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Human genomics and obesity: finding appropriate drug targets

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Abstract

The increasing prevalence of obesity worldwide has prompted the World Health Organization (WHO) to classify it as a global epidemic. Around the globe, more than a half billion people are overweight, and the chronic disease of obesity represents a major threat to health care systems in developed and developing countries. The major health hazards associated with obesity are the risks of developing diabetes, cardiovascular disease, stroke, osteoarthritis and some forms of cancer. In this paper, we review the prevalence of obesity and its cost to health care systems and present the relative contribution of environmental conditions and genetic makeup to the development of obesity in people. We also discuss the concept of "essential" obesity in an "obesigenic" environment. Though weight gain results from a sustained imbalance between energy intake and energy expenditure, it is only recently that studies have identified important new mechanisms involved in the regulation of body weight. The etiology of the disease is presented as a feedback model in which afferent signals inform the central controllers in the brain as to the state of the external and internal environment and elicit responses related to the regulation of food intake and energy metabolism. Pharmaceutical agents may intervene at different levels of this feedback model, i.e., reinforce the afferent signals from the periphery, target the central pathways involved in the regulation of food intake and energy expenditure, and increase peripheral energy expenditure and fat oxidation directly. Since obesity results from genetic predisposition, combined with the proactive environmental situation, we discuss new potential targets for generation of drugs that may assist people in gaining control over appetite as well as increasing total energy expenditure and fat oxidation.

Keywords: Genomic; Essential obesity; Energy balance

1. Introduction

1.1. Is obesity a disease?

The question as to whether obesity is a disease has been vigorously debated over the past two decades. Acute diseases such as pneumonia and injury are usually curable, and may not recur once healed. Chronic diseases, on the other hand, such as hypertension and obesity may go into remission and have undulating courses, but of long duration. Obesity is a chronic disease, whether it is judged from the standpoint of personal suffering endured by affected individuals or by the cost to public health systems and societies. Obesity results from chronic disruption of the energy balance. The long-term balance between energy intake and energy expenditure primarily determines the amount of energy stored in the body. When energy intake chronically exceeds energy expenditure, the resulting imbalance causes expansion of fat cells and, in some cases, increased numbers of fat cells. Hypertrophy and hyperplasia of fat cells represent the one and unique pathology of obesity. The enlarged fat cells are then likely to induce other metabolic disturbances leading eventually to other diseases.

Whether the culprit is increased food intake or decreased energy expenditure is generally unknown and probably it varies from case to case. It is likely that obesity results usually from both impaired energy expenditure and an inability to control food intake in an environment not conducive to physical activity and in which highly palatable food is widely and easily available. Regardless, the consequence of this long lasting imbalance is the obvious accumulation of fat. One of the most important questions is why the increasing fat stores do not provide a signal to the brain to reduce food intake in some people, but do so

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in others? Another question is why are some people not able to increase their metabolic rates or discretionary physical activity to match their inappropriately high levels of caloric intake?

Since the discovery of leptin and its receptors 5 years ago, it is now better recognized that obesity is not only a lack of willpower leading to "sloth and gluttony", but can also be the consequence of metabolic defects. However, prejudice and discrimination still plague the lives of the obese. The stigma often derives from the "thinness" cult of our society and, especially among women, a general dissatisfaction with one's body weight. Regardless of whether the impact of obesity is judged by the personal dissatisfaction of obese individuals and their families with their weight and shape, or by the cost to public healthcare systems, the problem needs to be taken seriously. Obesity must be considered as a chronic disease with considerable personal and societal ill consequences. Pharmaceutical companies now realize that there is an enormous economic opportunity if safe and efficacious drugs can be developed. This situation is analogous to what happened in the recent past with the development of drugs for mental health, which now benefit so many people.

1.2. Prevalence of obesity

The title of a 1998 report by the World Health Organization captures the problem of obesity very well (WHO, 1997). This report entitled, "Obesity; Preventing and Managing the Global Epidemic" defines this new threat and itemizes healthcare burden and cost to developed and developing countries alike. A consensus on the classification of overweight and obesity developed by the WHO and supported by the US National Institutes of Health is shown in Table 1.

In the United States alone, more than 100 million people are overweight or obese. By one estimate, obesity and related nutritional disorders are currently responsible for the death of 300,000 Americans per year, i.e. the leading cause of potentially preventable death after smoking. Many reviews have shown that obesity is a prevalent condition not only in North America and Europe but in most countries with established market economies (Seidell, 1997). In a recent review, Seidell (2000) reports some astounding numbers. Based on the research from the International Obesity Task Force (IOTF) and the WHO report, he comes to the conclusion that there are currently about 250 million obese adults (7% of the population) and 500 million overweight people worldwide. The sad news is that these estimates are very conservative and that prevalence rates of both obesity and overweight are on the rise all over the world. Also the prevalence increases with age up to 60–70 years of age (Seidell and Flegal, 1997). The major health hazards associated with obesity are the risks of developing diabetes, cardiovascular disease, stroke, osteoarthritis, and some forms of cancer (Table 2). Obesity has also a strong negative impact on the quality of life. It is associated with a lower social acceptance and integration for children and adults alike, a greater risk of psychological disorders, a higher absenteeism from work, a higher consumption of health care services, a lower personal income, and many other discriminatory factors.

Table 1
WHO classification of overweight in adults according to BMI (see WHO, 1997 and National Institutes of Health, 1998)

Classification	BMI (kg/m^2)	Risk of co-morbidities[a]
Underweight	< 18.5	Low (but risk of other clinical problems increased)
Normal	18.5–24.9	Average
Pre-obese	25–29.9	Increased
Obese class I	30.0–34.9	Moderate
Obese class II	35.0–39.9	Severe
Obese class III	≥ 40.0	Very severe

[a] Increased risk of metabolic complications at waist circumference ≥ 94 cm in men and ≥ 80 cm in women. Substantially increased risk at waist circumference ≥ 102 cm in men and ≥ 88 cm in women (see NIH Guidelines).

1.3. Costs of obesity

Around the world, for countries where the cost of obesity have been estimated, the burden ranges from 2% to 10% of total health care costs and is on the rise. Using a prevalence and population attributable risk-based approach to estimate the cost of obesity in the United States, Wolf and Colditz (1998) estimated its direct and indirect costs at 100 billion dollars per year. Using the same approach but with the new World Health Organization (WHO) criteria for obesity (Body Mass Index or BMI > 30 kg/m^2), Colditz and Mariani (2000) have subsequently estimated the direct cost of obesity at 70 billion dollars in 1995 or 7% of total health care cost. In addition, another 50 billion dollars must be added for the indirect costs associated to a loss of productivity of persons disabled by obesity. A recent study mandated by the American Obesity Association estimated the total cost of obesity to be $238 billion in 1999. Clearly, preventing and treating obesity would have a significant effect on the cost of healthcare in the United States and in other countries.

Using the same approach as Colditz, Levy et al. (1995) estimated that the cost of obesity in France was approximately 2% of health care costs in 1992. In the Netherlands, Seidell (1995) concluded that obesity was responsible for 4% of total health care cost whereas Segal et al. (1994) put this figure at 2% in Australia, the latter two values being in line with the estimates for Canada (Birmingham et al., 1999). Clearly, the estimates of the costs of obesity in developed countries around the world are strongly determined by the prevalence of the disease in these countries. Because of these alarming numbers, it is of no surprise that investments in obesity research by NIH and other national

Table 2
Relative risk (RR) for health problems associated with obesity (BMI > 30 vs. BMI < 25). (From WHO, 1997)

Greatly increased (relative risk ≫ 3)	Moderately increased (2 < RR < 3)	Slightly increased (1 < RR < 2)
Type 2 diabetes	CHD	Cancer (breast, endometrial, colon)
Breathlessness	Osteoarthritis (knees)	Fetal defects associated with maternal obesity
Dyslipidaemia	Hypertension	Impaired fertility
Gallbladder disease	Hyperuricaemia and gout	Increased anaesthetic risk
Insulin resistance		Low back pain due to obesity
Sleep apnea		Polycystic ovary syndrome
		Reproductive hormone abnormalities

funding agencies of the western world have risen over the past years. The cloning of leptin, in 1994, provided a major impetus to increase the research funding level in this field (Zhang et al., 1994). Currently, there are, for instance, four NIH-funded Obesity Research Centers in the United States and many nutrition centers with a strong emphasis on obesity. In view of the magnitude of the problem, there is, however, an urgent need for more funding for major research effort into the etiology of the disease, as well as on new strategies to treat, or better still, to prevent it. The prevention of obesity should be among the top priorities of the public health agenda in industrialized countries and help should be provided to developing countries. This of course cannot be achieved if the focus is only on the individual patient. As emphasized by the WHO report; communities, governments, the media and the food and entertainment industries need to work together to modify the environment so that it is less conducive to weight gain and obesity with its associated diseases (WHO, 1997).

2. Obesity in an obesigenic environment

2.1. Animal models

2.1.1. Single gene models

Naturally existing single gene mutations, resulting in obesity in rodents, have been cloned in recent years. After the characterization of the obese (ob) gene and its product, leptin (Zhang et al., 1994) and the leptin receptor (db) gene (Tartaglia et al., 1995), four other single genes responsible for obesity have been cloned, i.e. the fat gene (Naggert et al., 1995), the tubby gene (Kleyn et al., 1996; Noben-Trauth et al., 1996), the agouti gene (Wilson et al., 1995), and the mahogany gene (Nagle et al., 1999). The cloning of these rodent mutations and initial characterizations of the molecular basis for their effect on energy stores constitute a major advance in our understanding of the regulation of body weight in mammals. Already, these models have helped us to understand the relative contributions of the increase in energy intake, the decrease in energy expenditure, and the partitioning of ingested calories to fat storage. Access to such models and others to be uncovered or engineered for specific questions will aid in the identification of additional components of these pathways and will provide valuable information for understanding the etiology and pathophysiology of human obesity.

2.1.2. Polygenic obesity in rodents

Over the past few years, the number of quantitative trait loci (QTL) linked to body weight or body fat in animals has increased dramatically as a result of several genome-wide scans being reported. QTLs derived mainly from mouse and rat crosses are summarized in Table 4 of the 1999 update on the human obesity gene map (Chagnon et al., 2000b). More importantly, the table also contains information on the putative syntenic relationship of these QTLs with human chromosomes. Such information is very valuable for the global assessment of all the genetic evidence with the goal of establishing positional cloning priorities for human obesity.

2.2. Human obesity

2.2.1. Genes vs. Environment

Although lifestyle and environmental influences on obesity are readily accepted, it is now recognized that human obesity has an important genetic component as well. Obesity is characterized by a strong familial aggregation pattern. However, except for some rare Mendelian disorders, the vast majority of obese patients do not exhibit a clear pattern of Mendelian inheritance. Despite the large number of studies on the familial aggregation and the heritability of the obesity phenotypes, there is no unanimity among researchers regarding the importance of genetic factors. A more complete review of these questions can be found elsewhere (Bouchard et al., 1994, 1998; Maes et al., 1997) but a brief summary of the main findings is presented here.

More than 75 years ago, Davenport (1923) described the first comprehensive attempt to understand the role of inheritance in human body mass for stature. Among his findings, normal weight parents sometimes have obese adult offspring. He also observed the converse: obese parents frequently have normal weight adult descendants.

In the aggregate, his study demonstrated quite convincingly that BMI values were more similar among family members than among unrelated persons.

The level of heritability has been considered in a large number of twin, adoption and family studies. The level of heritability is simply the fraction of the population variation in a trait (e.g. BMI) that can be explained by genetic transmission. Results obtained by a number of investigators indicate that the heritability estimates depend on how the study was conducted and on the kinds of relatives upon which they are based. For instance, studies conducted with identical twins and fraternal twins or identical twins reared apart have yielded the highest heritability levels with values clustering around 70% of the variation in BMI. In contrast, adoption studies have generated the lowest heritability estimates, of the order of 30% or less. Family studies have generally found levels of heritability intermediate between the twin and the adoption study reports. A few investigations have included all or most of these kinds of relatives in the same analysis, and they have concluded that the heritability estimate for BMI in large sample sizes was between 25% and 40% (Bouchard et al., 1998).

The risk of becoming obese when a first-degree relative is overweight or obese can be quantified using a statistic called the lambda coefficient (λ). Lambda is defined by the ratio of the risk of being obese when a biological relative is obese compared to the risk in the population at large, i.e. the prevalence of obesity (Risch, 1990). Estimates of λ for obesity based on BMI data were recently reported (Allison et al., 1996; Lee et al., 1997; Katzmarzyk et al., 1999a). Data obtained from 2349 first degree relatives of 840 obese probands and 5851 participants of the National Health and Nutrition Examination Survey III (NHANES III) revealed that the prevalence of obesity (BMI $\geq$ 30) is twice as high in families of obese individuals than in the population at large (Lee et al., 1997). Moreover, the risk increases with the severity of obesity in the proband. Thus, the risk of extreme obesity (BMI $\geq$ 45) is about eight times higher in families of extremely obese subjects. More recently, using data from 15,245 participants aged from 7 to 69 years from the 1981 Canada Fitness Survey, it was shown that the familial risk of obesity was five times higher for relatives in the upper 1% distribution of BMI than in the general Canadian population (Katzmarzyk et al., 1999a). However, the latter study suggested that the familial risk was not due entirely to genetic factors as the spouse of a proband was also characterized by an elevated risk.

The susceptibility to obesity is therefore determined to a significant extent by genetic factors, but a favorable "obesigenic" environment is necessary for its phenotypic expression. In other words, in the presence of a genetic predisposition to obesity, lifestyle and environmental conditions largely determine the severity of the disease. Fig. 1 illustrates these synergistic relationships between genes and environment. The variability of the distribution of body mass index (or adiposity) in a given environment ("restrictive" in the left distribution or "obesigenic" in the right distribution) is mostly attributable to genes, whereas the average of the distributions is primarily determined by environmental conditions. An example can be derived from a population extremely susceptible to obesity and diabetes such as the Pima Indians. Those living in a "restrictive" environment in the remote Mexican Sierra Madre mountains have a much lower prevalence of obesity and type-2 diabetes mellitus than Pima Indians living in the Southwestern United States, in Arizona (Ravussin et al., 1994). The Mexican Pimas would fit the left distribution in the top panel of Fig. 1. In contrast, US Pima Indians have the highest prevalence of type-2 diabetes in the world (Knowler et al., 1990) and one of the highest for

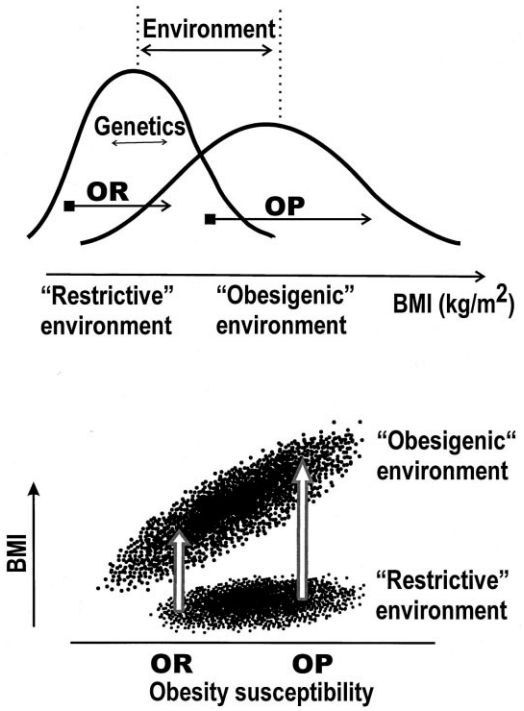

Fig. 1. This figure depicts the potential effects of gene and environment on adiposity assessed here by body mass index (BMI). Genetic susceptibility to obesity can be defined as a variable resulting from allelic variations at a set of obesity genes in low-risk (restrictive, left distribution) and high-risk (obesigenic, right distribution) environments. Top panel: In a "restrictive" environment in which caloric availability is limited and physical activity is high, individuals with a low genetic susceptibility (Obesity Resistant, OR) will have a very low body mass index. In contrast, those with a high genetic susceptibility (Obesity Prone, OP) will have a higher BMI (higher degree of adiposity), but still relatively low compared to the BMI distribution in an "obesigenic" environment. When these individuals move into an environment replete with high fat foods and low demand for physical activity, the overall distribution of adiposity will shift to the right. Obesity-resistant subjects will gain some weight but much less than obesity-prone subjects who will become frankly obese. Bottom panel: The same scenario is represented, showing the presence of a gene$\times$environment interaction. The "obesigenic" environment amplifies the effects of genetic susceptibility in obesity prone individuals compared to obesity resistant individuals.

obesity (Knowler et al., 1991). They are a reasonable fit to the distribution on the right. Fig. 1 also depicts the potential interaction between genes and environment in the development of obesity. For example, it is likely that when individuals from a population living in a "restrictive" environment characterized by a traditional lifestyle evolves towards an "obesigenic" environment, such as that found in industrialized countries, most individuals from this population are likely to gain weight. However, those with a high genetic predisposition for obesity will gain the most weight whereas those resistant to obesity will gain little weight (Fig. 1, bottom panel).

2.2.2. Concept of "essential obesity"

There has been considerable speculation concerning the reasons why the human genome could harbor genes predisposing to positive energy balance and obesity and at such a high frequency if one takes the genetic epidemiology estimates of heritability and lambda at face value. The most frequently stated theory is that of the "thrifty genotype hypothesis" (Neel, 1962), which is essentially as follows: during mankind's history, individuals and populations have evolved in restrictive environments in which food was not very abundant and required much physical work to obtain. Hence, survival mechanisms have evolved to confer a protection against periods of food scarcity. Often-cited examples of such populations include the aboriginal populations of Australia, navigators of the Pacific Islands, and the Pima Indians of the United States, who were typically exposed to alternating periods of feast and famine. The "thrifty genotype hypothesis" states that evolution in such a restrictive environment has progressively (or through genetic bottlenecks) selected for a "thrifty genotype," conferring survival advantages in periods of famine but resulting in liabilities in an affluent environment (Neel, 1999a,b). The hypothesis is not unreasonable, since the abundance of food and the lack of the necessity for physical exercise to acquire food are fairly recent phenomena. One implication of the "thrifty genotype hypothesis" is that it should not be surprising to observe that highly industrialized populations are now struggling with the problem of obesity due to rapid changes in environmental conditions. This has led to a second hypothesis, which states that obesity in our present environment is an "essential" condition, and only those with fewer obesity susceptibility genes (the former non-survivors) are now apt to resist our "obesigenic" environment and remain normal weight without conscious effort (Ravussin and Bogardus, 1992). However, many individuals overcome the development of obesity but only at the cost of constant dietary restrictions and regular physical activity regimens. The common thread among these two hypotheses is that what was an asset in early mankind history has now rapidly become a liability.

Because of the apparent role of genes in the predisposition to obesity, a search for obesity susceptibility genes was initiated in different human populations during the 1990s. Variants in candidate genes (coding and promoter regions), positional candidate chromosomal regions, linkage studies in families, and association studies in affected vs. non-affected individuals were typically used in the effort to identify genes of interest (Chagnon et al., 2000b; Barsh et al., 2000).

2.2.3. Candidate genes

As shown in Table 3, only a few single-gene mutations causally related to obesity have been detected in a small number of people. Mutations with strong effects were found in the leptin receptor gene (Clement et al., 1998), the leptin gene (Montague et al., 1997; Strobel et al., 1998), the pro-opiomelanocortin gene (Krude et al., 1998), the prohormone convertase 1 gene (Jackson et al., 1997), and the melanocortin MC_4 receptor gene (Cone, 2000; Hinney et al., 1999; Vaisse et al., 1998; Yeo et al., 1998;). More information can be found in a recent review on the genetics of obesity in animals and humans (Barsh et al., 2000).

Several obesity-related Mendelian disorders are also known, and the loci for several of them have been mapped. The latter are summarized in the latest annual human obesity gene map review (Chagnon et al., 2000b) and include the Prader–Willi Syndrome, the different loci for the Bardet–Biedl Syndromes, the Wilson–Turner Syndrome and many others. Once again, these syndromes in which obesity is only one of the clinical manifestations are not very prevalent and cannot explain the magnitude of the obesity problem in our present environment. About 23 have been described so far (Table 3). In addition, many investigators have screened for relevant sequence variation in candidate genes such as the Agouti gene, the uncoupling protein genes (UCP1, UCP2 and UCP3), all the melanocortin receptor genes, the neuropeptide Y receptor 1 and 5 genes, tumor necrosis factor alpha (TNF α), peroxisome proliferation-activated receptor-gamma (PPAR γ), and the β_3 adrenoreceptor genes to name only a few. The results of these studies have been rather disappointing and when associations were found, they were relatively weak (see below).

Table 3
Evolution of the human obesity gene map from 1995 to 1999. Rodent quantitative trait loci are also shown

Trait	Year				
	1995	1996	1997	1998	1999
Single-gene mutations	–	–	2	7	7
Mendelian disorders with map location	12	13	14	16	23
Candidate genes with positive findings	10	13	21	29	40
Rodent QTLs	8	24	55	67	98
Human QTLs	–	–	3	8	15
Other human linkages	9	18	20	30	35

2.2.4. Linkage studies

To date, the results of five genome scans for human obesity related phenotypes have been reported; one in Mexican Americans (Comuzzie et al., 1997), one in Pima Indians (Norman et al., 1998; Hanson et al., 1998), one in French families (Hager et al., 1998), one in Americans with extreme obesity (Lee et al., 1999), and one in French Canadian families from Quebec (Chagnon et al., 2000a). In these studies, the strongest linkages were observed on chromosomes 2P22-21, 10P12-3, 11Q22-24, and 20Q13. These different QTLs probably encode genes of importance for the susceptibility to obesity. The positional cloning of some of these QTLs is currently being pursued in several laboratories. However, one must also recognize that linkages with weaker statistical significance may also be of importance particularly when replicated in other data sets. An exhaustive list of published linkages to obesity phenotypes or subphenotypes is summarized on a yearly basis (Chagnon et al., 2000b).

2.2.5. Association studies

A good number of association studies have been conducted using DNA from case and control designs or comparing genotypes in samples characterized by heterogeneity in levels of adiposity. Results of these studies are summarized in Table 5 of the 1999 gene map (Chagnon et al., 2000b). Association studies based on small sample size seem to be particularly vulnerable to false positive or false negative findings. Therefore, one should rely only on studies, which have reasonable statistical power and on results that are replicated in different samples. At the present time, no strong definitive association with a mutation has been identified following these criteria. However genetic associations with levels of significance at $p < 0.001$ have been identified for variants in the following genes:

- sodium potassium ATPase alpha$_2$ and beta$_1$ genes with respiratory quotient (Katzmarzyk et al., 1999b);
- promoter region of the pro-opiomelanocortin gene with plasma leptin concentration (Hixson et al., 1999);
- haplotype of variants in the UCP1 gene and β_3 receptor gene with weight loss (Kogure et al., 1998);
- β_2 adrenoreceptor gene with BMI (Ishiyama-Shigemoto et al., 1999);
- UCP2 gene with BMI (Cassell et al., 1999) or energy metabolism (Walder et al., 1998);
- G protein β_3 subunit with BMI (Siffert et al., 1999) and
- adenosine deaminase gene with BMI (Bottini and Gloria-Bottini, 1999).

None of these associations has been proven to be the consequence of a mutation affecting the function or amount of a gene product.

As reviewed elsewhere, the number of genes and other markers associated or linked with human obesity phenotypes continues to expand and has now reached well over 200 (Chagnon et al., 2000b). Of course, some of these loci will prove to be more important than others, but many will eventually be found to be false positives. The main task remains to discover the combination of genes and mutations that contribute most to the predisposition to obesity in humans. Genetic association studies need to be supported by cellular work identifying the functional consequences of the reported polymorphisms. Beyond this goal, it will be critical to define the environmental circumstances necessary for the full phenotypic consequence of these genes or for the prevention of the full expression of the same genes.

3. Etiology of obesity

Weight gain results from a sustained imbalance between energy intake and energy expenditure favoring positive energy balance. However, this simple statement belies the complex, multi-factorial nature of obesity and the numerous biological and behavioral factors that can affect both sides of the energy balance equation. Fig. 2 shows the major paths involved in obesity grouped according to behavioral, metabolic, and biological influences. These pathways and factors have been reviewed elsewhere (Ravussin and Swinburn, 1993; Rosenbaum et al., 1997; Salbe and Ravussin, 2000).

Cross-sectional studies that compare lean and obese individuals have not provided true insights on the metabolic predictors of human obesity. Such studies have commonly reported that obesity is associated with high absolute energy expenditure, low respiratory quotient, high fat oxidation, insulin resistance, high sympathetic nervous system

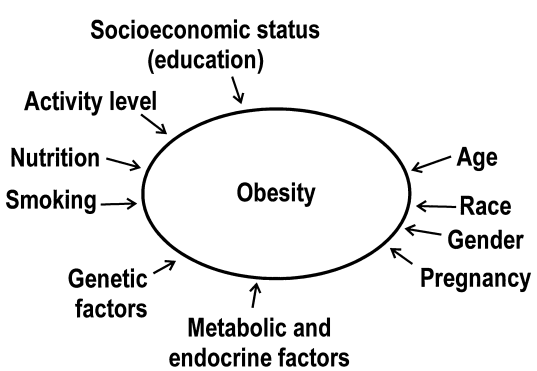

Fig. 2. This figure depicts the various causes of obesity grouped according to the behavioral (activity level, nutrition, smoking status, socioeconomic status), metabolic (physiological, metabolic, endocrine factors), and biological (genetic, racial, gender, age, pregnancy status) influences that predispose individuals to obesity.

activity, and elevated plasma leptin concentrations (Ravussin and Gautier, 1999). In contrast, longitudinal studies that follow the same individuals over time, have indicated that, relative to body size, low metabolic rate, high respiratory quotient, insulin sensitivity, low sympathetic nervous system activity and low plasma leptin concentrations predict weight gain over time (Table 4). Upon gaining weight, the original "abnormal" metabolic state becomes "normalized". Such a "normalization" with weight gain explains why cross-sectional studies have not led to the identification of metabolic risk factors for obesity. Weight gain thus causes an increase in metabolic rate, a decrease in respiratory quotient, a decrease in insulin sensitivity, an increase in sympathetic nervous activity and an increase in plasma leptin concentrations, all of which serve to counteract further weight gain. Therefore, it is not surprising that weight loss plateaus after a few months of therapy. Based on these observations, one could hypothesize that not only drugs inhibiting food intake but also drugs increasing energy expenditure and/or increasing fat oxidation will be efficacious in the prevention and treatment of obesity.

In the context of a discussion on the implications of recent progress for potential drug targets for obesity, it is useful to consider the etiology of the disease as a feedback model as proposed by Bray (1991, 1998) and Bray and Greenway (1999) and illustrated in Fig. 3. In such a model, afferent signals indicate to the central controllers in the brain the state of the external and internal environments as they relate to food, metabolic rates and activity behavior, to name but a few. In turn, these central controllers transduce these messages into efferent signals, governing the behavioral search for acquisition of food, as well as modulating its subsequent deposition into such energy storage compartments as adipose tissue, liver, and muscle and by modulating metabolic rates. Finally, a component of the system regulates ingestion, digestion, absorption, transport, and storage of the ingested foods, as well as other related metabolic and behavioral functions. Each of these components of the system can be targeted for the development of drugs. These new potential targets are discussed below in Section 5.

Table 4
Metabolic characteristics of obese and pre-obese individuals

	Obese (factors associated with obesity)	Pre- or post-obese (factors predicting weight gain)
Relative resting metabolic rate	High or normal	Low
Energy cost of activity	Normal	Low
Fat oxidation	High	Low
Sympathetic nervous system activity	High	Low
Insulin sensitivity	Low	High
Relative leptin concentration	High	Low

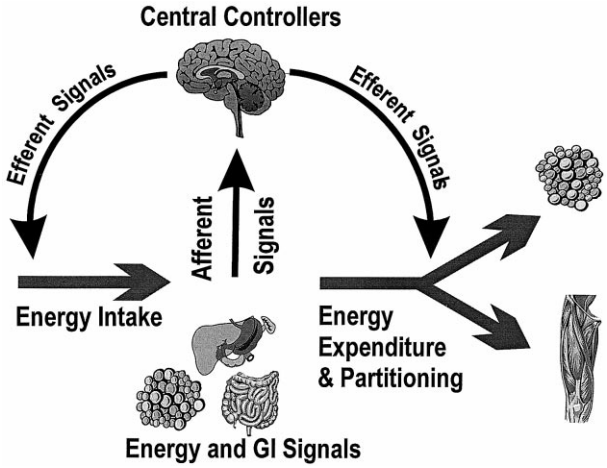

Fig. 3. This figure depicts a negative feedback model for the regulation of body weight. In this model, peripheral signals from energy stores (adipose tissue, muscle, and liver) as well as hormonal and gastrointestinal signals provide afferences to the central controllers in the brain, indicating the state of the external and internal environment as they relate to food, metabolic rates, and activity behavior. In turn, the central controllers integrate all the signals and transduce these messages into efferent signals governing the behavioral search for the acquisition of food as well as modulating its subsequent deposition into energy storage compartments such as adipose tissue, liver, and muscle by modulating energy expenditure. Afferent signals, efferent signals, and central controllers can all be targeted for new potential anti-obesity drugs (see Section 5).

4. Past and current treatment of obesity

4.1. Behavioral

Hippocrates advised that the way to lose weight was to eat less and exercise more. Twenty-four centuries later, "diet and exercise" is still the best medical advice given to patients. Behavioral modification or behavioral therapy has now become a standard component of most treatment programs. The goal is to modify the patient's lifestyle by providing support and rewards to sustain an increase in physical activity and a decrease in food intake. To achieve this, many different strategies have been developed by different investigators and tested in randomized clinical trials. For instance, it has been proposed to begin with children and to involve their families for a greater probability of success. Another strategy has been to implement work site programs with large participation from workers. The literature on behavioral therapy for obesity is extensive but not very conclusive (see Bray, 1998 for review.) However, it is well documented that even when obese individuals experience early success and lose weight, most regain the weight within 1 year and almost all of them within 5 years although higher rates of success have been reported lately (Wadden et al., 1999). For this reason, voluntary behavioral changes do not appear to be sufficient

for a successful treatment of the disease and most obese patients may need pharmaceutical support in their treatment.

4.2. Pharmacological

The beginning of modern obesity pharmacology as regards to obesity can be traced back a century ago, when the use of thyroid extract was first reported (Bray, 1998). At that time, it was made clear that the thyroid hormone extract caused an increase in metabolic rate, which was then believed to be low in obese patients. However, thyroid hormones had to be abandoned in most cases because of their adverse effects on the cardiovascular and skeletal muscle systems. In the 1920s, it was observed that dinitrophenol, present in chemical dyes, caused weight loss in the workers that were exposed to it. The effect was due to an uncoupling of the phosphorylation of ATP from oxygen consumption, but it was quickly shown that treatment with dinitrophenol was associated with significant side effects, such as neuropathy and cataracts. Amphetamines were then introduced and found to be efficacious, but also to be addictive.

Notwithstanding the limitations of current forms of treatment, it is now well accepted that safe, efficacious drugs to treat obesity can and should be produced. During the past 30 years, progress has been made in defining the mechanisms by which obesity could be treated. Many drugs have been used to modulate food intake, mostly by their effect on monoamines, such as norepinephrine, serotonin and dopamine (Bray and Greenway, 1999). Serotonergic drugs such as fenfluramine and dexfenfluramine were developed and approved for use until it was claimed that dexfenfluramine alone or in combination was associated with valvular problems in some patients and after which it was withdrawn from the market.

There are only two obesity drugs left on the US and other markets at this time, namely sibutramine and orlistat. Sibutramine is a sympatheto-mimetic drug, which increases centrally the re-uptake of norepinephrine, serotonin and to a lesser extent of dopamine. Initially developed as an anti-depressant, it has been shown to decrease food intake in a dose-related fashion (Bray et al., 1999). Sibutramine also seems to increase energy expenditure (Danforth, 1999). It is approved for long-term use, but is classified as a schedule 4 drug by the US Drug Enforcement Agency.

Orlistat, an inhibitor of hepatic lipase, can be classified as a drug that alters metabolism by inhibiting the gastro-intestinal absorption of triglycerides. On a 30% fat diet, orlistat produced a dose-dependent increase in fecal fat loss and a similar dose-related weight loss when used for a period of six months or more (Sjöström et al., 1998).

At present, there is no drug approved whose effect is to increase thermogenesis for the treatment of obesity. However, ephedrine and caffeine have been tested in double-blind studies and have been shown to produce modest weight loss (Astrup et al., 1992).

5. Potential targets for obesity drugs

According to the negative feedback model presented in Fig. 3, pharmaceutical agents may intervene at three different levels. First, small molecules can reinforce the afferent signals from the periphery. Second, such molecules can target the central pathways involved in the regulation of food intake and energy expenditure. Third, agents can increase directly peripheral energy expenditure and increase energy partitioning towards muscle. Some of these targets have been reviewed elsewhere (Halford and Blundell, 2000).

5.1. Afferent signals

The external environment and internal milieu provide signals that play a role in the control of feeding. External signals from sight, sound, smell, taste and touch all provide important elements in this feedback system. Gastrointestinal peptides have long been recognized as potential regulators of satiety. Cholecystokinine was one of the first peptides shown to reduce food intake (Gutzwiller et al., 2000). Glucagon and glucagon-like peptide-1 (GLP-1) both reduce food intake in animals and humans (Van Dijk and Thiele, 1999). Small molecules that may influence GLP-1 receptors (agonist activity), increase the release of GLP-1 from intestinal L cells, or increase the duration of action of GLP-1 could be candidates for drug therapies. Ghrelin, the natural ligand of the growth hormone secretagogue receptor is secreted by the stomach and inhibits fat oxidation (Tschöp et al., 2000). Enterostatin, the pentapeptide portion of pancreatic procolipase, reduces fat intake in some experimental models (Erlanson-Albertsson and York, 1997). However, data in humans have not been conclusive. Nutrients such as glucose, pyruvate, lactate, and 3-hydroxybutyrate seem also to be afferent satiety signals. They all reduce food intake when injected into experimental animals.

Leptin, however, is the best known and most studied afferent signal from adipose tissue and may be the most important hormone communicating information on body fat content to the central controllers of energy balance. Administration of leptin causes a decrease in food intake and an increase in energy expenditure (Huang and Li, 2000; Pelleymounter et al., 1995). These effects are driven by central regulatory mechanisms modulating orexigenic and anorectic neurons in the hypothalamus as well as activating the sympathetic nervous system in the brain stem. Clinical trials with leptin injections have shown that modest weight loss occurred at small doses but that local discomfort was registered at the injection site (Heymsfield et al., 1999). For these reasons, it is unlikely that leptin per

se will become an important obesity pharmacotherapy. However, the development of low molecular weight leptin receptor agonists remains an attractive and probably viable strategy. Such compounds would preferably be orally available and should cross the blood–brain barrier, thereby allowing a more potent stimulation of leptin receptors than a large protein, which is limited by saturable transport across the blood–brain barrier. Alternatively, sensitizers of the leptin pathway could be developed in the same way as insulin sensitizers.

5.2. CNS controllers

The central control systems for the regulation of food intake and energy expenditure are coordinated and controlled by neuronal systems converging on the ventral hypothalamus. It has been known for years that lesions in this region produce an increase or a decrease in the regulated weight, depending of the specific site of the lesion (Bray, 1991). It is also known that monoamines, including norepinephrine, serotonin, dopamine and histamine modulate feeding (Bray and Greenway, 1999; Halford and Blundell, 2000). The stimulation of the α_1 adrenoreceptor reduces food intake, whereas the stimulation of α_2 adrenoreceptors increases food intake in experimental animals. Receptors can be activated by agonist drugs, but also by releasing or inhibiting norepinephrine re-uptake in the vicinity of these receptors. Stimulation of dopamine receptors also reduces food intake probably by activation of the 5-HT_{2c}-receptor (Nonogaki et al., 1998). Recently, histamine receptors have also been identified as modulators of feeding. Antagonists of the H_3 receptor (an auto-receptor) could be targeted to increase the release of histamine in key central locations (Itoh et al., 1999).

One of the most recent developments has been the identification of neuropeptides that play an important role in the regulation of both, feeding and energy expenditure. These include neuropeptide Y, the pro-opiomelanocortin, and the melanin-concentrating hormone. Neuropeptide Y is among the most potent stimulators of food intake. Antagonists to either the neuropeptide Y Y-1 or the neuropeptide Y Y-5 receptor are being explored as potential agents for the treatment of obesity (Duhault et al., 2000). Another attractive target is the melanocortin receptor system. Indeed, alpha-melanocyte stimulating hormone (α-MSH) causes a decrease in food intake, and a mouse lacking pro-opiomelanocortin, the precursor of α-MSH, is obese (Yaswen et al., 1999). Agonist and antagonist peptides of the melanocortin MC_4 receptor have been developed and cause the expected effect on feeding, i.e., decrease and increase, respectively. Finally, humans with functionally impaired melanocortin MC_4 receptors are obese (Cone, 2000; Hinney et al., 1999; Vaisse et al., 1998; Yeo et al., 1998). The melanocortin receptor system therefore represents one of the major potential targets for the treatment of obesity. Agonists or allosteric enhancers of the melanocortin MC_4 receptor may prove to be efficacious in humans as previously shown in rats and mice. Antagonists to the melanin-concentrating hormone represent another potential approach for drug development. Melanocortin hormone knockout mice are lean, suggesting that the peptide may have a physiological role in the control of food intake, energy expenditure and body fat stores (Shimada et al., 1998). Finally, opioids seem to be important in the regulation of feeding, and μ and κ receptors antagonists may be useful targets to decrease food intake (Calo' et al., 2000).

5.3. Efferent signals

The endocrine and autonomic systems are efferent control systems involved in the regulation of food intake and body fat stores. Among the key hormones, growth hormone, catecholamines, corticosteroids, and insulin have been known for years. Energy expenditure can be divided in three major components, i.e. the resting metabolic rate, the energy expenditure for physical activity, and thermogenesis. Post-obese individuals are less effective in oxidizing fat and have lower metabolic rates than their normal weight counterparts who were never obese (Astrup et al., 1999). Since a low metabolic rate (Ravussin et al., 1988) and a low rate of fat oxidation (Zurlo et al., 1990) are risk factors for obesity, it is of interest to target molecular pathways involved in the regulation of energy expenditure and/or fat oxidation.

The ideal molecule to target energy metabolism at the periphery would be one that could both increase resting energy expenditure and fat oxidation. Several pharmaceutical companies are currently developing β_3 adrenoreceptor agonists for this purpose (Weyer et al., 1999). The original uncoupling protein (UCP1) found in brown adipose tissue has a well-established role in temperature and body weight regulation in rodents (Ricquier and Bouillaud, 2000). Whether UCP1, UCP2, or UCP3 play a role in the regulation of body weight in humans remains to be determined. Very recently, it was shown that overexpression of human uncoupling protein-3 in skeletal muscle of mice resulted in a lean mouse, suggesting that UCP3 may be a good target to increase metabolic rate (Clapham et al., 2000).

6. Future pharmacological treatment

There are a number of features that would be desirable in a next generation obesity medication. The first is obviously safety as the history of the pharmacological treatment of obesity has been marked by several disasters (Bray, 1998). This is particularly important because many people will seek pharmacological treatment for obesity, even if they have no clinical indication for drug therapy. Of course, an equally important feature for a new generation of drugs is efficacy. Future pharmacotherapy should be potent enough to induce a weight loss of at least 15% of

initial body weight on average. The mechanism of action will also be very important. Since almost all of the previous drugs were acting centrally and were associated with side effects, it would be preferable if some drugs of the next generation acted peripherally. Finally, since the pharmacological treatment of obesity requires lifelong therapy, the cost of such an agent should be affordable. If the cost of treating obesity exceeds the cost of treating its co-morbidities, then these new drugs are bound to fail on the market.

An important issue to keep in mind is the fact that the pharmacological treatment of the future will not cure obesity. Weight loss reaches a plateau after a few months of treatment as a result of many compensatory mechanisms having come into play and the re-equilibration of the energy balance (see Section 3 and Table 4). This reality has to be understood by both the patients and the health care providers if one wants to avoid the vicious cycles of frustration, which often occurs between parties when realistic expectations are not clearly established at the onset of the treatment (Garrow, 1992).

Because of the above, combination therapy, targeting different mechanisms, is likely to be more efficacious. For instance, during the first phase of a weight loss program, an appetite suppressant, in association with behavioral therapy, may be the most relevant approach (Fig. 4). However, after 2 or 3 months of weight loss, an agent that increases energy expenditure could be added to counteract the decrease in metabolic rate and sustain negative energy balance conditions. Together, an appetite suppressant and a stimulator of metabolic rate should be helpful in preventing some of the weight regain so commonly observed.

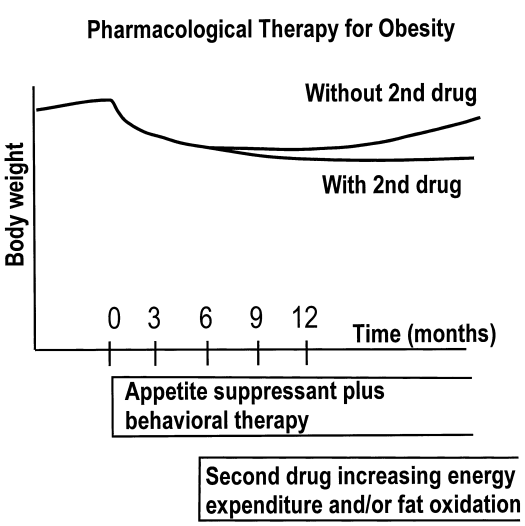

Fig. 4. This figure illustrates a scenario for using two drugs with different modes of action to treat obese patients. In a first phase, patients combine an appetite suppressant with behavioral modifications to rapidly lose weight. However, after a few months, due to counteracting mechanisms (decrease in energy expenditure and decrease in fat oxidation), a thermogenic agent is added to avoid the resistance to weight loss, which often manifests itself by a relapse in weight gain.

Table 5
Evidence necessary for the role of neuropeptides in the regulation of energy balance

- Central administration impacts food intake and/or body weight
- Expression of the protein/mRNA changes with energy balance
- Histochemical/electrophysiological evidence of implication in endocrine/neural pathways regulating energy balance
- Blockade of peptide action (antibody/receptor antagonist/antisense oligos) impacts energy balance
- Knock-out or overexpression impacts energy balance

Finally, further away in the future, the anticipated advances in human genomics and proteomics should make it possible to prescribe drugs designed to alleviate specific genetic deficiencies identified by genotyping for mutations at relevant genes. These advances will allow the development of a treatment a la carte approach.

In the pursuit of new pharmacological agents to target obesity via known or unknown mechanisms, pharmaceutical companies need to prioritize their efforts taking into account the levels of evidence described in Table 5. For the development of such a drug, one must show in preclinical models of obesity that the administration of the ligand to the targeted receptor or the modulators of enzymatic activity impacts food intake and/or energy expenditure. Second, the expression of the receptor and/or the ligand should be affected by changes in energy balance. Third, the histochemical/electrophysiological location of the target should preferably be present in tissues and areas previously described as being involved in the control of energy balance. Fourth, blockade or stimulation of peptide action by antibodies or oligo-nucleotides should impact on energy balance. Finally, knockout or overexpression of the receptor or the ligand gene should impact energy balance and cause a change in body weight and adiposity.

A list of some of the potential central targets for the control of food intake has been published by Bray and Greenway (1999). As presented above, these targets include monoamines, such as norepinephrine, serotonin, dopamine and histamine. On the other hand, the list of neuropeptides affecting food intake is growing every month. The major orexigenic neuropeptides are: neuropeptide Y (Duhault et al., 2000), melanin concentrating hormone (Chambers et al., 1999; Shimada et al., 1998), orexin A and B (Edwards et al., 1999; Sakurai et al., 1998; Yamanaka et al., 1999), dynorphin (Lambert et al., 1993), β-endorphin (Grandison and Guidotti, 1977), and galanin (Kyrkouli et al., 1990). On the other hand, many anorectic peptides have been discovered including αMSH (Abbott et al., 2000), GLP-1 (Edwards et al., 2000), corticotropin releasing hormone (CRH) (Benoit et al., 2000), urocortin (Bradbury et al., 2000), cocaine-amphetamine related transcript (Kristensen et al., 1998), neurotensin (Stanley et al., 1983), neuromedin U (Howard et al., 2000), calcitonin (Morley et al., 1996), amylin (Rushing et al., 2000), and enterostatin (Erlanson-Albertsson and York, 1997). Some

Table 6
Potential targets (pathways) for increasing energy expenditure or fat oxidation or for inhibiting adipose tissue proliferation (see text for references)

Pathway	Activation (+) or inhibition (−) to decrease obesity
Acetyl CoA Carboxylase β (ACC2)	(−)
Adrenergic (β3) Receptor	(+)
Carnitine Palmitoyltransferase 1 (MCPT1)	(+)
Diacylglycerol transferase (Dgat)	(−)
Ghrelin Hmgic	(−)
Leptin (LEPR)	(+)
Peroxisome Proliferator-Activator Receptor α (PPAR-α)	(+)
PPAR γ	(−)
PPAR γ Coactivator1 (PGC1)	(+)
Sterol Regulatory Element Binding Protein (SREBP)	(−)
Thyroid Hormones; (Thyroid β Receptor)	(+)
Uncoupling Proteins (UCP)	(+)

of these peptides not only impact food intake, but also energy expenditure in a reciprocal manner. All of the above targets have some degree of validation in pre-clinical models, or from gene knockout or gene overexpression studies. However, it should be noted that the melanocortin pathway, and especially the melanocortin MC_4 receptor, has the highest degree of validation, according to the criteria described in Table 5. Agonists to the melanocortin MC_4 receptor may prove to be very potent in decreasing food intake and probably in increasing fat oxidation. However, proof of concept studies remain to be performed in humans with orally bioavailable melanocortin MC_4 receptor agonist molecules exhibiting an acceptable toxicology profile. It is important to note that, in general, it is easier for chemists to generate small molecules antagonizing a pathway, rather than stimulating a pathway. Therefore, molecules targeting "orexigenic pathways" are likely to appear on the market before molecules targeting "anorectic pathways".

Table 6 presents some potential targets or pathways involved in an increase in energy expenditure and/or fat oxidation via central mechanisms or directly on peripheral tissues. At the present time, as mentioned earlier, the development of selective β_3-adrenoreceptor agonists targeting the human receptor is receiving the most attention (Weyer et al., 1999). Previous compounds were generated against the rat receptor and have typically shown problems of bioavailability or lack of selectivity in humans. Leptin remains an attractive target because of the dual effect on food intake and energy metabolism. Whether or not small agonist molecule of the leptin receptor can be generated remains to be shown. Alternatively, molecules causing an allosteric enhancement of endogenous leptin action may be a viable strategy since obese patients already have high plasma and cerebrospinal fluid leptin concentrations.

Thyroid hormones have always represented an attractive target for stimulating energy expenditure. However, because of the well-known side effect on the cardiovascular system, molecules acting predominantly on the thyroid beta receptor in the muscle may be a potential means to increase energy expenditure (Weiss et al., 1998) without unwanted effects. If uncoupling proteins can be activated only in desirable tissues, then they are likely to represent good targets for obesity (Ricquier and Bouillaud, 2000) Recent data from the knockout of the protein tyrosine phosphotase 1β indicate that inhibitors of this phosphotase may represent a viable way of increasing energy expenditure with a concomitant improvement of insulin sensitivity (Elchebly et al., 1999). Among other potential obesity targets one can propose diacylglycerol acyltransferase (DGAT) (Smith et al., 2000), peroxisome proliferation-activated receptor-alpha (PPAR-α) (Kubota et al., 1999), PPAR-γ (Guerre-Millo et al., 2000; Willson et al., 2000), peroxisome proliferation-activated receptor gamma coactivator 1 (PGC1) (Wu et al., 1999), carnitine palmitoyltransferase (Cohen et al., 1998), ghrelin (Tschöp et al., 2000) high-mobility group protein (HMGIC) (Anand and Chada, 2000), and sterol regulatory element-binding protein (SREBP) (Boizard et al., 1998; Kakuma et al., 2000). However, most of these pathways may need more validation before being considered true obesity targets.

7. Conclusions

With our growing understanding of the biology of the human genome, it is very likely that new targets will be identified and prioritized on the basis of the scheme presented in Table 5. A new generation of drugs with different mechanisms of action will be developed and used in combination therapy to treat the complex disease of obesity. Moreover, in the future, it is likely that the treatment of obesity will be characterized by growing individuality and sophistication. Regardless, it is certain that the five coming years will see an explosion of research on target identification and target validation for the pharmacological treatment of obesity. However, given the epidemic nature of obesity at this time, only public health measures and drastic public policy changes can modify the "obesigenic" environment (Egger and Swinburn, 1997). Without major societal changes, it is almost certain that the obesity epidemic will continue to spread around the world in the present century.

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