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Mediators Involved in Obesity and Modulation of Food Intake by Antioxidants

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Abstract

Introduction: Obesity is a disease that involves adiposity excess associated to diverse factors, including behavior ones, such as hormonal, adipocitarious, neural and intestinal. The excess of adipose tissue results in inflammation, which begins with secretion of pro-inflammatory adypokines, activating inflammatory T cells and resulting in imbalance between antioxidants and oxidants compounds. The recuperation of this defense system may occur through endogenous or dietetics origin. Diet rich in antioxidants is inversely bound to metabolic disturbances. Therefore, these compounds may be regarded coadjutant potentials in the prevention of obesity.

Objectives: To review and to summarize critically studies related to themes concerning antioxidants and food intake mediators.

Methods: It was done a narrative review about food intake mediators in humans related to obesity and antioxidants intake.

Results: Overweight individuals possess an imbalance between intrinsic signals related to appetite and a nutritionally balanced diet is fundamental to oppose obesity. The intake of food rich in antioxidant may be a strategy to reach metabolic homeostasis and the reduction of damage caused by obesity.

Conclusion: The antioxidant compounds present an anti-obesity potential effect due to food intake mediators' modulation for opposing damage caused by excess of adipose tissue deposition.

Keywords: Food intake mediators; Obesity; Antioxidants; Polyphenols; Anthocyanins

Introduction

Obesity is a complex disease, which involves the excessive adiposity accumulation associated to diverse factors both behavioral as hormonal, adipocitarious, neural and intestinal [1].

The excess of adipose tissue deposition secretes many bioactive substances involved in the regulation of insulin, arterial pressure and inflammatory estate such as leptin, adiponectin, InterLeukin (IL), Tumor Necrosis Factor alpha (TNF-α), among others [2]. A subclinical inflammation is observed subsequently to the adiposity excess which begin from the pro-inflammatory adipokine, such as leptin, which activates inflammatory T cells, causing a progressive inflammation [3].

On the subclinical chronic inflammation occurs an imbalance between antioxidant and oxidant compounds, which favors the installation of an oxidative stress process. The maintenance and recuperation of this defense system may occur through enzymatic or non-enzymatic systems, and this may be of an endogenous origin (through dismutase superoxide, catalase, glutathione peroxidase) or dietetic through the intake of food rich in Vitamin A (β-caroteno), Vitamin C (ascorbic acid), Vitamin E (α-tocoferol), copper, zinc, magnesium, selenium, caratenoids (lycopene) and phytochemical (resveratrol, catechins, quercetins, phenolic acid and others). These substances may act both as directly, neutralizing the action of free radicals, as indirectly, activating enzymatic systems capable of neutralize them [4]. Thus, oxidative stress is an important link between the intake of a hypercaloric diet and chronic diseases, such as obesity [5].

Food intake is modulated mainly through biological mechanisms such as homeostatic, which refer to hormonal regulators that initiate hunger and satiation (such as neuropeptide Y and tyrosine tyrosine peptide) or sign adiposity levels (such as leptin, ghrelin and insulin), which act in the hypothalamic encephalic centers and in the brainstem, sending and receiving signals according to available energetic substratum in order to keep a proper energetic balance; or may not be homeostatic (hedonic), which refer to awarding cerebral

system. So palatable food (rich mainly in fat and sugar) are consumed even after the energetic requirement being accomplished. On the other hand, non-palatable food (no sugar and fat) are not desired on the same way by the brain [6,7].

The influence of biological factors and their alterations induced by diets on corporal composition are not totally clarified yet [8]. Gastrointestinal system presents special chemoreceptors and mechanoreceptors that monitor quantity and quality of food intake and nutrients. Therefore, the information arrives at the hypothalamus through afferent nerve fibers that understand the signals related to current necessities [7]. Many hormones are involved in these feedback mechanisms between gastrointestinal tract and brain, and those hormones may be liberated before or after food intake, whether they are orexigenic or anorexigenic, always looking for the balance between intakes, spent and stocked energy. Among the involved mediators in such regulation, it may be mentioned Peptide Tyrosine Tyrosine (PYY), Pancreatic Polypeptide (PP), alpha-Melanocyte Stimulating Hormone (alpha-MSH), Peptide C, chemerin and beta-endorphin [9].

The homeostasis of these mediators depends on individual factors such as corporal composition and lifestyle, including exercise and nourishment [10]. Thus, a diet rich in fruits and vegetables is inversely linked to metabolic disturbances [11]. Grains, teas and wines are rich in polyphenols, which are natural substances composed by phenolic rings. Polyphenols might be classified as stilbenes, lignans, phenolic acids and flavonoids [12].

Polyphenols present many benefits for health due to their antioxidant potential effect, anti-inflammatory [13] and insulin potentiator, causing a plasmatic glucose reduction in diabetic [14] and obese people [15]. However, their effects on the regulation of neuropeptides and neural-hormones involved at food intake are not totally clarified [16].

The objective of this paper was to review studies for a higher understanding about the effect of antioxidants on food intake mediators.

Methodology

This paper consists on a narrative review of studies about food intake mediators' and their relation with antioxidants consumption.

It was done a bibliographical search on databases *PubMed, SciElo* and *Science Direct,* considering the following keywords: "food intake mediators", in association to "obesity", "antioxidants", "polyphenols" and "anthocyanins" and their respective correspondents in English: "food intake mediators", "obesity", "antioxidants", "polyphenols", and "anthocyanins".

In order to assess the action of food intake mediators, it was included interventions done in humans, which would assess their action over metabolic parameters associated to obesity. It was included studies with humans and animals to assess the action of antioxidants on food intake parameters, considering that the literature on the topic is still scarce.

Results

Many proteins involved in the arterial pressure, fat and glucose metabolism regulation, such as leptin and chemerin are adipokine secreted by adipose tissue [17]. It is also known that many cytokines and proteins of acute stage related to subclinical inflammation are highly found in obese patients. An imbalance between pro and anti-inflammatory cytokines induces the inflammation estate, which occurs when there is an adipose tissue, forming a cycle responsible for oxidative stress, until its cause is reverted [18].

The excessive intake of macronutrients is one of the biggest contributors for the increasing of obesity prevalence [19]. However, the act of eat excessively is not always something conscious or compulsive; studies show that there may be a defective answer of intrinsic signs related to appetite in overweight individuals [20-22].

The act of eating is highly related to many processes, which result in the energetic balance, such as hunger, satiation and repletion. Hunger is considered as the urge that leads to the action of eating; satiation is the period in which eating is interrupted and repletion is the period between meals, where there is an eating inhibition. This "food desire" may be, or not, due to a physiologic necessity, so it can be stimulated by hormonal signal due to lack of energetic substratum, such as olfactory or visual external stimuli [23].

The ingestion/expenditure of nutrients are controlled by neural structures, which involve specific neurochemical and neuroendocrine systems and, when it happens a commitment in these systems, occurs a consequent imbalance of eating behavior [24]. With this, there is a complex interaction between pre-absorbing, absorbing and post-absorbing stages, which determine food intake and energetic expenditure. Imbalanced intakes of macronutrients and micronutrients may induce an alteration of some mediators' production, which intervene directly on corporal composition, biochemical and clinical profile [25].

Thus, balanced diet is a fundamental strategy against obesity [26]. Potential mechanisms related to the benefits of a diet modification include: improvement of insulin resistance; improvement of insulin secretion depending on glucose at beta pancreatic cells; hunger/satiation system regulation through proper working of the mediators responsible for appetite and inflammation attenuation [27].

Many neuropeptides have been studied in order to better understand central factors related to ingestion control and obesity etiology [28,29,8].

Food intake mediators and obesity in humans

Many food intake mediators are responsible for energetic homeostasis and metabolic disturbances, which may proceed to an imbalance among food intake versus energetic expenditure [30].

PYY is an intestinal peptidic hormone secreted on post-prandial period proportionally to the ingested caloric quantity. This is secreted by L cells of distal portion of large and small intestine and it reduces intestinal mobility and, therefore, it improves satiation and reduces the intake of food [31].

Studies show that obese individuals present minor concentrations of endogen PYY in fasting and post-prandial period when compared to non-obese ones [32-34].

Brandão PP, et al. [35] assessed PYY concentration after and before meals in obese women with or without eating compulsion episodes. A total of 25 women from 32 to 50 years old were studied (9 eutrophic without eating compulsion episodes, 9 obese ones with eating compulsion episodes and 7 obese women without eating compulsion episodes). It was found difference on PYY levels when the thin women group were compared to the obese group (the obese ones presented lower levels). The group with eating compulsion episode presented the lowest levels of PYY, reinforcing its direct relation to the ingested caloric quantity and obesity.

In a study carried out to determine PYY effects managed peripherally over food intake and activation of enteric neurons and rhombencephalon found a reduction of 10% sucrose solution ingestion and activation of enteric neurons before the vagal dorsal complex, suggesting that these act peripherally before acting centrally [36].

Another determining factor of concentrations is the ingested caloric density, which directly influences the serum PYY concentration, thus presented an important relation to obesity genesis [37].

Another marker is the pancreatic polypeptide, a peptide hormone produced by special cells on pancreatic islet, called F cells, which, as with PYY, influence the energetic balance, for they reduce food intake [38]. This hormone may be produced also by exocrine way on distal intestine [39].

Studies showed that a higher secretion of PP is related to reduction of food intake and that circling levels of this hormone keep elevated up to 6 hours after the meal [40-42].

Low concentrations of PP were found concomitantly to the increase of NPY secretion (an orexigenic hormone) on the arched core hypothalamus on obese humans [43]. Edelsbrunner ME, et al. [44] observed that through knocking down the gene related to PP (gene Y4) occurs a higher food intake and a consequent gaining of weight in rats, confirming its anorexigenic action.

A study that assessed PP infusions effects done in the morning and afternoon in patients with Prader-Willi Syndrome (a genetic disease which leads to child obesity) observed a caloric ingestion reduction of approximately 12% [45]. With this, administration of PP in obese individuals might help to reduce the ingestion through ghrelin hormone concentration reduction (an orexigenic hormone) and thus control and restore the energetic balance [46].

Chemerin is a chemotactic adipokine, which connects to CMKLR1 receptor attached to the G protein that participates on the metabolic regulation of adipocytes, and, due to this its role on inflammation and metabolism may assist the understanding of this relation between obesity and chronic inflammation [47,48].

Besides many obese individuals present higher concentration of chemerin when compared to thin individuals, it was shown association of concentrations of this adipokine with triglycerides, arterial pressure, insulin resistance and corporal mass in non-diabetic individuals [48,49].

Schmid A, et al. [50] reported that oral ingestion of a lipidic emulsion, free from carbohydrates and proteins, regulates negatively the serum concentrations of chemerin in healthy humans. However, the molecular mechanisms of this regulation in humans are not clarified [50].

A good food intake mediator is the beta-endorphin, a peptide of melanocortins family found in organisms in lower concentrations under normal conditions, which may increase up to 10 times when in stress [51]. Studies show that central infusion of beta-endorphin stimulates food intake [52-54].

Considering that beta-endorphin is connected to the reward system under non-private conditions, it may be considered a good marker to assist the understanding of corporal composition and dietetic parameters, since its effects are related to palatable food intake and these are associated to overweight and obesity [55].

Alpha-MSH (hormone stimulating of alfa-melanocytes) also participates of the hedonic control of eating, as beta-endorphin, it is a neuropeptide of the melanocortins family [56]. It has an anorexigenic action and participates of intrinsic processes related to metabolic process on obesity [57].

The anorexigenic action of alpha-MSH seems to occur due to the neurotrophic factor stimulation derived from the brain (BDNF), an endogen protein responsible for regular synapses stimulated both peripherally as centrally, after the activation of melanocortin receptor [58]. In humans, mutations on the gene of MC4R receptor may result in cases of obesity, which might appear in severe form even in the childhood [59].

The mRNA expression of its receptor possesses a direct relation to adipose tissue on obese individuals [60], and its related to the increase of lipolysis on white adipose tissue [61], muscular insulinic sensibility [62], thermogenesis on brown adipose tissue [63] and reduction of insulin excretion on pancreatic beta cells [64], thus characterizing a good correspondent of subclinical inflammation [60].

Food intake mediators and antioxidants

There are growing evidences on the protection role of health through fruits and vegetables consumption, which are the main contributors for polyphenols intake [65-67]. These compounds' ingestion has presented effects on the plasmatic glucose concentration reduction in obese individuals, with metabolic syndrome and type 2 diabetes [14,15]. These effects happen mainly for its antioxidant action. Studies showed that polyphenols distribute largely on the tissues where they act as exogenous antioxidants on neutralization of free radicals and consequent attenuation of oxidative stress [68,69].

While a small part of polyphenols may be absorbed on the small intestine, the bigger part ingested on the diet is not bioavailable on the distal portion of the human intestine, exerting its biologic activity on the intestinal tract through the interaction of colon microbiota [70].

These compounds may act directly on the encephalon. Studies in rats showed that they pass the hematoencephalic barrier after assessing the catechins concentration (a category of flavonoids) in encephalic tissue after polyphenol extract intake. However, necessary concentration for this was not totally clarified yet [71-73]. Despite that, the effects of neuropeptides and neuro-hormones regulation involved to food intake deserve attention, for it is a potential prevention and treatment of disturbances related to food intake such as obesity, diabetes, and others [16].

The intake of grape extract rich in polyphenol for 10 consecutive days by rats increased significantly the catechin concentrations and epicatechins (kinds of polyphenols) on encephalic tissue, result which was not observed on the group that received a single dose, which suggest that the long term intake may improve its action [74].

Studies proved that polyphenols intake causes a reduction of factors related to metabolic syndrome and obesity through the suppression of fat absorption on the intestine, thermogenesis activation, attenuation of chronic inflammation and fat oxidation [75-79,14].

Some studies in humans and in cultures of animal cells helped to clarify the potential role of polyphenols on neuro-hormones modulation related to food intake and energetic homeostasis [80].

The insulin, an important hormone that regulates the glucose levels on blood, has its action empowered with the polyphenols intake, causing an improvement on insulin resistance in obese patients with type 2 diabetes and/or metabolic syndrome [16].

Lu C, et al. [77] assessed the administration of a green tea in rats submitted to a diet rich in fat and observed a reduction on the ghrelin levels, a orexigenic hormone, caused by polyphenols contained in the

drink.

It was found by Weickert a potential anorexigenic effect caused by isoflavone intake (polyphenol contained in soy) due to the increasing of PYY concentration in healthy women [81].

Considering that inflammatory factors and oxidative estate are related to obesity, the reduction of those by antioxidant action through diet might favor the metabolic homeostasis [82-85].

Conclusion

Food intake mediators are very important to energetic homeostasis. Disturbances on the working of orexigenic or anorexigenic mediators may cause a metabolic dysfunction and, consequently, adipose tissue accumulation and obesity. Due to the capacity of reduce the inflammation damage and oxidative stress observed in obesity, the antioxidant compounds present potential anti-obesity effect due to the modulation of food intake mediators. However, more studies are necessary in humans to clarify this effect.

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