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Current paradigms in the etiology of obesity

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ABSTRACT

The global prevalence of obesity continues to rise at an alarming rate and 37.7% of US adults are obese. Understanding the causes of excessive weight gain is extremely important, as it paves the way for the development of new therapies to control this epidemic. Obesity is a heterogeneous chronic disease where multiple factors interact to produce a state of positive energy balance leading to an increase in body weight. This review focuses on the major biological, environmental, and behavioral determinants of obesity. The key biological factors include genetics, brain-gut axis, prenatal determinants, pregnancy, menopause, neuroendocrine conditions, medications, physical disability, gut microbiome, and viruses. Propensity to develop obesity owing to one or more of these elements is exacerbated by environmental and behavioral influences. Environmental factors include food abundance, built environments, socioeconomic status, culture, social bias, and environmental chemicals. Behavioral factors comprise excessive calorie intake, eating patterns, sedentary lifestyles, insufficient sleep, and smoking cessation. It is essential to identify the determinants of adiposity in individuals with obesity to tailor prevention and treatment techniques effectively.

1. Introduction

Obesity is a major public health problem that spans the world. The worldwide prevalence of obesity continues to increase at an alarming rate [1,2] and in the United States, 37.7% of adults are obese [3]. The effect of this pandemic on health-related quality of life of affected individuals has been detrimental. There is overwhelming epidemiologic evidence of serious obesity-related comorbidity, specifically cardiovascular disease, type 2 diabetes, cancer, osteoarthritis, and psychological disturbance [4]. The resulting economic burden has expanded dramatically [5,6]. Thus, obesity is regarded as a public health crisis with an urgent need for action to reverse the observed trends [7]. The complexity of this disease lies not only in its breadth of complications but also in its multifaceted etiology [8]. Understanding the causes of excessive weight gain is extremely important, as it paves the way for the development of new therapies to control this global epidemic.

There has been an increased interest in understanding the role of genetics in obesity [9]. Nevertheless, the overwhelming upsurge in obesity prevalence in the past 2 decades cannot possibly be explained by genetic changes that could conceivably have occurred in this short duration [10,11]. Therefore, variations in obesity prevalence are influenced predominantly by environmental and behavioral factors, particularly increased calorie intake and reduced physical activity [12-14]. This work reviews the major biological, environmental, and behavioral determinants of obesity.

2. Etiology of obesity, a multifactorial disease

Although consumption of calories in excess of the body's ability to expend energy is key to storage of excess calories in adipose tissue [15], obesity is a heterogeneous disease where multiple biological, environmental, and behavioral obesogenic factors interact to bring about a state of positive energy balance [16-18]. Energy balance comprises energy intake, energy expenditure, and energy storage [19]. Energy is acquired through the intake of calorie-containing nutrients namely protein, carbohydrate, and fat, as well as alcohol. Energy is expended through 3 metabolic processes: resting metabolic rate, thermic effect of food (TEF), and physical activity-induced energy expenditure. Resting metabolic rate determines the amount of energy the body uses for metabolic activities at rest, and is relative to body weight, mainly fat-free mass. TEF (8%-10% of total caloric intake) represents the energy used for digesting and metabolizing ingested food. The energy spent through physical activity is the most variable constituent of energy expenditure, as it is proportional to the duration

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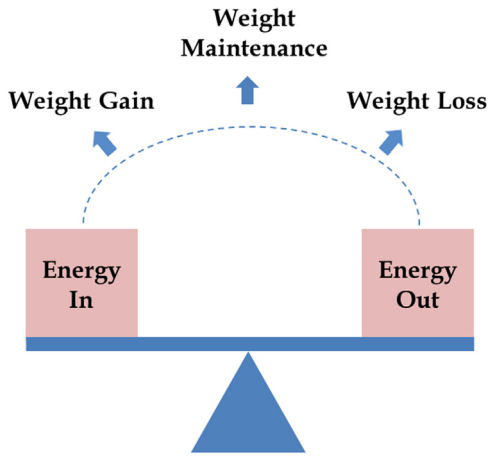

Fig. 1. Energy balance. In the human body, energy balance is the relationship between the intake of food and beverages (Energy In) and the expenditure of energy through the body's basal metabolism and physical activity (Energy Out). When Energy In = Energy Out for a prolonged period, body weight is maintained. However, when calorie intake exceeds the body's total energy expenditure (Energy In > Energy Out) for a prolonged period, a state of positive energy balance ensues, demonstrated by weight gain. Similarly, weight loss occurs owing to negative energy balance when energy expenditure exceeds energy intake (Energy Out > Energy In) persistently.(Color version of figure is available online.)

of physical activity in addition to the energy cost of that particular activity [20]. Stable energy homeostasis (Figure 1) is achieved when energy intake equals energy expenditure, thus representing a stable body weight. Changes in body weight occur when energy intake and energy expenditure are unequal, over a given time period [20]. Thus, energy intake in excess of energy expenditure creates a state of positive energy balance leading to an increase in body weight, predominantly as fat mass [21]. Hence, biological, environmental, or behavioral factors that influence body weight do so by altering energy intake or expenditure [20].

3. Biological factors

This section covers biological factors with an evidence-based association with obesity: genetics, brain-gut axis, prenatal determinants, pregnancy, menopause, neuroendocrine conditions, medications, physical disability, gut microbiome, and viruses. When one or more of these determinants is present, interaction with environmental and behavioral factors contributes to the expression of obesity.

3.1. Genetics of obesity

Despite the predominant effect of the environment and behavior on the propensity to develop obesity, there is an evidence of a genetic component to obesity [22]. In fact, studies of twins and adoptees suggest that up to 70% of the interindividual variation in fat mass has a genetic etiology [23]. Heritability of obesity has been implicated in all the aspects of energy homeostasis, such as food intake, TEF, spontaneous physical activity, and basal metabolic rate, [24]. For instance, data from the Quebec Family Study cohort was recently used to examine the influence of genetic heritability on body fat distribution and behaviors that affect energy balance. The authors detected significant genetic heritability for total body fat, fat-free mass, body fat distribution, basal metabolic rate, physical activity, macronutrient intake, and eating behavior. They also reported evidence of influence of gene-behavior interplay on these observations. These findings represent a polygenic basis for common obesity [25].

The discovery of the *ob* (Lep) gene that encodes the peptide leptin and learning that an alteration in this gene causes obesity elevated the interest of scientists in the genetics of obesity [26]. Thus, candidate gene and genome-wide association studies have led to the identification of more than 300 different genes and gene markers that are linked to obesity and appear to interact with the environment for obesity to be expressed [27,28]. This suggests the classification of obesity into 3 subgroups, from a genetics standpoint: monogenic obesity (single candidate gene defect, eg, leptin), syndromic obesity (chromosomal abnormalities, eg, Prader-Willi syndrome), and polygenic obesity (common obesity; multiple gene variants) [18].

3.1.1. Candidate genes and monogenic obesity

To date, several rare forms of severe early-onset human obesity have been identified, mostly stemming from mutations in genes controlling the leptin-melanocortin pathway that regulates food intake. These candidate genes [18,29,30] are listed in Table 1. The identification of these genes and continued research efforts toward the discovery of other potential candidate genes for obesity permit the diagnosis of affected individuals and the possibility of introducing effective treatment options.

3.1.2. Syndromic obesity

At least 25 forms of syndromic obesity are known. The following are some of the most common types for which the genetic basis is partly or fully understood: Prader-Willi syndrome; Bardet-Biedl syndrome; Alstrom syndrome; and Wilms tumor, aniridia, genitourinary anomalies, and mental retardation [31]. The most common form of syndromic obesity, Prader-Willi syndrome, is a complex genetic disease caused by alterations in gene expression on the paternally inherited chromosome 15q11.2-q13 region. The phenotype is characterized by short stature, overeating, excessive weight gain, cognitive disability, and behavioral problems. Obesity is the chief cause of morbidity and mortality among affected individuals [32,33].

3.1.3. Polygenic obesity

Of major clinical importance is the detection of genetic modifications with polygenic effects on body weight, as this represents most human cases of obesity, as opposed to the very rare monogenic forms of the disease [34]. Some obesogenic traits arise from

Table 1
Candidate genes associated with severe early-onset obesity. (Adapted with permission from Huvenne et al [30]).

Gene	Encoded protein	Obesity onset	Diagnosed cases
LEP	Leptin	First few days of life	Fewer than 100 patients worldwide
LEPR	Leptin receptor	First few days of life	Overall 2%-3% of severe early-onset obesity
POMC	Proopiomelanocortin	First few months of life	Fewer than 10 patients worldwide
MC4R	Melanocortin-4 receptor	Childhood	Overall 2%-3% of obesity in adults and children
PCSK1	Proprotein convertase subtilisin/kexin type 1	Childhood	Fewer than 20 patients worldwide
SIM1	Single-minded 1	Childhood	Fewer than 50 patients worldwide
NTRK2	Neurotrophic tyrosine receptor kinase 2	First few months of life	Fewer than 10 patients worldwide