Obesity, a frequent manifestation of limbic system dysfunction

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Summary

The multidimensional condition of obesity attracts the attention of many clinicians and researchers from the fields of medicine, pediatrics, neurology, gerontology, biochemistry, genetics, and surgery, who attempt to clarify the etiopathogenetic background of the disease, to introduce an efficient treatment, which might ameliorate the quality of the life and prolong its expectation. Although obesity is seldom the main cause of death, however, it is a potential risk factor for several co-morbidities, which could abbreviate the road of life. Several regions of the central nervous system, which mediate the regulation of food intake, body weight, and energy homeostasis are involved in the pathogenetic spectrum of obesity. Among them, the hypothalamus and the limbic system play a crucial role, in collaboration with the gut peptides, in developing a gut-brain axis, which controls food intake, energy consumption, and body weight, increasing the deposition of adipose tissue, with substantial psychological consequences, which in turn, via the amygdala, may stimulate furthermore the overfeeding tendency, aggravating the existing condition.

Key words: Obesity,hypothalamus, limbic system, amygdala, neuropetides.

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Introduction

Obesity is a serious multifactorial health problem, increasing gradually mostly in societies that have adopted a western-style of diet and everyday life [1, 2]. The worrying fact is that obesity is frequently associated with hyperphagia, hyperinsulinemia, and hyperleptinemia and that it would be a potential risk factor for several co-morbidities, such as hypertension, obstructive sleep apnoea, type 2 diabetes mellitus, fatty liver disease, heart disease, cerebrovascular attacks, vascular dementia, sleep disturbances, depression, neurodegenerative conditions, certain neoplasias [3,4] and even for death in patients with Covid-19 [5,6].

Many environmental and genetic factors [7,8] may act as a strong predisposition for obesity, which however is closely related to the limbic and hypothalamic role in food intake and body weight control [9,10,11].

Several regions of the central nervous system, which mediate the regulation of food intake, body weight, and energy homeostasis are involved in the pathogenetic spectrum of obesity [12]. Among them, the limbic system, which is closely connected with the hypothalamus, plays a crucial role in energy control and increases the deposition of adipose tissue [13,14].

The role of the Central Nervous System in obesity

The role of the hypothalamus

The hypothalamus, being a very small anatomical structure of the diencephalon, located at the floor of the third ventricle [15], is characterized by a high functional activity concerning stimulation of hormonal release, control of the autonomic nervous system, thermoregulation [16] adjusting of circadian rhythms[17], and controlling body weight [18].

Initially, it was thought that a 'hunger center' is developed in the lateral hypothalamus[19] and at the same time a 'satiety center' counteracts it, which is located in the ventromedial hypothalamic nucleus (VMN) [20, 21]. In reality, a substantial body of evidence revealed that many more areas of the brain, including the structures of the limbic system, the hypothalamic nuclei, and several mesencephalic neuronal networks are actively involved in appetite regulation, food intake, and body weight control [21].

Besides, a high-fat diet induces an increase in the circulation of inflammatory cytokines and initiates a chronic low-grade inflammatory response in the hypothalamus [22,23], consisting of astrocytic proliferation and activation of microglial cells and brain macrophages, a phenomenon that

was extensively studied at the experimental level [24,25].

The role of the amygdala

Weight gain, resulting in obesity, is frequently associated with morphological or functional alterations of the amygdala [26, 27, 28] in connexion with the ventromedial hypothalamus which leads to hyperphagia [29, 30], a decrease in metabolic rate, autonomic disequilibrium, and growth hormone (GH) deficiency, which would contribute to weight gain [31].

The rich connecting network of the hypothalamus with the thalamus, the hippocampus, the amygdala, the mammillary bodies, the prefrontal area of the cortex, the nucleus accumbens, the basal ganglia, the raphe nuclei, the cerebellum, and the cortex of the brain hemispheres play reasonably a substantial role in the influence of the mental activities and the psychological conditions upon the hypothalamic homeostatic role [32], with marked consequences on the food intake and the control of the body weight [33].

The gut hormones and the brain

In addition, gut hormones such as cholecystokinin, somatostatins amylin, ghrelin, oxyntomodulin, glucagon-like peptide-2, and glucose-dependent insulinotropic peptide are of essential validity in regulating body weight [34], given that they act as neurotransmitters within the central nervous system, developing a gut-brain axis, that controls food intake and energy consumption [35].

The dorsal vagal complex in the brain stem contributes greatly to the interpretation and relaying of peripheral signals and releasing proper information to the amygdala and the arcuate nucleus of the hypothalamus, among other diencephalic centers, which stimulate or inhibit food intake [36]. Thus, peptides such as Peptide YY, pancreatic polypeptide, glucagon-like peptide-1, and oxyntomodulin suppress appetite [37], whilst ghrelin increases the desire of taking food [38, 39].

Inside the amygdala and the arcuate nucleus (ARC) of the hypothalamus, a large number of neurons co-express neuropeptide Y (NPY) and agouti-related peptide (AgRP), which stimulate food intake [40], resulting in increased adiposity. NPY/AgRP and POMC/CART neuronal networks must be substantially influenced by circulating leptin, insulin, glucose, amino acids, and fatty acids.

BDNF and food intake

At the same time, the brain-derived neurotrophic factor (BDNF), which is highly expressed in the ventromedial hypothalamus suppresses food intake through the MC4R signaling system antagonizing the NPY neurons [41]. It is reasonable, therefore, that any degeneration of the BDNF-sensitive neurons may result in obesity [42]

A chronic high-fat diet may also induce degeneration of POMC/CART (co-expressing pro-opiomelanocortin) neurons and may affect autophagy and synaptogenesis, resulting in insulin resistance and cognitive impairment.

The limbic and hypothalamic autophagic pathway [43] is essential for the activation of orexigenic and anorectic neurons and for controlling food intake, especially in response to depression, anxiety, panic reactions, and various additional stress signals [44,45].

In a parallel way, impairments in the central signaling pathways of insulin [46], which gives an adiposity negative-feedback signal, and a decrease of leptin sensitivity are important etiological factors for energy imbalance and obesity development [47], since insulin and leptin are the main anorectic hormones that act in the arcuate nucleus, activating POMC neurons, which are characterized by a high density of leptin receptors.

The limbic and hypothalamic resistance to insulin and leptin action is also a main cause of obesity[48], given that the resistance to insulin and leptin anorectic function may lead to a continuous excessive food intake, as a mode of everyday life [59].

Inhibition or reversal of resistance to insulin and leptin by pharmacological factors, food restriction, or increased physical activity are frequently associated with reduced adiposity, underlining the role that these hormones play in the pathogenesis of obesity[50].

Intermittent fasting and endoplasmic reticulum stress

Intermittent fasting (IF), which sometimes is practiced as a popular and rather unscientific intervention for fighting obesity [51,52,53,54] increases the inflammatory reaction in the hypothalamus [55], a fact that plays a fundamental role in generating the resistance to leptin and insulin activity in the brain. The hypothalamic chronic slow inflammation aggravates the dysregulation of food intake [56,57], provoking overfeeding episodes and increasing adiposity [58], with substantial psychological consequences, which in turn, via the amygdala, stimulates furthermore the overfeeding tendency [59].

The pathogenetic background of the hypothalamic inflammation due to intermitted feeding may be associated with the Endoplasmic Reticulum stress (ER stress) of neurons [60], which is a mechanism driving inflammatory gene transcription and changes of neuropeptide gene expression [61, 62], increasing obesity susceptibility and insulin resistance, as it has been documented in rodent models of obesity [63, 64].

Any further investigation of the pathogenetic mechanisms, which may be involved in obesity, and particularly any attempt for therapeutic intervention would be beneficial for the billion of people on earth, who carry the increasing burden of obesity

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