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Neurological And Biochemical Aspects Of Eating Disorders

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ABSTRACT

Current studies on the epithalamic nuclei, referring to appetite, have further enriched the doubts about the pathogenesis of anorexia, bulimia and obesity, with the influence on the nuclei of the lateral hypothalamus, which produces lack of appetite thanks to the release of leptin, but which can also be produced by orexin, galanin, or hypocreatine. After food intake and consequent increase in fat levels, leptin - composed of alpha-MSH (an anorectic peptide, melanocyte-stimulating hormone) and CART (peptide regulated by cocaine and amphetamine) - is high in the blood, activating the arcuate nucleus and increasing adrenocorticotropic hormone (ACTH) and thyroid-stimulating hormone (TSH). The metabolic rate is high in obese people, because it is proportional to being overweight: they are less effective in counterbalancing or adjusting their metabolic needs. Modernly, the metabolic phase is valued, in which adenosinotriphosphatase exerts a special power. The mobilization of fat, containing more triglycerides, occurs by the degradation of these into glycerol and free fatty acids, which are transported together with albumin. This transformation is possible because an enzyme, lipase, is activated by epinephrine, glucagon, ACTH, TSH and somatotropin. Mobilization depends on the activation of intracellular lipase. These stimuli are studied, but the influence of glycemic levels - hypo and hyperglycemic - on the action of insulin, or not, and the amount of corticosteroid, lysine, carnitine and the cupric cofactor dopamine-beta-hydrolaxilase, which converts dopamine into norepinephrine, and its low can produce anorexia nervosa, is recognized.

Key words: Anorexia; Behavioral; Biochemical; Bulimia; Neurological.

Abbreviations

ACTH: Adrenocorticotropic Hormone

AgRP: Agouti-Related Peptide

Alpha-MSH: Alpha-melanocyte stimulating hormone

ATP-ase: Adenosine triphosphatase
Beta-LPH: Betalipotrophin
Cyclic AMP: *Cyclic* adenosine monophosphate
NPY: Neuropeptide Y
TSH: Thyroid Stimulating Hormone

Introduction

Current studies on the epithalamic nuclei, referring to appetite, have further enriched doubts about the pathogenesis of anorexia, bulimia and obesity, with the influence on the nuclei of the lateral hypothalamus, which produces a lack of appetite thanks to the release of leptin, but which can also be produced by orexin, galanin, or hypocreatine (1,2). The action of these neurohormones is not yet clarified, however, current knowledge has shown that anorexia and bulimia are not monosymptomatic psychoses, but a syndrome of the limbic system, installed in individuals with an archaic and bumpy ego on which the parents' witch messages act. The sick end up moving in a world of bizarre objects, confusing fantasies with reality: food would be impregnated with bad things, hence they suffer from thanatic diseases (Thanatism being understood as a form of unconscious self-destruction, due to the predominance of the death instinct) whose main cause is the hatred of the mother or her substitute. Patients move in a world of "bizarre objects", confusing fantasies with endocrinological clinic and analytic clinic. There are obese people who gain weight "by eating air", in the words of the patients themselves, because even under a severe diet and maintaining a satisfactory pace of physical exercise, they have difficulty losing weight. The hypothesis is that there is a constitutional metabolic error.

Brain mechanism

Anorexia (lack of appetite) and bulimia (episodes of voracity for food, with forced vomiting) are psychosomatic diseases. Unconscious fantasies stimulate or inhibit the nuclei of the lateral hypothalamus, producing, respectively, in the case of anorexia, leptin or hypocreatine (a hormone that also controls sleep and wakefulness, encoded by the OB gene and which activates the arcuate nucleus), one counterbalancing the other. Orexin, when increased in the blood, tends to decrease leptin (3).

On the other hand, after ingestion of food, with the dilation of the stomach, the stimulation of the ventromedian hypothalamus is produced, which increases the level of cholecystokinin, which contributes to the control of satiety. After food intake and consequent increase in fat levels, leptin - composed of alpha-MSH (an anorectic peptide, melanocyte-stimulating hormone) and CART (peptide regulated by cocaine and amphetamine) - is high in the blood, activating the arcuate nucleus and increasing adrenocorticotropic hormone (ACTH) and thyroid-stimulating hormone (TSH). The genetically obese mouse (OB-OB) has increased beta-endorphin and decreased leptin, which increases the level of neuropeptide Y (NPY), an anxiolytic (4).

Found in the central and peripheral nervous systems, NPY is a 36-amino acid protein that influences neuroendocrine function and behavioral events such as eating and satiety. NPY and Agouti-related peptide (AgRP) produced in the arcuate nucleus are connected to the paraventricular nucleus

and the lateral hypothalamus, as they stimulate the secretion of TSH and ACTH, and are called orexigenic peptides. In anorexia, there is a decrease in leptin, prolactin, 17 beta-estradiol, cytokines, interleukin, and transforming growth factor beta 2 (TGF -beta 2), while in bulimia, leptin may be normal, as well as cortisol (5), which contributes to a differential diagnosis. The dilation of the stomach also produces, in the brain stem, a stimulus for the production of endorphins, which cause well-being. In anorexia nervosa, the small dilation of the stomach will already produce cholecystokinin discharge and, thus, satiation is premature, due to vagal stimulation and insulin stimulation. The obese, on the other hand, in order to produce enough endorphins and cholecystokinin to feel satiated, need great dilation of the stomach (6-8).

Drugs that increase serotonin in the brain are appetite suppressants. Dopaminergic neurons project axons through the lateral hypothalamus to the forebrain; the craving for food is controlled by the dopaminergic function in the nucleus accumbens. The locus ceruleus, in turn, can influence almost all parts of the brain, increasing the brain's ability to respond to stimuli (general alert when the individual is vigilant) (3).

Plasma mechanism

The plasma mechanism occurs through the increase of free fatty acids in the plasma, which, in turn, are influenced by lipase. It is stimulated by pituitary betalipotropin (beta-LPH), ACTH, TSH, somatotropin, triiodothyronine, epinephrine, and glucagon (Figure 1). On the other hand, there would be a drop in adenosiphosphatase in erythrocytes - which would depend on enkephalin -, a drop in cholecystokinin - which would act at the center of society (9) - and a change in cytokine (10).

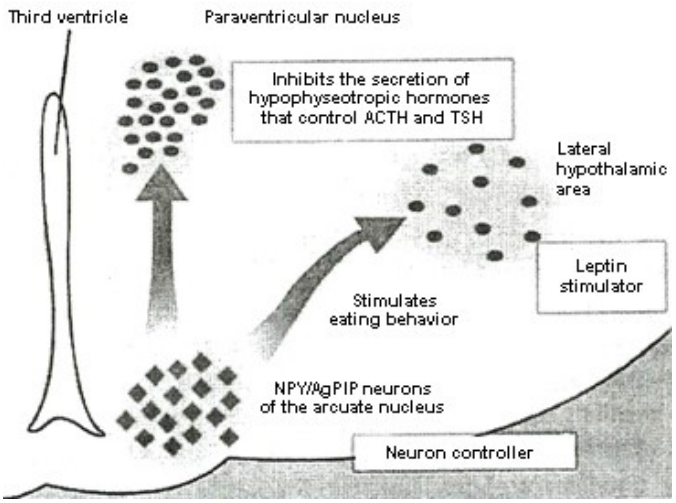

Figure 1. Paraventricular hypothalamic nuclei (ACTH and TSH controller), lateral nuclei (appetite controller, and arcuate nuclei (Y and AgRP neuron controller) adapted from Bear et al., 2002 (3).

Peripheral mechanism

In this mechanism, the lack of peripheral use of glucose would produce hyperglycemia. This disorder seems to be of a genetic nature (obese and hyperglycemic Mayer rats) (11), due to a deficiency of 3, 5, 3-triodothyroacetic acids, which exert a lipocytic effect by inhibiting phosphodiesterase, increasing plasma glycerol and producing hydroprolinuria; leptin, however, is decreased.

Biochemical factors

In the constitutional obese, there must be, therefore, a metabolic error (12), an alteration in the production of pituitary lipogenic hormone (13,14) or an increase in free fatty acids in plasma (largely attributable to excessive uncompensated synthesis, to a sufficient availability of alphaglycerophosphate necessary for complete esterification into triglycerides). An altered peripheral use of glucose may also occur, since free fatty acids depend on the greater use of the latter at the level of adipose tissue. The metabolic rate is high in obese people, because it is

proportional to being overweight: they are less effective in counterbalancing or adjusting their metabolic needs.

Modernly, the metabolic phase is valued, in which adenosinotriphosphatase exerts a special power (9). The mobilization of fat, containing more triglycerides, occurs by the degradation of these into glycerol and free fatty acids, which are transported together with albumin. This transformation is possible because an enzyme, lipase, is activated by epinephrine, glucagon, ACTH, TSH and somatotropin. Mobilization depends on the activation of intracellular lipase in a process controlled by cyclic adenosine monophosphate (cyclic AMP), which is formed by the action of adenylyl cyclase - probably related to the beta-adrenergic receptor - located in the cell membrane. Cyclic AMP would act as a second mediator - similar to the first, hormones.

Prostaglandin would act by inhibiting the adeniciclase system. Enkephalin increases the potential for cyclic AMP activity, and the excess of enkephalin occurs thanks to the body's own requirement, which, in turn, further increases the potential of cyclic AMP. Note that the adipocyte membrane in the genetically obese mouse is more fluid. This fluidity is normalized if we place the animal at a high temperature. The defect includes adenosine triphosphatase (ATP-ase) activity (Na+-K+), hormonal regulation of cyclaseadenylate for isoproterenol and glucose transport. Such defect is improved after the normalization of the fluidity of the membrane (15).

The action of the adenosino-triphosphatase system is valued to differentiate constitutional or metabolic obese people from other types of obese people. Flier et al. found that obese individuals have ATP-ase, 22% lower in erythrocytes than in non-obese individuals; regarding norepinephrine, calories rise 40% less in thin people, as well as there seems to be a greater amount of intracellular sodium (a process that involves less energy expenditure) (9).

The action of catecholamines and thyroid hormones stimulate catabolic processes, lipodomobilization and lipases, although their clinical applications for metabolic or constitutional obese patients have no effect on body weight normalization. It seems that amphetamines have a mechanism of action analogous to that of catecholamines, that is, they stimulate lipodomobilization and depress the appetite center; however, this action can cause dangerous side effects in psychotic personalities, leading them to mental breakdown.

In New Zealand, in a special strain of mice, the NZO, there is an entirely different variety of obesity, the so-called Mayer's hereditary hyperglycemia. These animals have extraordinary sensitivity to cold and succumb within a few hours. The feed of these animals can be ingested quickly, but it is consumed fractionally by the body for hours. Studying these mice, Mayer formulated the glycostatic theory: according to this researcher, it would not be the glycemic level, but the use of glucose at the level of the nervous system. Hyperglycemia, as a deficiency of glucose phosphorylation or even hexokinase, would not be used in the hypothalamic system, because the level of effective glucose would be low; however, potassium and phosphorus would decrease their actions, because with high effective glucose, there would be a decrease in potassium and phosphorus. Mayer considers that the glucose of the nerve centers can be measured indirectly by the consumption of glucose in the peripheral tissues, which is done through the difference between arterial and venous glucose, a difference that he

called delta-glucose, and which would be related to the caloric metabolism of each person (11).

The fat cell is a terminal organ under the control of the nervous system, with a tendency to store and mobilize. Stimuli coming from the peripheral tissues would inform the appetite-controlling nuclei. These stimuli are studied, but the influence of glycemic levels - hypo and hyperglycemic - on the action of insulin, or not, and the amount of corticosteroid, lysine, carnitine and the cupric cofactor dopamine-beta-hydrolaxilase, which converts dopamine into norepinephrine, and its low can produce anorexia nervosa (16).

When the lateral zones of the hypothalamus are destroyed (Figure 2), anorexia is produced, and the stimulation of these zones, on the contrary, leads to bulimia. The ventromedian nuclei would exert an inhibitory action on the lateral zones. This set is called the "feeding center" and the one regulated by the arcuate nucleus and the amygdala is called the "satiety center" (this concept is more accepted) (3).

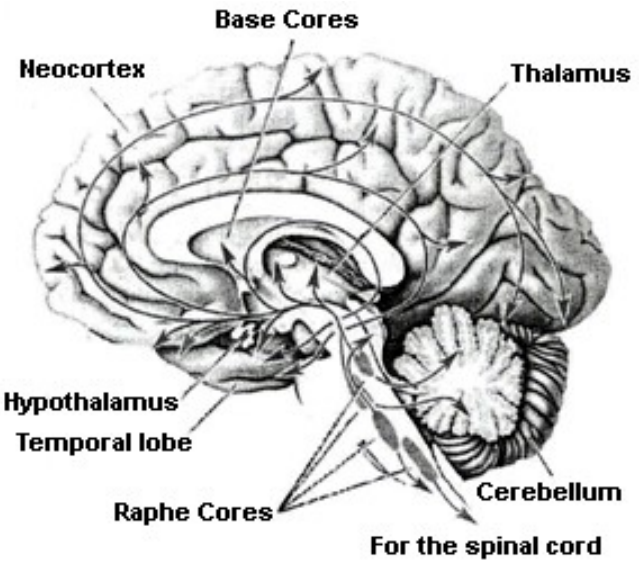

Figure 2. Appetite and satiety zones and the importance of the amidalian brain (raphe nuclei).

The latter would indicate the moment when one should stop eating food. Bulimia is, therefore, a tributary of the excitation of the ventromedian nucleus of the hypothalamus and greatly reflects conscious and unconscious conflicts. Certain neurotic obese people eat not out of hunger, but out of the need for security: food would be a symbol of security. Dexedrine increases the electrical activity of the ventromedian nucleus and therefore increases the inhibition of the hunger center (lateral zone), hence the loss of appetite.

The hypothalamus is under the control of the cerebral cortex, since in frontal leucotomy and internal frontal hyperosthesis the appetite increases, which leads the patient to gain weight. There are several reports in the literature correlating brain trauma with altered electroencephalography and the onset of bulimia, confirming the appetite and satiety zones (17).

There seems to be no doubt that there must be something in the blood that regulates appetite. The experiments in parabiosis mice (a yellow obese person with a heterozygous dominant gene and another who does not develop obesity) confirms the existence of an increased blood concentration of an appetite-controlling substance called leptin, which influences the hypothalamic nuclei. An increase in leptin decreases orexin or hypocreatine.

A genetically obese (OB/OB) mouse has decreased leptin. The drop in leptin level increases the level of NPY and AgRP, which originate in the arcuate nucleus and which, in turn, inhibit the paraventricular nucleus and activate the lateral hypothalamus, increasing appetite, thanks to the production of the peptide melanin-concentrating hormone (MCH). Increased leptin levels in the blood are detected by

the arcuate neuron that contains alpha-MSH and CART peptides. One hypothalamic nucleus seems to control the other, even though it is not close. An alpha-MSH, an anorectic peptide, and AgRP, an anorectic peptide, exert opposite effects on feeding behavior, due to the interaction with the melanocortin 4 receptor (MC4) in hypothalamic neurons, mainly orexin (3).

Galanin produces effects similar to orexin, leptin or hypocreatine in controlling appetite, being stimulated by triglycerides. Galanin produces the synthesis and release of luteinizing hormone (LH). Such correlation is important to explain the presence of ovarian alterations, both in anorexia nervosa and in animals without dopamine. They behave as if they like the food, but do not desire it - they do not look for the food, but if there is any around, they eat it. Stimulation of dopaminergic axons in the lateral hypothalamus produces food cravings (as occurs in bulimia) without increasing the hedonic effect of the food. The increase in serotonin in the brain decreases appetite, as in the action of dexfenfluramine. The pituitary principle - beta-LPH - is the precursor to the activity of other peptides. From this beta-LPH, melanotropin (beta-MSH) and endorphin are derived. The beta-endorphin antibody reacts with beta-LPH. In the brain, amino acids and their incorporation are synthesized for the formation of ACTH, beta-LPH and endorphins.

In Cushing's Syndrome obesity, ACTH and beta-LPH have increased levels (7), as well as in hirsute women due to hyoperandrogenism (18). The injection of naloxone prevents food intake in both normal rats and rats with hypothalamic lesions, and the decrease in food intake is more pronounced in the latter. Genetically obese animals have a higher endogenous amount of beta-endorphin. If we inject morphine or endorphins into the ventromedian hypothalamus of animals with no appetite, it will increase considerably; ipso facto, if we inject the opioid antagonist naltrexone, we will produce the suppression of hyperphagia (19), although O'Brien et al. have not confirmed the effect in the human species (18).

Psychological and clinical factors

Due to the correction of the hypothalamic center with the cortex, obesity can be explained, motivated by psychic conflicts. Rats under emotional stress (Ader-Frieman type) show increased ketone bodies, glycemia and free fatty acids, and decreased blood iron and epinephrine in the adrenal glands (20). Obese children (38%) show iron deficiency, moderate low zinc, as well as alterations in serum immunoglobulin levels (complements C3 and C4) and in the number of T and B lymphocytes, which facilitates a higher incidence of infection (21).

In men, salivation decreases in depressed patients (who complain of dry mouth). Durrant & Royston studied salivation in obese women, the feeling of hunger and the amount of calories ingested and concluded that salivation was slightly proportional to the energy ingested; however, hunger and appetite did not vary significantly (22).

The stimulation of this hypothalamic mechanism of appetite regulation does not seem to be due to the type of diet, nor to caloric intake, but to weight maintenance, if it remains constant and ideal. In this way, the thin person who eats a lot of cream daily, for example, may gain weight, but, over time, he will begin to feel disgusted and lose the pounds gained. The same fact occurs with gastrectomy, which does not prevent obesity, due to excitation of the hypothalamus; rats eat little, but often.

The normal individual eats only enough to satisfy his appetite. The appetite of the obese, however, is exaggerated, hence the therapeutic failure due to the fact that it is not possible to leave him chronically hungry. Anorexic people work, but the individual does not eat them all his life, which leads him to gain weight again. Some people fail to lose weight, not only because of an exaggerated appetite, but also because of a lack of willpower, and because anorexics cause them great nervous excitement. Excess appetite often reflects psychic dissatisfaction. In certain cases, obesity would not only be caused by overeating or lack of physical exercise, but also due to decreased energy consumption, as they burn fewer calories, thanks to a genetic defect. These are, however, hypotheses that need to be confirmed.

In anorexia nervosa, there is no unconscious fantasy of expulsion of the evil object (e.g., food-symbol). In bulimia there is a lack of pressure mechanism, with numerous clinical symptoms appearing due to the correlation of these symptoms with other hormonal changes in the hypothalamus, such as amenorrhea or various types of depression, obsessions, hypochondria, hysteria, munchies anxiety (something good that passes in the throat) and dependence.

Anorexia can be of three types: completive, neurotic and psychotic (which can lead to suicide). The differential diagnosis is made through hormonal measurements and tests: growth hormone, ACTH, TSH, follicle-stimulating hormone, LH, norepinephrine, pheniglycol, prolactin, cortisol, estradiol and dehydroiso-androsterone, in addition to the Games, Rorschach and Eysenck psychological tests. Anorexia is the "first cousin" of schizophrenia; anorexia and bulimia are paralogical psychotic somatizations, creating fantasies of another engendering - daughter glued to her mother or a neo-object (the food-symbol) that sticks to it (23) -, with rumination, regurgitation, with changes in body image, ending up causing security (adhesive identification) or becoming a self-punishment (kummerspeck) or aggression against another (assaulting to be assaulted).

Treatment should be medication (antipsychotic drugs, cortisol, vitamin B complex in high doses, primozide, olanzapine, risperidone and aripiprazole) associated with psychoanalysis or group analysis, with family orientation (Millieu Therapy) aiming to achieve "portance", thus transforming the "bad-mother" analyst into a "good-mother". In the case of the morbidly obese person who needs to undergo partial gastrectomy, he must be well guided during the preoperative period to avoid crises of affliction, anger and despair, motivated by the fact that he can no longer satisfy his compulsive and voracious desire - that is, hedonia - because he will be sick if he eats all the desired food. This patient will need psychotropic medications (Neozine, etc.).

During lactation, mothers, through the rêverie, induce the formation of a "hunger engram". If they excessively value food, with feedings at all times, they transform this food into a symbol of pleasure or displeasure, security or insecurity; in short, a bad or good object. This fact will lead to a confusion of values in the individual. Right or wrong experiences will be encoded in the brain, as breast sucking is the first way to express love.

Anorexia, bulimia and morbid obesity, in our view, are not monosymptomatic psychoses; they are a syndrome of the limbic system, installed in individuals with archaic and bumpy ego. As we have al-

ready pointed out, the sick end up moving in a world of "bizarre objects", confusing fantasy with reality, whose food would be impregnated with bad parts. Such theories could explain certain types of obesity, but not the mechanism of essential obesity. This may be explained by the imbalance in the action of somatotrophic hormones: ACTH (glucocorticoids and mineralocorticoids), antidiuretics, insulin, glucagon, ATP-ase erythrocyte; and, mainly, between the lipid mobilizing principles (7,13): leptin, orexin and dopamine (5). The obese, as well as the thin (in anorexia nervosa), overestimate their body scheme. The first "needs" to be obese and the second "needs" to be skinny in order to be able to punish themselves.

The works of Glucksman & Hirsch (24) and Garner et al. (25) - through photographs to visualize parts of the body and Eysenck's psychological test, which reveal self-stimulation - prove the importance of this self-perception of body schema. Such experiences explain, in part, the need that obese patients have to change doctors: in addition to the shame of remaining in front of the same professional without having lost weight, a new specialist would be a new stimulus to consciously try to lose this body image. However, unconsciously, obese patients need to have this image in order to punish themselves and, sometimes, attack someone; it is thanatism.

In anorexia nervosa there would be a feeling of inefficiency: when looking at one's own skeletal body, the anorexic would be relieved not to see there the "bad object" introjected into the adipose tissue. A similar fact would occur with a certain type of obese person: he would have to "verify" that the bad object is introjected into the adipose tissue, in order to be able to punish himself even more; it would be a distortion of body image motivated by feelings of despair. Such distortion of body image would be processed from the first period of molding, during lactation, thanks to the feeling of ambivalence towards the mother; the individual becomes unable to develop satisfactorily his feelings concerning his own bodily ego, due to hostility towards the mother.

Meyer and Pudel studied appetite in women, isolating a group that could not see food and another that could observe various types of food but could not eat it at will. The authors concluded that hyperphagic reactions may be secondary to emotional disturbances, and it is therefore possible that there is an etiological factor in obesity. However, children and the elderly may not have emotional polyphagia. Satiation disorders vary with age and body weight, as obese older people do not show slowness in food intake. The sudden dilation of the stomach, thanks to the stimulation of the satiation center, is, in obese people, slower, that is, there seems to be a deficiency in the brain in detecting the amount of food that can be assimilated, a factor of paramount importance to regulate the amount of food and calories ingested (26).

In anorexia nervosa, however, this reflex is hyperactivated, that is, as soon as the stomach dilates, appetite ceases. The end of the absorption of food from a meal could not explain the cessation of hunger, that is, the satiety caused by the ingestion of food would also be linked to what said food would symbolize. Stunkard reports that the presence of stomach contractions in obese women during fasting does not usually refer to the feeling of hunger, epigastric voidness, or the desire to eat (27).

Bulimia mold period

In our view, the excess or lack of appetite, although innate, would also depend, in the first months of life, on the baby's contact with the mother: this is the first period of molding. However, Hebb understands that the feeling of being satiated is not innate and will depend on education (28). Bruch is of the opinion that the genetic factor is influenced by the environment. The newborn is no longer the blank slate of the homunculus: the child can learn, over certain periods of time. As far as appetite is concerned, he learns from the moment of birth (28).

There are two types of appetite: hunger for food and hunger for what food symbolizes or represents (affection). It is in the latter case that insatiability becomes important, as such conditions depend on the first relationship with the mother. This, not being able to recognize the child's crying - when it is motivated by hunger, the need for affection or because the child is dirty, wet, hot, etc. - can induce disorganization in the baby in relation to appetite. Hence the importance of the efficacy of psychotherapy for the obese: the therapist must know how to distinguish the various types of anguish of the patient - related, or not, to food. There is a consensus on the understanding of innate hunger, and it must also be considered that environmental factors can potentiate the instinctive condition.

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In memoriam: Luiz Miller de Paiva.

Conflict of interest

None.

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