer from obesity-related condition, which can be treated by weight reduction. 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 before pharmacotherapy outside clinical trials can be recommended for younger patients [72].

CLOSING REMARKS

Obesity can be viewed as a disturbance of complex homeostatic mechanisms controlling energy balance in the body. The very complicated, 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 PI3-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 stimulates protein synthesis and hence cell growth and hypertrophy in response to growth factors and amino acids [17]. Thus anti-obesity pharmacotherapy with an impact on these pathways may have potential to induce aneuploidy and tumorigenic dedifferentiation of normal cells.

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 also to be determined. Recent advancements 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.

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ABBREVIATIONS

AR = Adrenergic Receptor

ALBP = Adipocytes Lipid Binding Protein

ANP = Atrial Natriuretic Peptide

AMPK = Adenosine Monophosphate 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 Kinase-Signal Transducer and 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 Proliferator Activated Receptor α & γ

PGC-1 = Peroxisome Proliferator Activated Receptor-γ 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, UPC-2, UPC-3 = Uncoupling Proteins

ZAG = Zinc-α_2-Glycoprotein.

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