

To be, or not to be obese – That’s the challenge: A hypothesis on the cortical inhibition of the hypothalamus and its therapeutical consequences

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Summary

Today, obesity is the most urgent unsolved medical problem, with the threat of a decreased life expectancy rate for the first time in medical history. Many obese subjects try to lose weight by dieting and exercising, without success on a long term basis. The only therapy with some effect is bariatric surgery with the impact of sustainable adverse effects only suitable in morbid obesity. Why are the therapies to treat obesity not working?

Within the last years, we have become more aware of the role of the brain in energy homeostasis. The three main players within the brain controlling our weight are the cortex for cognition, hypothalamus for vital body functions and limbic-reward system for emotions.

One hypothesizes that the failure of the cortex to inhibit the hypothalamus is the main cause of obesity. The evolutionary old hypothalamus constantly seeks for a positive energy balance, always in endeavor to avoid any energy shortage in the future. The hypothalamus is executing its tasks in a parallel mode. It can coordinate a set of vital

routines independently, yet simultaneously. For e.g., energy balance, salt balance, body temperature and sleep are executed even in a coma. The hypothalamus is primitive but stable.

The cortex in humans is, compared to rodents, much bigger and more complex, while the hypothalamus bears more similarities between these two species. The cortex in humans is evolutionary younger and represents higher cognition, an unique human feature. In contrast to the hypothalamus, the cortex focuses on one problem at a time, thus functioning on an attention-based manner. Due to this serial mode, the cortex uses a large part of its capacity for one problem at a time. Therefore, it can solve more complex calculations than the hypothalamus by thinking about one problem after another. It is even strong enough to veto the hypothalamus, if necessary.

If the concentration on weight loss is distorted, the hypothalamus is free of inhibition by the cortex, and the subject will gain weight again. It is suggested that this is why diets do not work in the long term. In anorexic patients, the cortex is fully occupied to control the hypothalamus resulting in extreme weight loss. In obese subjects, the cortex is less disciplined and the hypothalamus will take control again to stimulate positive energy balance. From this viewpoint, the limbic-reward system interacts both with the hypothalamus and the cortex to achieve demands by emotional motivation. The last part of this paper describes a therapeutic strategy based on this hypothesis. We propose a dual approach to fight obesity. First, interventions should be implemented that remind the cortex to control the hypothalamus and second, to stimulate physiological feedback to the hypothalamus.

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Here in this well-concealed spot, almost to be covered with a thumbnail, lies the very main spring of primitive existence – vegetative, emotional, reproductive – on which with more or less success, man has come to superimpose a cortex of inhibitions.

Harvey Cushing (1932)

Introduction

Today, obesity is one of the most urgent unsolved medical problems; for the first time in medical history life expectancy is set to decrease [1] and [2]. Many obese subjects try to lose weight without success [3]. The only therapy, with significant effect, is bariatric surgery with the impact of sustainable adverse effects, only suitable in morbid obesity [4]. Why are the therapies not working?

Since 1995 leptin has been found, a fat-derived hormone that feeds back to the hypothalamus [5]. Researchers rediscovered the central role of the brain in energy homeostasis, a forgotten paradigm that had been generally accepted in the 19th and the beginning of the 20th century [6].

In a basic view, the three main players within the brain regulating energy homeostasis are the hypothalamus (vital body functions), the prefrontal cortex (cognition) and the limbic-reward system (emotions). Brainstem and spinal cord modulate feedback to these areas and have an executive function.

Hypothalamus

In view of evolution, the hypothalamus is relatively old [7]. It is situated deep in the brain and coordinates a range of vital functions. These include energy reserves, water content, electrolytes, body temperature, reproduction, blood pressure and day–night-rhythms. If one of these vitals is disturbed, the hypothalamus reacts by inducing emotions such as hunger, thirst, fatigue or anger, leading to behavior that will re-establish homeostasis [8].

The hypothalamus needs to be informed about the body and its milieu to control it. It receives information from the body by blood borne factors and the autonomic nervous system. For e.g., to ensure energy levels remain constant the uptake, reserves and disposal of energy are monitored regularly [9] and [10]. The hypothalamus calculates an adequate output depending on the sensory information, which is translated to the body by hormones and nerves [11], [12], [13], [14], [15], [16], [17] and [18].

The importance of this region in the coordination of energy homeostasis is illustrated by the fact that tumors, or congenital syndromes, in the hypothalamus can lead to extreme phenotypes such as morbid obesity, in Prader–Willy-Syndrome, or anorexia [8], [9], [19] and [20].

To understand the recent increase in obesity prevalence, it is important to realize that the hypothalamus prevents acute overfeeding, but in the long term favors a positive energy balance and stimulates weight gain [21], [22], [23], [24] and [25]. Evolution prepared us to live in difficult circumstances surviving with a permanent shortage of nutrients, low ambient temperature and infectious diseases, by securing the efficient uptake and storage of energy. The hypothalamus has not yet adapted to the fact that we have supermarkets, cars, remote controls, central heating and antibiotics.

Organization in specialized nuclei within small networks is a characteristic quality of the hypothalamus and makes it a genuine multitasking region. For e.g., the suprachiasmatic nucleus is assigned to generate day–night-rhythms [15] and [26]. The arcuate nucleus receives signals from the blood by a permeable blood–brain-barrier and the lateral hypothalamus and ventromedial nucleus are important in feeding [27]. This anatomical organization in specialized nuclei and small networks that function relatively autonomously makes the hypothalamus a stable brain region. Even in the vegetative state with loss of cortical functions you find circadian rhythms and other hypothalamic functions can sustain [28], [29], [30] and [31].

At present, there is no successful therapy against obesity directed at the hypothalamus. Attempts have been made to manipulate feedback to the hypothalamus by hormones such as leptin or peptide YY. Unfortunately, after an initial period of weight loss patients re-gain weight [32], [33] and [34]. It seems logical that such a vital region as the hypothalamus has to be stable and resistant to solitary changes. The hypothalamus uses multiple sources to estimate the amount of energy stores, which seems a safe method to prevent life-threatening states such as malnutrition. Pharmacological or anatomical interventions of the hypothalamus would lead to severe adverse effects, due to the anatomically and functional compact form in which the vital functions are compressed. It seems that one compound is not strong enough to mislead the hypothalamus. Already for billions of years the hypothalamus is rigorous in its task to increase energy stores in preparation for the next period of energy depletion.

Cortex

The evolutionary changes of the cortex from rodents to human are impressive. In contrast to the hypothalamus that is relatively comparable between rodents and human, the cortex evolved significantly in size and organization. This is illustrated by the fact that the total brain weight from rodents to human increased by factor 700, while the hypothalamus increased only by factor 2 in volume. The proportion of the cortex by volume is 31% in rodents and 77% in human [\[35\]](#), [\[36\]](#) and [\[37\]](#).

One could compare the human hypothalamus with a hamster in ourselves, always trying to gain weight. If we do not use our cortex to control our hypothalamus, we behave like a hamster.

The cortex in humans accounts for complex cognitive processes, such as life planning by reasoning and thought and the integration of our cultural and bodily needs [\[38\]](#), [\[39\]](#), [\[40\]](#) and [\[41\]](#). The cortex has a high grade of plasticity. It can learn from reports of experience by other human beings without the need to have had this experience by itself. In contrast to the hypothalamus, the cortex is organized in extensive networks and less in localized functions and nuclei.

Due to the complexity of the cortex, views on its structure and functions are a continuing debate. However, it is plausible that the prefrontal cortex is the region where self-regulation and inhibition of inappropriate behavioral responses take place [\[42\]](#), [\[43\]](#) and [\[44\]](#). Other regions of the cortex such as the orbito-frontal, cingulate and insular cortex are connected to the limbic-reward system and play a role in emotions and reward response [\[45\]](#). Cortico-limbic mechanisms of reward appear to be under executive control of the prefrontal cortex, which shows a significant lateralization [\[46\]](#). The control of food intake by the prefrontal cortex is translated into physical activity by the motor associated cortex [\[45\]](#). The prefrontal cortex has a top-down control of other brain regions such as hypothalamus, limbic-reward system and motor regions [\[23\]](#). If the hypothalamus senses a shortage of energy stores, it can stimulate the prefrontal cortex by its projections to the cortico-limbic system to think of food, but the prefrontal cortex has the power to inhibit these impulses to eat. For e.g., overweight patients can lose weight after being informed of the unhealthy consequences of obesity and thus change their food habits [\[47\]](#) and [\[48\]](#). However, studies show that cognitive therapy directed to the cortex has not been successful in the long term. After an initial period of weight loss the patients re-gain their previous weight and sometimes more [\[49\]](#) and [\[50\]](#).

Until 50 years ago, in industrialized countries, the tandem of cortex and hypothalamus had no conflict due to life style. The cortex could leave the daily work of vital functions to the hypothalamus. The latter would be reliable to ensure that the body would not run out of energy stores. In present day obesity is prevalent – the cortex wants to lose weight while the hypothalamus still wants to gain weight, a new unprepared situation that generates a conflict in the brain.

Limbic-reward system

The third player, the limbic-reward system is a network of cortical and subcortical areas consisting of limbic cortex, amygdala, hippocampus, thalamus and striatum that are associated with positive and negative emotions [23] and [51]. Feelings motivate our behavior because it makes us feel good or bad. Positive feelings about feeding are called hedonic eating [42]. If the hypothalamus senses dehydration, the limbic-reward system will give us bad or aggressive feelings and reward us with relief and pleasure when drinking [42], [43] and [44]. If we are going to spend a huge amount of money in a risky investment with the perspective of a significant revenue, the prefrontal cortex recognizes possible advantages and dangers. The chance of an extensive monetary backup makes us happy and safe, while the risk of losing our money makes us feel unhappy and frightened [46] and [52]. The sum of these feelings will influence our behavior. The interaction between the limbic-reward system and the cortex can result in unfavorable behavior, for e.g., the reinforcement of overeating or risky behavior in gambling. However, therapeutic approaches that try to change the emotions in obese people did not succeed to reduce weight on a long term basis [47]. Emotion directed therapy becomes even more aimless since a growing number of obese subjects feel just happy being obese [53].

Failing of isolated therapies directed to a singular region

In conclusion, the single therapies directed to only one of the main players in the brain, (hypothalamus, cortex and limbic-reward system) did not lead to effective therapy in obesity. Food intake is not a disease, but a precondition of life. A countless number of factors that stimulate a positive energy balance have been conserved in our genome. Because a single treatment for obesity would have to interfere with a significant number of essential physiological processes, no effective intervention with tolerable adverse effects is available. The exception is bariatric surgery in morbid obesity. Eating is a

necessity not a disease. That is why a golden bullet or pill against obesity is not a realistic option in the future.

Hypothesis. Distraction of the prefrontal cortex during weight loss results in disinhibition of the hypothalamus

If the cortex in humans is larger than the hypothalamus and can inhibit the drive to gain weight, why is it so difficult to lose weight?

The prefrontal cortex is our working memory. It is able to perform the so-called “executive attention”, a term to describe the (cognitive) control of our reactions to thinking, internal and external stimuli [40], [54] and [55]. I hypothesize that executive attention and working memory allow the prefrontal cortex to use its capacity efficiently in solving problems. This phenomenon is known as attention – the fact that we concentrate on a certain problem. In contrast, the hypothalamus has a function related organization with designated nuclei and small networks for certain tasks. While the cortex is strong in being able to calculate complex problems, its weakness lies in the need to concentrate on one problem at a time and to perform its tasks after each other (serial mode). In contrast, the hypothalamus has more multitasking properties (parallel mode) and is therefore more stable in its output.

The different processing modes explain why the cortex is unable to control the hypothalamus in every moment: the cortex cannot focus attention exclusively on weight loss, it needs to shift priorities to fulfill its different tasks throughout the day. In contrast, the hypothalamus is pushing for weight gain continuously.

As an example, successful dieters are losing food control if they are challenged with cognitive distraction [56]. A low degree of self-regulation in toddler’s predicts obesity a few years later [57]. There is a direct correlation between lower education and the risk of obesity [58] and [59]. This might be an illustration of the fact that this social demographic are less trained to use their prefrontal cortex to concentrate on a healthy life style. In contrast, anorexic patients generally have a higher education and are trained to perform executive attention efficiently [60]. Eventually it leads to the extreme when they continuously use the cortex for controlling the subcortical area’s inducing food intake. Life-threatening weight loss and even death might be the consequence.

A new combination therapy directed to prefrontal cortex, hypothalamus

Within this paper the proposed approach to cure obesity is based on a combination therapy consisting of two branches directed at the prefrontal cortex and hypothalamus, as individual targets. Current obesity therapies fail because they are directed either, to the hypothalamus (e.g., hormones), the cortex (e.g., cognitive or behavioral therapy), or to the limbic system (e.g., emotional therapy). It is expected that a combination therapy will have a synergistic effect. This is because the major mechanisms of the brain, that result in obesity, are attacked from multiple sites.

The first branch of the therapy will address executive attention and working memory in the prefrontal cortex. It will direct the disadvantage of serial processing by the prefrontal cortex and the fact that distraction results in less inhibition of the hypothalamus during weight loss. It will be necessary to remind the distracted prefrontal cortex to focus on weight loss.

Modern personal electronic devices provide the opportunity to interact with patients in their daily life. Desk computers and mobile devices such as smart phones and laptops can reach the patient through the internet. The software should interact several times a day with the user, without demanding too much effort and attention. The user should experience the weight program as enjoyable. The limbic-reward system is used to further stimulate motivation by progress feedback.

The second branch of the combination therapy will target the hypothalamus. In contrast to the prefrontal cortex the hypothalamus is a stable brain region with relatively low plasticity compared to the cortex. It is crucial to accept this. In other words, to accept the hypothalamus as it is. We will provide the hypothalamus information that suggests energy stores are, or will be, sufficient within the near future. This is accomplished for e.g., by slow weight changes to prevent a panic reaction of the hypothalamus that induces weight re-gain (YoYo effect). The hypothalamus uses multiple ways to perceive the amount of energy to be ingested. This process starts with the vision and the smell of food. This is followed by the tactile experience of cooking and finally the processed information from mouth, stomach, intestinal tract and liver during digestion. Fast food skips the first steps, therefore the hypothalamus only receives a part of the information of the calories that are (going to be) taken up. This is why fast food results in less satiety, leading to more food intake. Thus, the challenge will be to stimulate structured shopping and preparation of food in relation to hypothalamic feedback regarding calorie intake. Finally, shortage of sleep is an important risk factor for obesity. The therapy will stimulate healthy physiological circadian rhythms.

Summary

This hypothesis might help to understand why eating behavior is so difficult to change. The prefrontal cortex focusses to use its whole capacity to deal with complex problems. Since information is processed serially, the prefrontal cortex can be distracted by other problems demanding attention. In contrast, the hypothalamus is relatively primitive but stable, since it performs its tasks simultaneously. Thus, distraction of the prefrontal cortex during weight loss results in disinhibition of the hypothalamus and consequently weight gain. It is important to stress that the cortex, hypothalamus and limbic system interconnect intensively and none of them is solely responsible for the control of energy balance.

This therapy addresses the prefrontal cortex and hypothalamus individually and uses the limbic-reward system. It is expected that a combination therapy will have a synergistic effect, because the most important mechanisms of the brain that result in obesity, are targeted from multiple sites.

Conflict of interest statement

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