Intrinsic Control and Environmental Factors in Food Consumption Related to Obesity

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Abstract

Obesity results from a complex interaction of genetic, hormonal, physiological, anatomical, psychological, behavioral and environmental factors causing an imbalance between energy intake and energy expenditure. According to the World Health Organization, the estimated number of obese people around the world has doubled from 1980, meaning that more than 600 million people worldwide are obese.

Obesity is associated with low-level chronic inflammation and represents a major risk factor for cardiovascular and metabolic diseases, but also some cancers. Centers that regulate food intake and energy balance are placed in the hypothalamus. Chemical signals are transmitted between hypothalamic neurons, and those neurons also affect the secretion of different hormones that are important for maintaining energy balance and metabolism. Moreover, genetic predisposition is also a risk factor for obesity development. Key neuronal populations for maintaining energy balance are the orexigenic agouti related peptide (AgRP)/neuropeptide Y (NPY) neurons and the anorexigenic proopiomelanocortin (POMC) neurons. This review attempts to present the prevalence and the major pathways regulating energy balance that may be affected by many environmental and social factors, such as emotions and human behavior, and can lead to obesity.

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Epidemiology of obesity

Increased accumulation of fat tissue leads to obesity. The most common ways to evaluate obesity are by the calculation of the body mass index (BMI), the measurement of waist circumference (WC) and the calculation of the ratio of the circumference of waist and hip

(WHR). A BMI of 20-25 kg/m2 is considered normal; 25-30 kg/m2 is overweight; 30-40 kg/m2 is defined as obesity and >40 kg/m2 is defined as extreme obesity. For children and adolescents, a BMI >95 percentile is considered overweight/obesity (1). A waist circumference (WC) of at least 88 cm for women and 102 cm for men is defined as obesity (2). A WHR above 1.0 in male subjects and above 0.6 in women is considered as an obesity pattern (3). The prevalence of obesity in the general population is increasing worldwide. Based on the Nutrition Examination Survey (NHANES) 1999–2000 in the USA, the prevalence of overweight in adults was 64.5% and the prevalence of obesity was 30.5% (4). The most comprehensive overview of the prevalence of obesity is provided by the World Health Organization (WHO) Global Status Report on noncommunicable diseases 2014 (5), which showed that the age-standardized prevalence of obesity in adults aged 18 years and over (cut-off point set to BMI ≥30 kg/m2) in the USA was 33.7%. Canada had a prevalence of obesity of 28%, Mexico 28.1%, Argentina 26.3% and Brazil 20%. The same publication reported that in Europe, the prevalence of obesity among the general population is as follows: UK 28.1%, Slovenia 25.1%, Spain 23.7%, Croatia 23.3%, Italy 21%, Germany 20.1% Turkey 29.5, France 23.9% and Bosnia and Herzegovina 17.9%. Interestingly, in Asia the prevalence of obesity was significantly lower: the prevalence of obesity was in China 6.9%, India 4.9% and Japan 3.3%. Australia has a prevalence of obesity in the general population of 28.6%. In Africa, there is a wide range of obesity prevalence, from 28.9% in Egypt to 10.5% in Zimbabwe, 11% in Congo and 11.4% in Cameroon (5). Based on WHO data, in 2014 more than 1.9 billion adults aged 18 years and older (39% [38% of men and 40% of women]) were overweight. Of these over 600 million adults were obese—about 13% of the world's adult population (11% of men and 15% of women). The worldwide prevalence of obesity more than doubled between 1980 and 2014 (5).

The prevalence of obesity is linked to the prevalence of various cardiometabolic diseases, such as diabetes mellitus. Recently, in 44 observational or clinical studies that were evaluated in a systematic literature review by Colosia et al, the obesity prevalence in T2DM subjects was determined based on BMI or WC (2). Based on BMI, the prevalence of obesity in that population group was 30-85.5% in Asia, 32.7-64.1% in Europe, 26.8-64.3% in North America, 32.5-59% in South America and 32-42.5% in Africa. The prevalence of obesity in T2DM patients based on waist circumference was 56-67% in Europe, 54.6% in Africa and 20-81% in Asia. However, there were no studies taking into account obesity based on WC in that publication, and not all countries were covered by the examined studies (2). Due to its effects on hormonal balance, autonomic system function and various organ functions, obesity represents a significant risk factor for many other chronic diseases such as hypertension, atherosclerosis, diabetes mellitus and chronic kidney disease..

The pathophysiological mechanism of obesity

The development of obesity is a consequence of several pathophysiological factors. First of all, it is an imbalance of food intake and energy expenditure. The central control of energy balance by the hypothalamus and the feedback loop of peripheral metabolic factors from the gastrointestinal and endocrine system, including adipose tissue, are very important factors, particularly in obesity related to chronic stress and other cardiometabolic diseases. Genetic predisposition accounts for approximately 30% of the risk for obesity development (6). The most recognized mutations are those of receptors or hormones related to the regulation of feeding behavior, and subsequently energy balance: e.g. mutations of the leptin gene and the leptin receptor gene, the mutation of the proopiomelanocortin gene (POMC) and mutations of genes for melanocortin receptors (e.g. MCR-4) (7). These conditions lead to pathological obesity with other metabolic and hormonal imbalances.

Central control of dietary intake (energy balance)

An individual's energy intake and expenditure must be balanced over time to ensure adequate

body composition and function (8). The quantity of food intake is regulated on a short-term basis, which controls the intake of food at each meal, and long-term, which is mainly concerned with the maintenance of normal quantities of body energy stores (9). The main homeostatic system involved in the regulation of energy balance is located in the hypothalamus, and the nucleus arcuatus has a central role in these processes. It functions by integrating neural and nutrient signals with hormonal signals that arise in the small intestine, liver, pancreas, adipose tissue and brainstem (10). The total daily energy intake is a function of the size, frequency, and qualitative composition of meals, and the perception of hunger and the decision to initiate a meal are determined by complex interactions between genetic, social, learned, environmental, circadian, and humoral factors (11).

Centers for the control of hunger and satiety are located in the hypothalamus, Stimulation of the lateral nuclei causes hyperphagia (their destruction has the opposite effect), while stimulation of the ventromedial nuclei causes satiety and aphagia (8). Other areas add to the complexity: Paraventricular nuclei destruction leads to excessive eating, dorsomedial nuclei destruction leads to depressed eating, and arcuate nuclei are centers where several hormonal signals from the adipose tissue and gastrointestinal tract are integrated to regulate food intake (9). In addition to these main structures of the homeostatic system, an important role is played by the brain's reward system — located in proximity to the hypothalamus with its main nodes centered on the ventral striatum. It includes the nucleus accumbens, the ventral pallidum, and the ventral tegmental area (10).

Evolutionary development led to the emergence of protective central mechanisms that are focused on the resistance of fat loss and on the maintenance of body weight, crucial features that helped enable the survival of the human species throughout time (12). Unfortunately, such a system predisposes humans to obesity in times of abundance, with all the known adverse effects. Obesity has become one of the leading medical challenges

of the 21st century (11). "Hunger hormones," like orexin and ghrelin, as well as high-calorie food, incite individuals to eat, while "satiety hormones" like leptin, insulin and other so called "brain-gut peptides," suppress feeding behavior (12). Weight increase and obesity can result from long-term imbalance between the hunger and satiety signals (12).

There exist two neuronal populations that are crucial in energy balance homeostasis and are located in the arcuate nucleus of the hypothalamus: the orexigenic agouti related peptide (AGRP)/neuropeptide Y (NPY) neurons and the anorexigenic proopimelanocortin (POMC) neurons (10). Activation of the POMC neurons decreases food intake and increases energy expenditure. On the other hand, activation of the NPY-AGRP neurons exerts opposite effects, increasing food intake and reducing energy expenditure, with both of these neuronal groups having significant interaction (8). These neuronal groups are the main targets of hormones that regulate appetite, including leptin, ghrelin, insulin, cholecystokinin and others. POMC neurons secrete the alpha-melanocyte-stimulating hormone (MSH), which acts via several types of melanocortine receptors (MCR) and through them leads to a reduction in food intake and an increase in energy expenditure (9), as discussed below. AGRP are antagonists of MCR, increasing food intake. NPY increases appetite and is produced when energy reserves in the body are low (9).

Chronic stress and obesity

Stress is an incentive that occurs in response to certain experiences, representing the state of disrupted hemostasis. The organism reacts to stress via the central and peripheral segments of the autonomic nervous system and via the hypothalamic-pituitary-adrenal (HPA) pathway. Response to stress can be acute condition, and is necessary for the maintenance of homeostasis, or chronic stress, which is prolonged and may cause some disease states. Acutely, within a few hours, glucocorticoids act to inhibit the secretion of CRH and ACTH. That physiological effect is noticeably altered in

Figure 1. *Chronic stress and central mechanisms of weight gain*
Due to constant activation of the HPA axis during chronic stress, there is a marked increase in secretion of POMC, ACTH and glucocorticoids, which leads to enhanced blood glucose levels and increased insulin secretion. Persistent elevated insulin levels decreases sensitivity or number of insulin receptor in the NPY/AgRP region and reduce inhibition of the orexigenic neurons that leads to obesity.
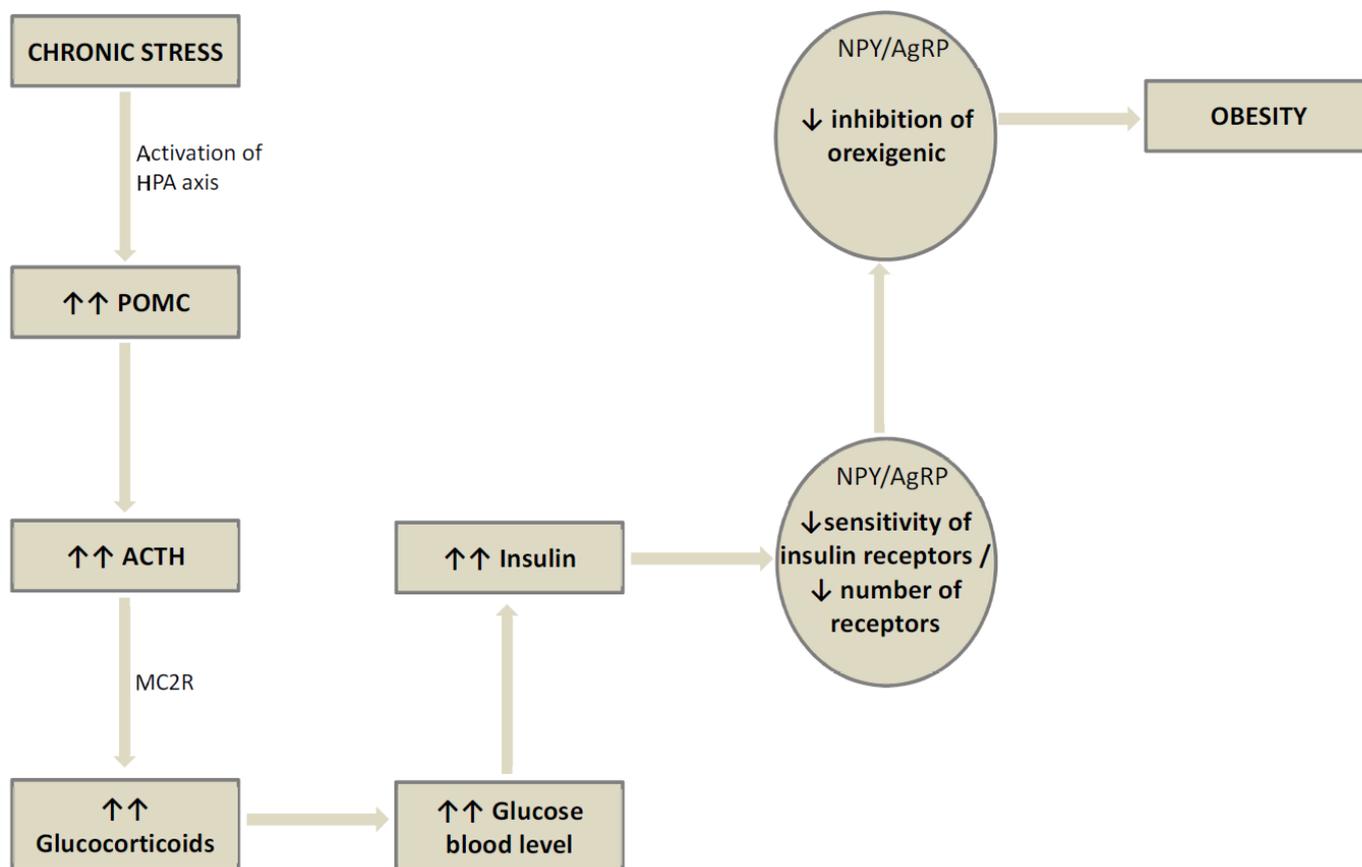
chronic stress, where the effect of glucocorticoids on the brain is excitatory (13-15).

Many recent studies have shown that chronic stress may contribute to an increased risk for the development of obesity and other metabolic diseases. One of the elementary responses to stress is mediated by the activation of the para-ventricular nucleus of the hypothalamus that secretes a corticotrophin-releasing hormone (CRH), which stimulates the secretion of adrenocorticotrophin (ACTH) from the anterior pituitary gland. ACTH binds to its MC2R receptors on the adrenal cortex and thus stimulates the secretion of cortisol (13-15). Cortisol causes the elevation of blood glucose and insulin concentration, whose long-term effect may cause insulin resistance and diabetes mellitus type 2.

The long-term effect of chronic stress on the HPA axis leads to increased accumulation of visceral fat, but it also has been shown that obesity represents a state of chronic systemic low-grade inflammation that may cause an impaired function of the HPA axis. In the state of chronic stress, glucose metabolism is disrupted. The increased secretion of ACTH and hence a high level of glucocorticoids, primarily cortisol, is associated with weight gain and the high production of proinflammatory hormones and adipokines by adipose tissue depots (15-17).

The main central targets of insulin (and leptin) action are the POMC and AgRP neurons of the arcuate nucleus of the hypothalamus. Some studies suggest a major physiological importance of insulin receptors in the brain in the long-term modulation of energy balance, whereas the disturbance of the insulin receptor

gene may cause increased body fat and high plasma levels of insulin and leptin (18). Chronic stress also increases the activation of the sympathetic nervous system, and thus contributes to impaired glucose tolerance and to an increased risk for developing of cardiovascular events (19). Thus, chronic stress that activates the HPA axis, as well as the sympathetic nervous system, may progressively contribute to the occurrence of obesity and metabolic syndrome (Figure 1).

The role of MSH receptors

It is well accepted that the central melanocortin signaling pathway has a critical role in the maintenance of energy balance, and it is known that peptides generated from POMC have a key role in controlling food intake and weight gain (20, 21). Melanocortin receptors present a distinct family of G-protein-coupled receptors; they are coupled to adenylate cyclase and exert their effects primarily by activating a cAMP-dependent signaling pathway (20). Melanocortin receptors are differently distributed in various kinds of tissue and differ from each other in their affinity for binding various melanocortins and/or their antagonists, agouti signaling protein (ASP) and agouti-related protein (AgRP) (20).

Prohormone convertase 1 (PC1) is expressed in pituitary corticotrophs and produces ACTH, while the expression of PC1 and prohormone convertase 2 (PC2) within the hypothalamus leads to the production of α-, β- and γ-MSH (7). The actions of ACTH and melanocortins are mediated by specific interactions with five melanocortin receptors (MC1R to MC5R), two of which, MC3R and MC4R, are predominantly expressed within the central nervous system, and in the context of human energy balance and body weight regulation, they— especially MC4R— have the most important role (7,22). MC1R is expressed in pigment-producing cells of the skin and hair, and when α-MSH binds to it the production of pigment melanin is stimulated. Also MC1R is expressed on cells of the immune system, wherefore α-MSH has anti-inflammatory effects (7). MC2R is an ACTH receptor expressed in the adrenal cortex, while

MC3R is expressed in the brain (mainly in the hypothalamus, cortex, thalamus and hippocampus), and over it γ-MSH plays a role in cardiovascular functions and sodium and energy homeostasis (7). The β-MSH peptide performs its action in weight regulation by binding to MC4R, helping to maintain energy balance (7), and in this context has the most important role. MC5Rs are expressed at low levels in numerous tissues, including the sebaceous gland, where it has a role in sebaceous secretion (7).

It is thought that the anorectic effect of POMC neurons is mediated via α- and β- MSH. Human and animal studies have shown that a lack of MC4R leads to obesity, hyperphagia and insulin resistance (23, 24), and in obese persons β- MSH mutations rather than α-MSH (25). As mentioned above, melanocortin receptors are distinguished by their ability to bind ligand, and under normal physiological conditions, ASP doesn`t have a role in the regulation of food intake since it antagonizes MC1R, but when ASP is synthesized from dermal papilla cells in very high concentrations, it acts as an antagonist of MC4R (20). It is thought that AGRP binds to neural MC3R and MC4R, and in genetically obese mice AGRP is overexpressed, indicating that AGRP has a physiological role in feeding behavior (20). No effect was observed on MC1R and MC2R. MC4R is specific since it binds both antagonists, ASP and AGRP, while MC3R binds AGRP, and MC1R binds only ASP (20).

Food availability – food quality (salt/sugar)

As never before, the food-based dietary diversity strategy has been put into the focus of worldwide political attention and has social, cultural, economic and environmental benefits (26). Although it is well known that dietary habits and health effects depend on ethnicity, gender, region and city (27), there is a widespread intention to improve world population health and individual health through diet (28). In the past, the concept of food quality was quite different compared to the present day, where an important role is given to modern marketing and

sophisticated industrial production methods of processed food rich in added sugar and salt (29). In the everyday diet, the sugar content has tripled during the last 50 years, and there is critical concern about dietary fructose, which has various negative effects on body metabolism (30). It is even popular to compare its effects with those that result from alcohol intake. Both metabolic processes are predominantly based on glycolysis, generate reactive oxygen species and result in a similar disease range (31).

Kitchen salt, sodium chloride, has a very important role in the food industry. The consumption of salt, even much more than is necessary for normal homeostatic process in the human organism, attenuates bitter taste and enhances taste in general. Bakery products, a widely available and popular food category for every age group, are considered to be a major hidden salt source.

In general, even though the word "addiction" has a negative connotation, much research suggests that consuming salty, sweet and fatty foods, for example fast food meals, can produce similar neurophysiological effects as in certain addictive drugs, leading to human obesity in the general population (32). That kind of processed food induces effects that are overwhelming to our brain-reward circuitry in a way natural food does not (30). Innovative solutions need to be implemented by the food industry to replace sodium with more acceptable substances without customer dissatisfaction (33).

The World Health Organization has taken aim at a 30% reduction in global salt intake by 2025 (34). Croatia is an example of a country with an organized national program for the reduction of excessive salt intake, with the goal of helping to develop consciousness about the negative impacts of salt on hypertension (35).

Social interactions as extrinsic factor (mirror neurons)

When discussing the physiological mechanisms related to food intake, we cannot avoid discussing what food means to human beings in addition to being simply "body fuel". How does one distinguish between food as an elementary human need and food as part of social and emotional interaction? The external influence on individual food consumption is very complex; it depends on a variety of factors, and therefore some studies were overlap in the search for proper answers (36). Human beings have a tendency to imitate the behavior of others including behavior related to food intake, a phenomenon that is known to exist in the animal world as well (37). Through many psychological studies, it has been argued that the act of perceiving another person's behavior creates a tendency to behave similarly oneself, which is called the "chameleon effect" (perception-behavior link) (38). In recent history, this and many similar correlations were explained by the discovery of "mirror" neurons —a distinct and intriguing group of neurons whose activities have been located in many different cortical areas, but were most extensively investigated in the ventral premotor region F5. They can transform specific sensory information into a motor format. Moreover, we can say in a way that "motor" or "sensory" neurons have an impact on either execution or observation, and the "mirror" neurons have both (39). They have a huge role in learning during the first developmental periods of life (40). The described functions of mirror neurons can be used to explain the adoption of the first dietary habits from our parents and other close persons, because imitation is a fundamental method through which children learn from their parents, including choices of food and food quantity. According to that concept, obese children display an altered conscious perception of their own weight (41). In that sense, the mirror neurons may represent independent neurophysiological pathways to stimulate overeating and in that way increase calorie intake (37). Furthermore, the perceived trend which includes a lack of physical activity combined with high calorie meals leads to a high BMI, and together they have been referred to as the "big two" contributors to obesity (41,42). As well as having a negative effect (43), peer relationships can also have positive influences on developing everyday habits (44). For instance, peer group physical activity is the strongest

predictor for individual physical activity (40). It is not well explained, but stigmas also have a huge effect on food intake, whereas with some exceptions, negative characteristics are assigned to those people who consume large amounts of food (45). By applying a multidisciplinary approach and using sophisticated neuroimaging methods, more useful information could be obtained not merely about the relationship between mirror neurons and food intake habits, but also about human behavior in general.

In conclusion, the pathophysiology of obesity includes the complicated interaction of the autonomic nervous system and hormonal system with the neuropeptide feedback loops from the gastrointestinal system to the hypothalamic centers that regulate energy homeostasis. Moreover, it is significantly affected by human behavior, emotions and food intake. Thus, obesity is a preventable risk factor for other cardiometabolic diseases.

Disclosures

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