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Chapter 14

Human Obesity: An Overview of the Mechanisms and the Basis for Treatment

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Summary

Obesity is increasing at a very rapid rate and still defies an effective treatment. The major reason is that weight maintenance is a vital function with multiple levels of control and a therapeutic intervention at one or some of them will last only for a limited time span and will be offset by all the others. Probably the highest level of this hierarchy is the voluntary one and at least for a long term result we must rely on it

Introduction

Obesity is a complex and frequent condition commonly approached with excessive simplification. The definition has gone through many different stages. In the 50' the vogue was to use the metropolitan life insurance tables [1] as a reference to evaluate the degree of overweight / fatness. Then the more precise concept of Body Mass Index (BMI) prevailed. Although the BMI [2] that is calculated as $\text{kg}/\text{height}^2(\text{mt})$ [2] is a rather crude measure of obesity certainly represents a marked advantage. Then the realization came that the overall weight as a measure of obesity is not acceptable and that the composition of the body is critical. A subject of 80 kg and 170 cm with 40% fat and 60% lean body mass is certainly

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different from an individual with the same anthropometric measures and 25% fat and 75% lean body mass. Actually the most common measure of obesity is the abdominal circumference, or the waist to hip ratio [3].

Pathophysiology

The pathophysiology of obesity has been always interpreted as the altered balance between calories ingested and calories used, and graphically represented as a two arm old fashioned scale. However we should now be well beyond the simplistic concept of the laws of thermodynamics [4].

It is inescapable that obesity is due to *relative* overeating, which means that the excess fat deposition depends also on the characteristic of each individual to burn the energy ingested and / or stored in the fat compartment of the body and not being able to match the caloric ingestion to that need. Starting from this simple concept the idea was that overeating means having an overindulgent mindset. In Dante's *Inferno* gluttons for punishment are forced to lie in a vile slush produced by ceaseless foul, icy rain [5]. But to think of the caloric need as a composite of basal metabolic rate plus the energy expenditure due to physical activity is an oversimplification. Also thinking of caloric ingestion as the simple sum of the caloric content of the foods ingested is not any more tenable. Rather we know from animal studies and from the clinical observation that the regulation of appetite is enormously complex

Probably the best way to understand the phenomenon obesity is to analyze what appetite, energy storage and energy consumption mean for the human being and their role in survival and evolution.

The control of appetite is a primary function, obviously strictly related to survival. This function must also exhibit a high degree of flexibility because must be adaptable in the short term to the changing environment and the changing situations. A convincing explanation is the hunter gatherer context of the primeval periods of the animal life on earth, when was critical to accumulate fat in periods of abundance to use during famine [6]. Without effective control mechanisms of this function life on earth would be long extinguished. We should visualize the human body as a 2 compartments model, like an automobile: the lean body mass, including muscle, liver, brain, kidney, red blood cells, enzymes, in brief all the metabolic and structural machinery, as the motor; and fat as the fuel. This is an extreme oversimplification that may help to understand how the body deals with the fat deposits. Of course having fuel on board is critical, thus nature endowed the body with a redundancy of systems to increase fat deposits and to decrease caloric consumption to save fuel but less mechanisms to slow down the loading. The process of refueling the fat compartment has sophisticated sensors that continuously monitor the internal environment (the size of the fat deposits) and the external environment (sensory clues), both highly integrated and interconnected and a voluntary control system able to override them. There is probably more than the simple "refueling" of energy in this complex regulatory system. If we accept to learn from the animal kingdom we should remember that some oviparous animals use to eat the shells of the eggs to recover the calcium, and some children or pregnant women with mineral deficiency do the same (a condition called "pica", the abnormal eating of something that is considered developmentally inadequate) [7], which means that the monitoring system has

element-specific sensors, not only controlling the fat mass but also every single constituent of the body. It is probable that some inconsiderate attempt at dieting may cause the depletion of materials that are already borderline depleted, and this may lead to increased appetite in the unconscious attempt to recover what is missing.

The regulation of appetite thus is a sophisticated integration of peripheral and central signals. The peripheral signals are represented by an array of hormones and peptides coming from the adipose organ itself, from the gut, from the internal organs (liver, pancreas) and integrated in the brain by complex and largely unknown circuits with the external afferences. This system is also highly interconnected with the control of the reproductive system for obvious anthropological reasons [8].

It is borne out from the daily experience that there are a few lucky individuals who must do nothing to keep their weight the same. Maybe their weight is 68 kg at 20 years of age and will be no more that 72 kg till the end of their life. Maybe they eat much one day but almost unnoticed by anyone they restrain automatically their food ingestion for the next days till equality. Maybe they really eat more than others, las they affirm, but we almost never check their body composition. Some of them will have a greater prevalence of muscle over fat, and muscles use more energy, or may be they sleep better which helps maintain weight, or they are more physically active, sometimes imperceptibly. However even after taking into account all these possibilities and many others we are left with a percentage of true “overburners” of calories, or maybe calorie wasters.

It is however correct to mention that the very concept of calorie is questionable. Although a critical reference the number that should express the energy a calorie is just a number without true physiological and clinical meaning. We should rather speak of “metabolizable energy”, or the difference between the gross energy of consumed foods measured by bomb calorimetry and the energy contained in feces and urine.[9] To get a rough idea of what will be available for storage of fat we must subtract from the number expressing calories per gram of a nutrient the dispersion during the cooking/processing of the food, and even more relevant the thermodispersion during the digestion plus the actual energy used during the process of transformation of the food ingested into absorbable material plus what is involved in the chemical/physical reaction post absorption and the fecal / urinary loss. Thus “a calorie is not truly a calorie”. The most reasonable point of view is that there is considerable variation in the true caloric supply according to the quality, quantity, type of food, the percentage composition of the meal, the subject eating the food and. his/her metabolic and endocrine environment. These mechanisms probably exhibit a considerable day to day variation. Another contributing factor to the difficulty of calculating the true caloric yield of a diet is the different thermic effect of each foods. It is probable that the greatest energy expenditure is induced by the protein [10]

A Simplistic Structure of the Appetite/ Eating System

In order to improve the comprehension we will describe the most relevant players of the most well known levels of control of this sophisticated system.

The most peripheral positive stimuli are those connected to the senses, like smell and sight. These peripheral impulses have been largely manipulated and exploited by the agricultural industry to increase the business. A blatant example is the occult advertising, the colorful packaging, the concocted positioning of the food in the supermarkets shelf, and many others well described recently. [11]

Another level of control, mostly negative is at the gastrointestinal level. Among the most well known players, now largely used for the treatment of diabetes probably the foremost is GLP-1. [12] This substance is produced at the ileal and colonic level by the L cells, has a very short half life and is rapidly destroyed at the cellular level and in the circulation after nearly 1.5 minutes. This peptide that can suppress appetite, increase insulin secretion, decrease glucagon secretion, delay the intestinal transit time thus slowing the carbohydrate absorption. All these actions are favorable for diabetics and are largely exploited by the pharmaceutical industry with many available drugs, and many more in the pipeline. Another signaling peptide is GIP whose role is still incompletely defined [13]. There are a number of other substances secreted, at least in part at the GI level. Among them are CCK [14] and leptin [15], others are NPY [16] and Ghrelin, discovered in 1999 secreted by the stomach and acting on the hypothalamus [17]. Although these substances proved to be extremely promising in the experimental animal their role in the human is still not clear and far from being introduced into the pharmaceutical armamentarium. Another important relay station is represented by the autonomic nervous system transmitting signals to the hypothalamic centers controlling appetite. Here we will discuss some of the most well known of these substances

Leptin. Leptin, secreted ubiquitously, and in greater amount by the adipose tissue can inhibit appetite [18]. Although its role is probably yet not totally known Leptin may well be the substance that continually monitors the expansion of the adipose tissue and informs the brain when the deposits are full. More intriguing is the possibility that Leptin may actually inform the brain centers of the potentiality of the vascular tissue to expand and support the expansion of the fat compartment [19]. Leptin deficiency leads to a monstrous adiposity in animals and has also been identified in children, who respond to the therapeutic use of the substance [20]. Characteristically Type 2 diabetic patients are leptin resistant [21]. At present the therapeutic role of this hormone in the common obesity has not been defined, and apparently there is nothing in the pipeline of the pharmaceutical companies.

CCK. the hormone Colecystokynine (CCK) has been considered a main trigger of satiety [22]. The hormone can be found in the brain and the gut. [23] The substance essentially works as a neurotransmitter and its functions are not specific, but differ in each tissue. This might be a cause of concern for human use, although the substance proved to be a powerful inhibitor of appetite

Adiponectin, popularly known as the “good hormone”, is mostly associated with insulin sensitivity [24, 25]. Low levels of this substance are found in subjects with insulin resistance [26, 27]. Adiponectin levels are inversely related to the expansion of the adipose tissue and increase with weight loss [28]. The clinical counterpart is the presence of low levels of adiponectin in the obese. [29] However the most intriguing although controversial aspect of Adiponectin is its role in reducing inflammation [30].

Grelin. This ubiquitous substance is mainly produced in the stomach and has potent appetite stimulating properties [32]. The levels are decreased after meals and increase during fasting and starving or wasting conditions, consistent with the role of this substance in protecting the lean body mass.

These substances interact at the level of the brain, mostly in the ventromedial and lateral parts of the hypothalamus where their action is mediated by a series of complex neuropeptides and hormones. The control exerted by these substances can be overcome by the voluntary control, at least in man. Many hormones, like the thyroid hormones, cortisol and the sex hormones may modulate the neurotransmission and have profound effects on appetite. A reduction in brain dopamine levels may increase appetite and serotonin activates some neurons and melanocortin-4 receptors, or MC4Rs, to curb appetite and at the same time block other neurons that normally act to increase appetite. Drugs that block serotonin reuptake in the neurons thus increasing the level of this substance at the receptor are a primary target of therapeutic drug research. Other important substances are the NPY [32] and AgRP [32] (Agouti related Peptide) secreted by neurons with the same names. These substances stimulate feeding and thus are called orexigen. They carry out the appetite regulatory effects of leptin and ghrelin. POMC (Pro-opiomelanocortin) inhibits food intake and is secreted by POMC neurons that are thus called anorexigenic neurons [33]. There is a high level of interplay among all these neurons, so that the net effect under normal conditions is regulatory. Another important peptide is the α -melanocyte stimulating Hormone (α -MSH) that also inhibits appetite. All these signals are probably integrated at the level of the hypothalamus by the adipostat function exerted by the local neuronal cells [34]

We know a lot on many different substances participating in this enormously sophisticated control system, but we are still missing the great picture and the interactions among them. For example we know that the quantity and quality of sleep and the sleep pattern may affect the release of many of the fore mentioned hormones. [35]

The hormonal environment is not probably the only major player, or at least not the only one. The intestinal microbiota seems to have a role, by itself or as a modulator of the hormonal environment. The germ free animals have a lower fat mass even if eat the same as the control animals [36]. Many experiments demonstrate that obese and slim persons have a very different intestinal microbiota. Although this is not surely proof of cause-effect the modulation of weight with antibiotics may be such [37]. A suggestive hypothesis is that the intestinal microbiota may modulate the chemical environment by directing the metabolism of food, and in turn induce the proliferation of some hormone producing cells.

Another relevant aspect of the control system of body weight is the distribution of fat. There is a great difference between the fat enclosed in the visceral cavity and the subcutaneous fat. Simply stated the fat ingested tends to accumulate inside the visceral cavity (visceral fat), and when the content reaches a certain quantity there is no more room and the excess is moved to the subcutaneous depot. In some individuals the subcutaneous tissue, specially of the lower portion of the body cannot accommodate fat beyond a certain limit, and if the subject continues to eat the abdomen becomes overfilled. After a certain limit the fat that cannot be accommodated anywhere else invades the liver and the pancreas with consequent harmful physical and chemical effects. The invading fat exerts a compression, but most important secretes some toxic inflammatory substances (cytokines) that may destroy the surrounding tissue. Probably the things are not so simple because the subcutaneous adipose tissue is further subdivided by fasciae and this anatomical disposition may well have also functional bearings.

Furthermore and perhaps more relevant is the existence of at least two different types of fat cells [38]. The common white cells characterized by central accumulation of fat and the peripheral disposition of the organules, and the brown fat more metabolically active whose

principal function seems to be the production of heat. Of course for the same level of introduction of calories the presence of a large number of brown fat cells makes a hypocaloric diet more effective. The exact role of the brown fat is still largely unknown, but is now evident that there may be a degree of interconversion between these two cells and this phenomenon may exert a critical regulatory role on the fat accumulation. The subdivision of subcutaneous fat into different strata delimited anatomically by fasciae must contribute to this regulation, but unfortunately at present we have only conjectures on the meaning of this arrangement.

Critical for the human health is the intrinsic property of the white fat to produce many hormonal substances, among which angiotensin, leptin and even more important the cytokines [39] inflammatory peptides that can cause local damage in the liver and pancreas, and systemic effects on the circulatory system. In the case of liver and pancreas the damage may vary from the mechanical compressive effect to the liver steatosis and steatohepatitis or liver cancer, and to the disruption of the pancreatic beta cells.

The cytokines may be released locally and also reach the systemic circulation. The circulating cytokines can cause systemic inflammation and damage to the arteries of the coronary or the other arterial districts and this probably concurs to the heightened risk of premature atherosclerosis of obesity and diabetes [40].

Non Medical Treatment

When one comes to the clinical arena the situation is more complex. While must be recognized that all the hormonal, neurologic, gastric, microbial and other factors mentioned intervene and condition the evolution of the body weight, it is undeniable that there is a voluntary control that can overcome all the others. Thus using an appropriate strategy obtaining a weight loss at the individual level is relatively simple provided that certain conditions are respected. Retaining the weight is a greater challenge. On the other hand an intervention at the population level poses greater difficulties because there are many complex economical, historical, cultural, lobbyist, developmental factors interplaying and all should be included in the scope of a strategy of intervention at the population level. The simplistic educational intervention is surely doomed to failure, at least at the level of the adult population, and equally the more courageous but ingenuous reduction of the portion size.

There are at least two main problems at the individual level, the person that must lose weight, and the diet prescribed. We will deal with these aspects separately.

We will not deal with the drug therapy in this session, however at present there is no definitive medical treatment and to succeed a drug should be continued forever. If used the drugs should be incorporated within a strategy as a first step reinforced by interventions aimed to the maintenance of the weight obtained. In selected cases drugs might be used in courses.

In our opinion it is naïve to involve the physician himself and the patient on a weight loss therapy attempt without prior consideration of the motivational state that conditions the probability of short and long term success. This unwary action may expose both to the frustration of a failure. A widely used and intelligent model to consider before starting a weight loss treatment is the “transtheoretical model”. [41, 42] according to this model the

patient can be in one of these stages, *Precontemplation* - "people are not intending to take action in the foreseeable future, at least the next 6 months" → *Contemplation* - people are prepared to make a change within the next 6 months → *Preparation* - "people will probably act soon, possibly within one month" → *Action* - people have made specific overt modifications in their life styles within the past 6 months → *Maintenance* - people in the relapse-prevention state, for a period of at least 6 to about 5 years → *Termination* - individuals having zero temptation and 100% self-efficacy. Although the stages are usually consecutive this is not always true, and unfortunately a regression is eventually possible. We found this model very effective in our practice. Instead of wasting time and being continuously frustrated the best option is to discourage action in the precontemplation and contemplation phase and try to push the subject to a better level. The paradigmatic subject in a precontemplation state is the fat male/female sitting, patting his/her protruding abdomen and telling the doctor "we should throw off some weight". He does not even assume any responsibility to say "I should". This is not the case for a weight loss therapy!

There are many other factors to consider before starting a weight loss program, the number of relapses, the family history, the opportunity for the patient to come to the office for an intensive follow-up, the economic condition and many other factors that may affect unfavorably the prognosis.

The dietary plan itself is a very difficult problem to cope with. It is now certain that a rigid dietary plan will not last for long and the gram / ounces count must be reserved to very special situations. Furthermore with the advancing knowledge of nutraceuticals, a widely disputed term and science that is defined by the test edition of the *Merriam-Webster Dictionary* as follows: "*A food stuff (as a fortified food or a dietary supplement) that provides health benefits*" [43] and of nutrigenomics, the study of the effects of foods and food constituents on gene expression there has been a shifting pendulum among the proponents of the high protein diet, the high CHO, the low Fat, the High Fat, the intermediate position. In this review we will summarize the most important aspects of this debate:

1. at present the use of high protein diets seems superior to the high CHO diets at least to obtain a short term greater reduction in weight [44] Furthermore at least one observational study demonstrated that with a ad libitum diet the % of carbohydrates in the diet was positively correlated with an increase in the % of the more dangerous lipoprotein pattern B. Another well done study demonstrated a greater weight reduction although non statistically significant, a marked reduction in triglycerides, and a minor reduction in HDL.[45] A diet with 30% protein content and an exceptionally low 20% carbohydrates was able to lower dramatically the blood glucose level in 8 male subjects with type 2 diabetes mellitus. [46] There are some reasons for concern with these diet, among which the risk of osteoporosis, a scanty supported risk of kidney damage, and risk of acidosis
2. the fat content of a diet should favor the Monounsaturated fatty acids (MUFA) and reduce at maximum the saturated fatty acids (SFA) content [47]
3. the calcium [48] and vit D [49] content of the diet seem to play a positive role on weight control
4. there are reports on many other dietary components indicating a possible role, but unfortunately their clinical relevance is far from proven

Another critical aspect of the treatment is the removal of those external influences manipulated by the industry and well defined in an interesting recent paper.⁸ The author identifies numerous mechanisms of induction to hyperalimentation, like the marketing strategy of the supermarkets, the colorful packaging, the brand effect induced with the ads, the exploitation of the inborn preference for sugars, the manipulation of environmental suggestions at restaurants and many others. The intervention aimed at thwarting these cunning expedients could represent an important option if coupled to the information campaigns that up to now did not produce significant results, although the foreseeable conflict with the agricultural industry would surely be a problem. Another strategy to be considered is to create a supplementary alarm system. Since all the obese have lost the warning signals that tend to limit the caloric ingestion a consistent possibility is to create an external warning signal. Two very good candidates are the use of tight dresses [50] and the daily use of a scale in the morning to check gross deviances from the usual weight. Furthermore there are a number of behavioral changes that may help overcome the external pressure and develop more healthy habits [51, 52, 53]

Conclusions

The development of obesity must be considered the derangement of a critical regulatory function aimed at guaranteeing the survival of the individual and of the species. Since this is a highly regulated system is extremely unlikely that one single intervention at any level of these interacting circuitries may restore what we consider normalcy but the organism itself may nor perceive as such. The escape mechanisms that tend to accumulate energy tend to prevail in most cases. At present the best option we have is to intervene at the highest level on the voluntary control

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