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Molecular genetics of human obesity: A comprehensive review

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ABSTRACT

Obesity and its related health complications is a major problem worldwide. Hypothalamus and their signalling molecules play a critical role in the intervening and coordination with energy balance and homeostasis. Genetic factors play a crucial role in determining an individual's predisposition to the weight gain and being obese. In the past few years, several genetic variants were identified as monogenic forms of human obesity having success over common polygenic forms. In the context of molecular genetics, genome-wide association studies (GWAS) approach and their findings signified a number of genetic variants predisposing to obesity. However, the last couple of years, it has also been noticed that alterations in the environmental and epigenetic factors are one of the key causes of obesity. Hence, this review might be helpful in the current scenario of molecular genetics of human obesity, obesity-related health complications (ORHC), and energy homeostasis. Future work based on the clinical discoveries may play a role in the molecular dissection of genetic approaches to find more obesity-susceptible gene loci.

1. Introduction

Obesity is a multi-factorial disorder, a condition characterized by an excess of body fats. It is more prevalent in the developed countries, but in recent years, it dramatically increased in the developing countries [1]. If it continues by the same rate till 2030, the numbers could rise to a total of 2.16 billion overweight and 1.12 billion obese individuals, or 38% and 20% of the world's adult population, respectively [2]. Energy imbalance reflects a state of positive energy balance (Fig. 1) owing to the genetic predisposition of obesity over recent decades [3]. The genetic aspects of obesity lead to mutations in various genes responsible for controlling appetite and metabolism. Over the past two decades, several strategies have been employed for the identification of genetic determinants of obesity. It includes studies of severe forms of obesity, genome-wide linkage studies (GWLSs) as well as GWAS and analyses of candidate genes. Moreover, based on recent information, about 127 sites in the human genome have been reported to link with the development of obesity through GWAS findings [4]. Since 2005, GWAS approach has led to breakthrough and advancement in the insights into the genetic determinants of common obesity. Single-nucleotide polymorphism (SNP) and animal models suggest genome-wide screens to identify common genetic variants associated with obesity. In this perspective, non-synonymous single-nucleotide polymorphisms (nsSNPs) are used as a potential biomarker to identify the deleterious and neutral effects on protein function. Modern research tools and extensive studies will lead to an understanding of genes and their interaction to cause obesity, which may help with successful interference and treatment [5]. Among these GWAS findings, the first

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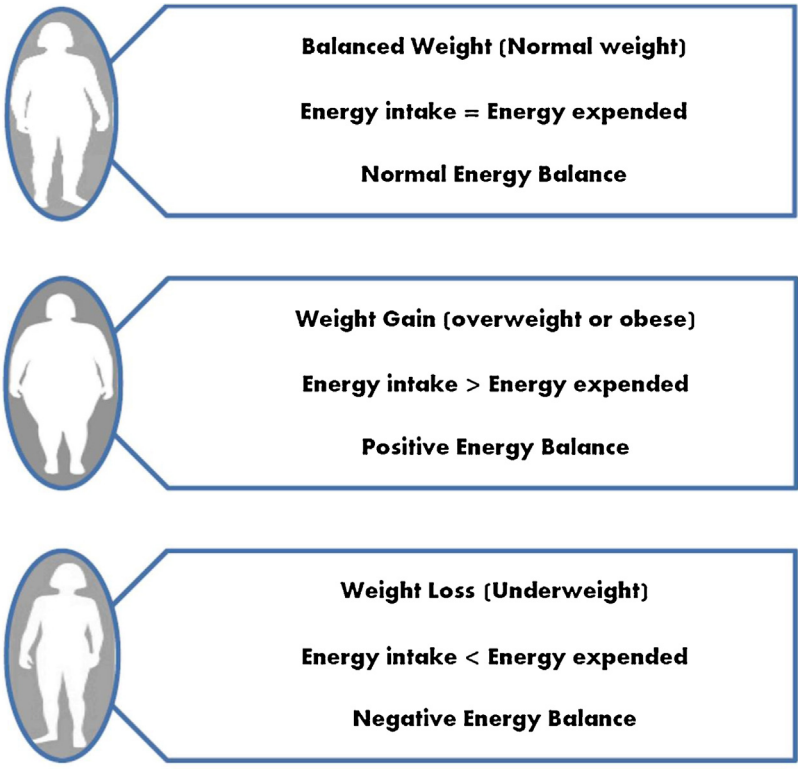

Fig. 1. Energy balance: positive energy balance due to overeating, accumulation of fat and weight gain leads to overweight and obesity, whereas negative energy balance due to under-eating, loss of appetite, anorexia nervosa and some digestive diseases lead to underweight.

obesity-susceptible locus identified was the FTO (fat mass obesity associated) gene. This gene has the biggest effect on obesity phenotypes risk till date. Each risk allele in FTO was shown to be associated with a 1–1.5 kg increase in body weight and a 20–30% increase in obesity risk [6,7]. Gene–environment interactions (GEI) lead to cause obesity and several metabolic disorders [8]. Epigenetics is the study of heritable changes in gene function without modifications in DNA sequences [9]. Epigenetic changes like DNA methylation, chromatin remodelling, packaging of DNA around nucleosomes and histone modification may also lead to GEI, metabolic disorders and obesity [10–12]. In this review, it is planned to explore the current insights into the molecular genetics of human obesity, ORHC, and energy homeostasis.

2. Overview of signalling molecules and regulation of feeding behaviour by central nervous system (CNS)

Two scientists, Hetherington and Ranson, have demonstrated that hypothalamus plays an important role in the regulation of energy metabolism [13]. During 1950s and earlier, it was hypothesized that the intake of food was closely related to the accumulation of fats in the body. But in the late 1970s and early 1990s, several satiety signals like pancreatic glucagon, bombesin and cholecystokinin were identified to check the presence of food [14,15]. The following signalling molecules play an important role in the feeding behaviour regulated by the hypothalamus of CNS:

- *Leptin*: it is secreted by white adipose tissues mediated directly through the CNS and inhibits food intake. Leptin conveys information to the hypothalamus regarding the amount of energy stored in adipose tissues and helps in the suppression of appetite and stimulates energy expenditure [16]. It affects metabolic processes like fatty-acid oxidation by activating AMP-activated protein kinase [17]. It also controls the reproductive functions and puberty in females [18,19]. In addition, leptin also affects the immune response by influencing regulatory T (Treg) cell function [20]. With the help of leptin receptor (OB-R), leptin actions are mediated and regulated [21]. In humans, four different OB-R isoforms are there, out of which only the long form of the leptin receptor (OB-Rfl) is able to perform the complete signalling action of OB-R by means of JAK-STAT (Janus kinase-signal transducer and activator of transcription) pathway [22];
- *Insulin*: it is secreted by pancreatic β-cells and functions similar as leptin for adiposity signal processing. It stimulates the uptake of glucose and deposition of glycogen in the liver and decreases the release of glucose from the liver. It interacts with specific receptors in the arcuate nucleus of the hypothalamus and reduces food intake and body weight regulation [23]. In one study, it was shown that glycogen metabolism is a mediator in

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