Obesity Pathogenesis: Role of CNS

Subjects: Others

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Obesity is a serious health problem because it is rapidly expanding and at the origin of intense morbidity and mortality, especially due to the diabetes that accompanies it.It is not possible to cure it effectively, except with bariatric surgery, which is highly invasive and with many limitations. Trying to understand the mechanism of this efficacy, the studies point towards the correction of the altered control by the CNS of food intake and energy homeostasis. At the biomolecular level, the possibility of a pharmacological therapy based on the modulation of the post-synaptic receptors of glutamate, in particular of the NMDA GluN2A and GluN2B subunits, is foreseen.

Keywords: Obesity pathogenesis ; Mechanism of metabolic surgery ; Obesity and diabetes therapy ; NMDA receptors modulation

1. Introduction

Diabetes and obesity have been classified as the third and fourth leading health risk factors, respectively, in the world [1]. Their growing prevalence cannot be countered or even limited, and they are considered to be epidemics. Adiposity-based chronic disease is probably the greatest noninfectious epidemic of the 21st century.

2. Why Is the Spread of Obesity So Rapid?

Role of Epigenetics: Development Programming

The cause of the rapid spread of obesity is partly related to the spread of a lifestyle characterized by a marked reduction in physical activity and a high-calorie diet.

However, the main cause is to be found in genetic adaptations [2], which cannot involve a change in the DNA sequence (because this would require a very long time to manifest). Rather, the change involves epigenetic modifications, a hereditary process of gene expression independent of the classical Mendelian laws [3]. Epigenetics causes organisms to adapt during the first phase of fetal development in a manner that renders them able to cope with changes in the environment [4]. In this phase, called development plasticity, epigenetic modifications are known to be of crucial importance in the development of neural circuits responsible for energy homeostasis and in the integration of autonomic reflexes [5][6].

3. How Can Negative Environmental Conditions Influence The Development of Obesity?

According to the theory of development programming [7], maternal conditions cause adaptive epigenetic changes in the fetus that influence the development of its organs, particularly the brain [4], in view of an adverse post-natal environment [8]. Nutritional excesses are among the most important stimuli of negative fetal programming [9]. In the case of obesity, a metabolic aptitude to caloric accumulation is transferred to the unborn child who, in a subsequent environment with abundant food availability, would be predisposed to the obesogenic phenotype (evolutionary mismatch) [4]. This phenotype is transmitted to subsequent generations even in the absence of further environmental stimuli and, indeed, despite their absence (transgenerational effects) [10] (Figure 1).

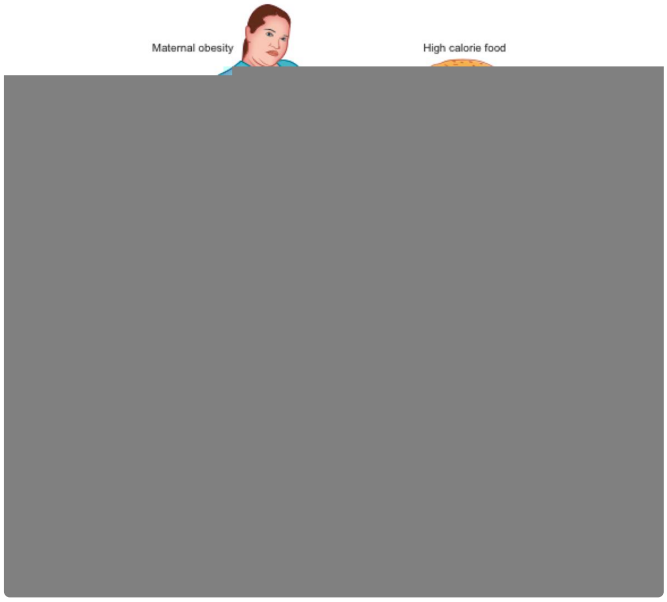

Figure 1. Maternal obesity and overeating at the origin of epigenetic changes that lead to neurologic-based generational predisposition to obesity.

In animal models, it has also been shown that a change in synaptic activation (synaptic plasticity) is induced in the reward system [4] followed by an inadequate response to the consumption of highly energetic food in concomitance with the pregnancy period [2][11]. This is due to the epigenetic alteration of the expression of dopamine and opioid-related genes present in the mesocorticolimbic circuits [12].

4. How could the dysfunction of energy homeostasis control be responsible for obesity?

The control of energy homeostasis is performed by various brain sectors that interact with each other [13] (Figure 2).

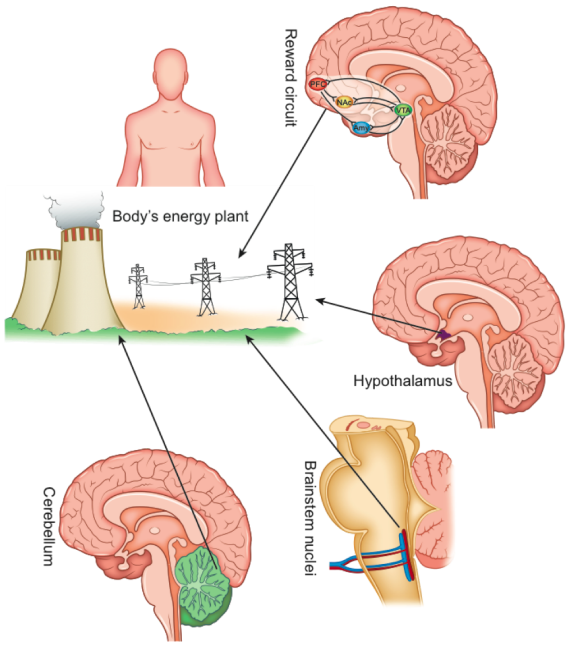

Figure 2. The main sectors of the central nervous system (CNS) that control the body's energy homeostasis.

4.1 The reward system

The emotional aspects (sensitivity to rewarding stimuli) of non-homeostatic eating behavior (i.e., hedonic food consumption, not activated by energy needs) are determined by the reward system, a grouping of dopaminergic brain structures and neuronal pathways that communicate with each other through the dopamine neurotransmitter and the

opioids [14][15]. Chronic consumption of rewarding foods can cause a downregulation of dopamine receptors to attenuate their over-stimulation [16]. Decreased dopamine receptor availability may cause or exacerbate increased food intake as a form of self-medication in which the individual tries to compensate for a reduced reward experience [17].

According to a widely accepted theory called “Reward Deficiency Syndrome” or “Hypodopaminergic Theory” [18], by reducing food intake, withdrawal symptoms appear, such as anxiety, nervousness, dysphoria, and insomnia in both humans [19] and experimental animals [20], and the appetitive and consumer behavior is accentuated [14]. This helps to explain weight loss resistance and why any weight loss induced by calorie restriction recovers very quickly [14].

4.2 The brainstem and the gut–brain axis

The vagal brainstem neurocircuits that regulate food intake and energy homeostasis, through the disorders of their synaptic connections, play an important role in the pathogenesis of obesity and type 2 diabetes mellitus [21]. Enteric hormones stimulate the receptors of a vast network of vagal nerve fibers. Vagal afferent neurons (VAN), located in the nodosum ganglion (NG), innervate the intestine and terminate in the NTS. These afferent vagal fibers integrate gut-derived signals to regulate meal size [21]. From the NTS, impulses start towards other regions of the brain, including the hypothalamic and limbic nuclei, which play a significant role in the processing of neuroendocrine, behavioral, and autonomic functions related to weight control [22] and modulating their functions (such as motivation and pleasure): this is the so-called gut–brain axis [23]. In addition, through the adjacent dorsomedial nucleus (DMV), the NTS connects with the main splanchnic organs that control the metabolism, i.e., the endocrine pancreas and the liver. The deterioration of the synaptic connection with the DMV (synaptic maladaptation) leads to a disordered modulation of the splanchnic organs with their consequent dysfunction (altered production of insulin and glucagon, and impaired hepatic synthesis and release of glucose) [24].

4.3 The hypothalamus

The various nuclei of the hypothalamus play an important role in maintaining energy homeostasis by responding to peripheral hormonal and neural signals, and are activated to control any reduction in adiposity [14]. According to the set point theory, the hypothalamus keeps the quantity of adipose tissue (energy reserve) constant by controlling its utilization and accumulation [14]. According to this theory, in obesity the set point is fixed at a higher level, and this represents another significant obstacle to effective and long-term weight loss . Furthermore, within the hypothalamic lateral, dorsomedial, and peri-fornical regions neurons are present that secrete the orexin neuropeptide, which causes an increase in spontaneous physical activity (SPA) and energy consumption [25]. Other important roles in energy homeostasis are played by the cerebellum and areas of the cortex.

5. Effectiveness of metabolic surgery: which could be the mechanisms?

Bariatric surgery, is currently the most effective therapeutic approach for obesity (consistent and lasting weight loss) and Type 2 DM (average improvement in HbA1c was 2.1% in operated patients compared to 0.3% in patients undergoing intensive medical care) [26]. Metabolic improvements occur within days or weeks following surgery, even before significant weight loss occurs. Therefore, mechanisms are triggered that go beyond simple weight loss and calorie restriction [26].

Surgical procedures sever the branches of the vagus nerve, altering its connection with the brainstem’s dorsal vagal complex (DVC) and other brain areas with which it is linked, in particular those of the reward system [27].

5.1. Changes to feeding

Consequences are: the change in tastes and the apparent aversion to more caloric foods (especially lipids) and the shift towards healthier foods such as fruit and vegetables, in addition to a reduction in the duration and size of meals (even in the presence of weight loss which is usually a powerful stimulus to eat) [14][28][29]. Surgery corrects the dopaminergic dysregulation in the reward system and restores its sensitivity [28][30]. Thus, the peripheral signals are again able to cause satiety and overeating stops [18].

GLP-1 has been evaluated after various bariatric surgeries to determine if it played a role in the dramatic energy-metabolic improvement. It was found that GLP-1 levels increase up to six times after RYGB surgery [31]. Although the topic has been the subject of much debate [32], despite this high increase, GLP-1 cannot be considered the main actor of the improvements because the same effects are obtained in animals deficient for the GLP-1 receptor [33]; the administration of the analogue of GLP1, liraglutide, does not achieve the same effects [33] and when Exenedine-9 (the GLP-1 receptor antagonist) was administered after RYGB, although worsening of glycemic control was observed, there was no return to

the initial altered glucose tolerance [34]. It should also be borne in mind that the activity of enteric hormones is predominantly local (paracrine, on vagal fiber receptors) as they are rapidly degraded. Only a limited portion of these hormones also enters the circulation, carrying out their action remotely.

5.2. Change in GLP-1 activity

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5.3. Alteration of vagal afferent neurons

Chronic consumption of a high-fat diet (HFD) causes alterations in the properties of vagal neurons that are sufficient to cause hyperphagia and weight gain, a demonstration that abnormal gut–brain signaling is the triggering factor for obesity [35]. Thus, the high-calorie diet or overfeeding act on two sectors: that of the reward brain by desinsitizing dopamine receptors and causing food addiction and that of alterations in both the function and of the structural integrity of the afferent vagal neurons and of the vagal nuclei of the brainstem by altering the gut-brain-liver axis. These abnormalities regress after RYGB with positive effects on the visceral and gastrointestinal reflexes mediated by the vagus [36].

5.4. Reduced hepatic glucose production (HGP)

It is now certain that the exclusion of the foregut is the main culprit of the benefits of metabolic surgery [37][38]. Diabetes and obesity are characterized by excessive hepatic glucose production. Metabolic surgery, which interrupts (or reduces) the contact between food and the duodenal mucosa, could interfere with afferent and efferent GI-brain connections [39] and determine rapid improvement of the metabolic context in operated patients (regardless of weight loss) through the reduction of HGP [38] (Figure 3).

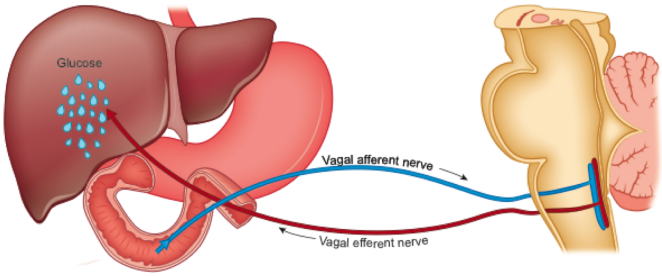

Figure 3. Nervous control of hepatic glucose production by nutrients in the first part of the intestine, through the brainstem vagal nuclei.

5.5. Accelerated gastric emptying in sleeve gastrectomy (SG)

In SG, which is currently the most practiced type of metabolic surgery (in which the stomach is reduced to about 20% by dissecting it along the greater curvature), the passage of food into the duodenum is preserved but, notwithstanding, it exerts an anti-diabetic effect similar to RYGB which is not due to the restriction of the stomach volume [40]. The anatomical upheaval of the gastric structure by SG, modifying the food gastric processing, inevitably affects the neuro-hormonal functions of the duodenum.

5.6. Modification of the hypothalamic set point

Following bariatric surgery and consequent changes in vagal inputs, this set point could be reset to a normal level, and the defense of excess body fat interrupted [41]. Patients report experiencing less (rather than more) appetite, even in the face of significant weight loss . Furthermore, a resumption of spontaneous physical activity cannot be excluded through the reactivation of the hypothalamic neurons that produce orexin, thus contributing significantly to weight loss [42].

6. Main targets of non-surgical therapeutic approaches to obesity

6.1. Modulation of glutamate receptors

The post-synaptic N-methyl-D-aspartate (NMDAR) receptor, activated by the neurotransmitter glutamate, plays critical roles in the physiological function of the mammalian central nervous system (CNS). Among the receptor's various subunit identities (which confer distinct pharmacological and biophysical properties on the receptor and, consequently, on neuronal processes [43][44]) the subunits GluN1 and GluN2A-GluN2B are involved in the control of nutrition and energy homeostasis [43][45] (Figure 4). Positive allosteric modulators (PAMs) (a group of substances which connect to binding sites different from those of the other agonists of the receptor to modify its response to the stimulus) have been identified that could modulate the activity of these subunits and correct their potential dysfunction at the origin of obesity [46][47].

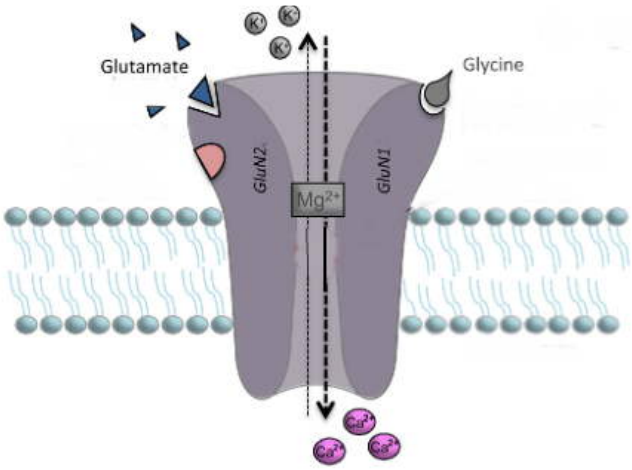

Figure 4. The NMDA receptors with two of its four subunits: GluN1 and GluN2 and their main binding sites. It acts as a gate on the cell membrane to allow the entry and exit of electrolytes that determine post-synaptic activation (from: Duman, R. (2018). Ketamine and rapid-acting antidepressants: a new era in the battle against depression and suicide. *F1000Research, 7*).

6.2. Physical methodologies

6.2.1 Electrical stimulation of the vagus nerve

The central role of the intestinal vagus nerve in the origin of obesity (as described above) makes it a valuable target of physical treatment [48]. Percutaneous CT-guided cry-ablation of the posterior vagal trunk causes appetite reduction and weight loss in subjects affected by mild or moderate obesity [49]. A similar effect is obtained by repeated electrical stimulation of the left cervical branch [50].

The ability to selectively modify the plasticity of various brain sectors through afferent vagus stimulation (VNS), which triggers the release of acetylcholine and norepinephrine, represents a remarkable opportunity to treat a variety of brain dysfunctions, including those at the origin of obesity [50].

6.2.2 Brain neuro-modulation

Deep brain stimulation is an invasive but non-damaging neurosurgical procedure which, through electrodes implanted in the brain, sends electrical impulses that reversibly modify the activity of nerve cells and is capable of positively influencing eating behavior in obesity [51][52].

Non-invasive brain stimulation (or transcranial magnetic stimulation is a technique in which the electric current of a coil placed on the skull generates a magnetic field that induces a parallel intracranial current [53]. Activation of the cortex is provoked, obtaining an improvement of various forms of addiction [54] and obesity [55]—understood as a food addiction condition—thus reducing food intake [56]. The main target of this treatment is the dorsolateral prefrontal cortex, responsible for self-control in food intake [53][57]. Beneficial effects have been obtained in various alterations of eating behavior, including binge eating [53]. Some limitations still need to be resolved, such as the need for repeated applications and the difficulty in accurately detecting targets, but this could represent a promising therapeutic path [53][56].

7. Conclusions

Obesity has reached epidemic proportions. The mechanisms can be found in the dysfunction of various sectors of the CNS that are responsible for energy homeostasis and are conditioned by epigenetic alterations. At present, the most effective and long-lasting therapy for obesity and related diabetes is metabolic surgery (which, however, is not universally practicable and is not devoid of side effects). Researchers' efforts should be directed towards further clarification of the neuro-hormonal bases of obesity and of the therapeutic mechanisms of surgery, aiming to identify drugs that will be active on the receptors of the various neurotransmitters involved, and modulating the activity of the vagal nervous system on the control of energy homeostasis and gastrointestinal functions. Particular attention may be warranted for the allosteric activation of the GluN2A and GluN2B subunits of NMDA receptor. The final purpose would be to achieve the same surgical effects by means of non-surgical methods [58].

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