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Research lectures

Obesity: Pathophysiological concepts

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Obesity is defined as an accumulation of body fat to the extent that health may be negatively affected. The accumulation of body fat indicates failure of the system that ensures energy homeostasis by correcting for environmental influences, behavior, psychological factors, genetic makeup, and neurohormonal status [1,2]. There is a spectrum that ranges from genetically determined obesity to behaviorally determined obesity, with most patients having a mix of these two causative factors. The pathophysiological mechanisms vary over time. During the weight-gain phase, the energy imbalance is primarily related to environmental and behavioral factors. Subsequently, profound changes affecting the anatomy, biology, and function of fat tissue develop.

1. Biology and behavior

Genetic factors exist that confer susceptibility to the effects of the environment and of behaviors [3–6]. Susceptibility may also result from intrauterine or postnatal genetic imprinting [7–11]. However, genetic factors cannot explain the dramatic increase in the prevalence of obesity that is associated with lifestyle changes. Behavior also plays a key role. A number of factors may lead to an increase in food intake, including availability and palatability of foods, conviviality, cultural attitudes, work-related eating habits, and eating disorders. A complex set of neurohormonal circuits conveys information about the absorptive and postabsorptive periods, energy reserves, sensory input, nutritional status, and environment [12,13]. In the hypothalamus, the four structures most closely involved in these circuits are the paraventricular nucleus, arcuate nucleus, ventromedial nucleus, and dorsomedial nucleus. These structures emit anabolic and catabolic effector networks. The *anabolic system*, which increases food intake and energy storage, involves neuropeptide Y and agouti gene-related protein (AgRP). Other substances that increase food intake include the alpha2 catecholamines, opioids, the hypocretin/orexin system, and the reward system. Leptin, melanocortins, serotonin, and beta catecholamines inhibit food intake. Other signals, such as insulin, act on the hypothalamus. Endocannabinoids increase the motivation to eat [12,13].

2. Fat cell abnormalities

White fat is composed of mature adipocytes, adipocyte precursors, endothelial cells, macrophages, blood vessels, nerves, lymphatics, and connective tissue. Fat is an endocrine and paracrine organ that exhibits remarkable plasticity [14–16]. Fat accumulation is related to adipocyte enlargement (hypertrophy) caused by an increase in the amount of triglycerides contained in each cell. However, beyond a threshold, the cell can no longer enlarge and increased fat storage requires an increase in the number of adipocytes (hyperplasia). Fat tissue hyperplasia occurs via the proliferation of stem cells, which subsequently differentiate into adipocytes. Once differentiated, the cells cannot recover their previous precursor status and remain available for fat storage. Therefore, the amount of body fat cannot decrease below a floor determined by the number of adipocytes. The

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physiology of energy reserves involves not only the balance between intake and expenditure, but also the storage capacity of the fat tissue.

3. Society and environment

The prevalence of obesity is strongly dependent on social and economic factors. It correlates negatively with academic achievement, income, and job title. Changes in economic conditions and lifestyle lead to changes in the nutritional, familial, and social environment that may increase the risk of obesity in susceptible individuals. Eating habits are crucial. The availability of food, calorie density of widely available foods, serving sizes, and many other factors influence the risk of obesity. We are now in uncharted territory: our traditional model for eating is not relevant to modern lifestyles, and the profound changes in eating habits are not conducive to good nutrition. Furthermore, we spend far less energy than in years past, as a result of changes in clothing, heating, and means of transportation; of a decrease in the need for manual work and efforts to obtain food; of the increasing availability of services; and of the decrease in the energy cost of consumption activities [17,18].

4. Consequences

The scale of excess mortality associated with obesity increases in inverse proportion to the age at onset during adulthood. Obesity is significantly associated with hypertension, diabetes, hyperlipidemia, coronary heart disease, heart failure, respiratory failure, cholelithiasis, osteoarticular disease, and several cancers [1,2]. The fear of fat is now a cultural standard that is constantly reinforced by undue medicalization of weight and health issues. This epidemic obsession with weight is becoming a social phenomenon. The discrimination and stigmatization to which patients with severe obesity are subjected to cause severe guilt and can have burdensome psychological and social consequences.

5. Conclusion

Obesity, a disease of society and economic transition, is spreading at an epidemic pace throughout the world. In most cases, environmental, behavioral, and biological factors interact to cause obesity. When designing treatment strategies, the potential for disease progression and the heterogeneity of individuals with obesity must be borne in mind [19].

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