Review article

Mitochondrial dysfunction in obesity

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ABSTRACT

Obesity leads to various changes in the body. Among them, the existing inflammatory process may lead to an increase in the production of reactive oxygen species (ROS) and cause oxidative stress. Oxidative stress, in turn, can trigger mitochondrial changes, which is called mitochondrial dysfunction. Moreover, excess nutrients supply (as it commonly is the case with obesity) can overwhelm the Krebs cycle and the mitochondrial respiratory chain, causing a mitochondrial dysfunction, and lead to a higher ROS formation. This increase in ROS production by the respiratory chain may also cause oxidative stress, which may exacerbate the inflammatory process in obesity. All these intracellular changes can lead to cellular apoptosis. These processes have been described in obesity as occurring mainly in peripheral tissues. However, some studies have already shown that obesity is also associated with changes in the central nervous system (CNS), with alterations in the blood-brain barrier (BBB) and in cerebral structures such as hypothalamus and hippocampus. In this sense, this review presents a general view about mitochondrial dysfunction in obesity, including related alterations, such as inflammation, oxidative stress, and apoptosis, and focusing on the whole organism, covering alterations in peripheral tissues, BBB, and CNS.

1. Introduction

Obesity is defined by the World Health Organization (WHO) as an accumulation of abnormal or excessive fat that may impair health [1]. The World Obesity Federation reports that obesity is considered an epidemic, and is recognized as one of the most important public health problems facing the world [2]. Since 1980, obesity has more than doubled around the world. By 2014, more than 1.9 billion adults were overweight, and over 600 million of them were obese. This indicated that 39% of adults aged 18 years or older were overweight and 13% were obese [1]. Obesity is a major risk factor for several other diseases, such as diabetes, cardiovascular diseases, respiratory diseases, musculoskeletal disorders, and some types of cancer [1–3].

Obesity causes several changes in the body, such as inflammation [4–7], oxidative stress [8,9], mitochondrial dysfunction [10,11], and apoptosis [12,13]. It should be noted that peripheral tissue has been the major focus of these studies. However, some studies have already shown that obesity is also associated with changes in the BBB [14–16] and in the brain [17,18], particularly in the hypothalamus [19–21], and in the hippocampus [22–24].

Therefore, the objective of this narrative review was to provide a general view about mitochondrial dysfunction in obesity, including related alterations, and focusing on the whole organism. The review was conducted by searching PubMed and SciELO. We selected articles related to the topic published in the last 10 years.

2. Inflammation in obesity

The energy imbalance between calories consumed and calories expended is considered the main cause of obesity [1]. Adipose tissue responds to excessive intake of nutrients through adipocyte hypertrophy and hyperplasia [25]. This way, obesity is characterized by increased storage of fatty acids in an enlarged mass of adipose tissue [5].

Adipose tissue, along with its important role in energy storage, is an important endocrine organ [5,26]. It produces many bioactive molecules, such as cytokines, which are called adipokines (or adipocytokines) when secreted by adipose tissue, and they serve not only as regulators of the systemic metabolism, but have immunoregulatory properties as well [26–30].

Obesity leads to changes in the production of adipokines [5]. Blood flow can be impaired, with consequent hypoxia, caused by the progressive increase of the adipocytes and the enlargement of adipose tissue. Hypoxia is related to necrosis and infiltration of macrophages in adipose tissue [31]. Infiltrated macrophages form crown-like structures that surround adipocytes, leading to the overproduction of adipokines, which include proinflammatory mediators, such as tumor necrosis

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factor alpha (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6) [5,6,32]. At the systemic level, altered adipokine secretion may lead to increased food intake and reduced energy expenditure by actions in the hypothalamus, as well as decreased muscle and liver insulin sensitivity [5].

Thus, obesity may be viewed as a low-grade chronic inflammation, detected by the elevation of inflammatory markers and cytokines, and by the presence of macrophages infiltrated into the white adipose tissue [6,26,33]. This low-grade chronic inflammation in the adipose tissue spreads to a systemic inflammation and contributes to the onset and progression of associated metabolic disorders, such as insulin resistance, type 2 diabetes mellitus, hyperlipidemias, and atherosclerosis [27].

As for the mechanisms that cause inflammation of adipose tissue in obesity, the accumulation of lipids leads to adipocyte hypertrophy, which induces the activation of pro-inflammatory pathways, especially by the nuclear factor kappa B (NFκB). In addition to increasing the number of macrophages, obesity induces a pro-inflammatory state in these cells. Then, the activated macrophages secrete abundant pro-inflammatory adipokines [4].

TNF-α, which is mainly produced by macrophages, also appears to be an important contributor to the adipokine deregulation in adipocytes. Adipocytes from obese individuals overproduce adipokines in response to the TNF-α. This hyperresponsiveness is mediated by TNF-α-receptor-1 (TNFR1) and by the hyperactivation of the NFκB pathway. TNF-α also induces lipolysis, which leads to the release of free fatty acids. Saturated fatty acids, in turn, bind to the Toll-like receptor 4 (TLR4) on the surface of both adipocytes and macrophages, and further activate NFκB signaling, increase the production of TNF-α and other pro-inflammatory adipokines, such as IL-1β and IL-6 [4,26].

Furthermore, the food itself can have an immediate effect on circulating inflammation markers, since a transient increase in inflammatory markers is seen in the circulation within hours after eating a high-fat meal [21]. Elgazar-Carmon and colleagues [34] demonstrated that a high-fat diet is related to neutrophil infiltration into the adipose tissue of mice. In this sense, the most widely studied dietary components in the induction of inflammation are saturated fatty acids [35]. The inflammatory process present in obesity is illustrated in Fig. 1.

Furthermore, studies conducted in the last decade have shown that obesity and its comorbidities are not just peripheral tissue disorder, but involve changes in the CNS [17,18,36]. It has been shown that both excessive consumption of saturated fats and obesity can lead to changes in the BBB [14–16] and brain lesions [17,18,20,21,23].

3. CNS alterations in obesity: BBB permeability, microglia, and astrocytes

Obesity is associated with changes in BBB integrity [15,37]. BBB is a regulatory barrier between the CNS and peripheral circulation. It is composed of specialized endothelial cells with the function of preventing the diffusion of certain molecules between the CNS and the circulation. The homeostasis of BBB is altered by metabolic changes present in obesity [15]. A high-fat diet can lead to obesity and chronic peripheral inflammation, causing the release of cytokines. This, in turn, has deleterious effects on brain function, such as BBB change, and neuroinflammation. Peripheral inflammation and increased BBB permeability lead to leukocyte migration to the brain, which aggravates neuroinflammation [16].

Ouyang and colleagues [15] have shown that obese mice presented suppression in the metabolic activity of several microvessels that make up the BBB. Further studies were conducted to evaluate the hippocampus, a brain area involved with learning and memory. Freeman and Granholm [38] identified a reduction in BBB integrity in the hippocampus of rats fed a diet rich in saturated fat and cholesterol. A study conducted by Davidson and colleagues [39] also showed increased BBB permeability in the hippocampus of rats fed a western diet, rich in saturated fat and sugar.

In addition, Buckman and colleagues [40] identified that high-fat diet-induced obesity in mice leads to increased recruitment of monocytes to the CNS. These results indicate that in obesity peripheral immune cells can be recruited to the CNS in a similar way that macrophages are recruited to the white adipose tissue, contributing to the inflammatory response [40].

This recruitment/migration of peripheral immune cells to the CNS, as well as changes in BBB permeability, can provide the activation of glial cells, such as microglia and astrocytes, which plays a key role in neuroinflammation [37,41,42]. In this sense, it has been demonstrated that a high-fat diet and obesity are associated with the activation of microglia and astrocytes [20,41–44].
4. CNS alterations in obesity: hypothalamus and hippocampus

The balance between energy intake and energy expenditure is controlled by a complex biological system, managed by the CNS, and failures in this system may be related to obesity [45,46]. Homeostatic control of body energy balance is exerted by neurons located mainly in a brain structure called hypothalamus [45].

Excessive intake of saturated fats (found in foods of animal origin, such as fatty meats, lard, and dairy products) causes an inflammatory process in the hypothalamus, affecting its functioning [19,20,21,45,47]. Milanski and colleagues [47] showed that saturated fatty acids activate Toll-like receptor 2 (TLR2) and TLR4 in the hypothalamus of rodents, stimulating the production of pro-inflammatory cytokines, such as TNF-α, IL-1β and IL-6 and, consequently, can signal pathways that lead to the destruction of neurons responsible for appetite regulation. Moreover, excess nutrients supply, particularly saturated fatty acids, can also trigger endoplasmic reticulum stress, which, in turn, can also activate inflammatory pathways [47,48]. Thaler and colleagues [20] showed evidence of increased gliosis in the mediobasal hypothalamus of obese individuals, suggesting that, similarly to what occurs in rodents with obesity induced by high-fat diet, obesity in humans is associated with lesions in hypothalamic neurons.

The inflammatory process resulting from a high-fat diet and consequent obesity is also associated with impairment of the hippocampus, a brain structure related to cognition, memory, learning, and emotions [18,23,37,49,50]. In this context, Park and colleagues [51] showed that high-fat diet intake impaired neurogenesis in the rodent hippocampus, as well as increased lipid peroxidation and decreased brain-derived neurotrophic factor (BDNF) levels. Boitard and colleagues [22] identified that high-fat diet intake led to increased expression of pro-inflammatory cytokines in the rodent hippocampus.

5. Oxidative stress in obesity

The inflammation and oxidative stress are interrelated in obesity [52]. Inflammation-related mechanisms that occur in obesity may increase the production of reactive oxygen species (ROS) [28,52,53]. The body has an antioxidant system to curb ROS levels and control the damage. This system is divided into non-enzymatic and enzymatic. The non-enzymatic defense system includes antioxidant compounds of dietary origin, such as vitamin E, vitamin C, carotenoids, uric acid, and polyphenols. The main enzymatic antioxidants include the superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPX) enzymes, which act by means of prevention mechanisms, preventing and/or controlling the formation of ROS [54,55].

The oxidative stress process originates from the imbalance between ROS production and antioxidant defense, in favor of excessive production of ROS or to the detriment of the speed of their removal by the antioxidants [54]. Oxidative stress can lead to the oxidation of biomolecules, such as lipids, proteins, and DNA, with consequent loss of their biological functions and/or homeostatic imbalance, whose manifestation is the potential oxidative damage against cells and tissues [54]. Moreover, by damaging cell structures, the oxidative stress can trigger or potentiate an inflammatory response [53]. Therefore, a balance between oxidant compounds and antioxidants is essential for adequate organ and tissue functioning [54].

An increase in the production of ROS is one of the several cellular responses to excess nutrients supply in obesity [9,28,52,56]. In addition to inflammation, a chronic imbalance in the energy metabolism due to excessive food intake, obesity, and physical inactivity may contribute to the increase of ROS production, and in turn, excess ROS may lead to mitochondrial dysfunction [57,58].

In this context, a study conducted by Bonnard and colleagues [59] showed that a high-fat high-sucrose diet causes mitochondrial changes in muscle tissue of mice, along with ROS production. Freeman and colleagues [60] identified that there was an increased production of ROS in the brain (prefrontal cortex and hippocampus) in diet-induced obese mice. Ma and collaborators [61] have identified oxidative damage and mitochondrial dysfunction in the brain and plasma in rats with high-fat diet-induced obesity. A study also identified that, with the increase of adipose tissue, the activity of antioxidant enzymes, such as SOD, CAT, and GPX, was significantly reduced [28].

Another important source of ROS is the Nicotinamide Adenine Dinucleotide Phosphate Oxidase (NADPH oxidase), a multiprotein complex that is expressed both in phagocytes and endothelial cells [62]. Chen and Stinnett [63] showed that high-fat diet activates NADPH oxidase and mediates the expression of TLR in vascular tissues of diet-induced obesity mice. Marchesi et al. [64] also report that perivascular adipose tissue of New Zealand obese mice showed increased superoxide production and NADPH oxidase activity.

Excess production of ROS and inflammation may lead to mitochondrial dysfunction [65]. Furthermore, excessive nutrient intake and obesity lead to changes in the mitochondria, which favors the generation of ROS and the development of oxidative stress [28,66].

6. Mitochondrial dysfunction in obesity

Mitochondria play a central role in energy metabolism. The primary function of mitochondria is to produce energy for the cells in the form of adenosine triphosphate (ATP) from food substrates (carbohydrates, lipids, and proteins) [67–69]. In addition to ATP production, mitochondria are involved in the production and elimination of ROS [70]. The mitochondrial respiratory chain generates ROS during ATP production and, therefore, represents the main source for the production of ROS [62].

Metabolic imbalance of nutrient signal input, energy production, and/or oxidative respiration results in ‘mitochondrial dysfunction’ [69]. Mitochondrial dysfunction is classically defined as the incapacity of mitochondria to generate and sustain sufficient ATP levels [71]. However, the term is also used to define maladaptive physiological responses of mitochondria that undergo metabolic perturbations, such as irregularities in substrate catabolism, calcium buffering, iron transport, mutations in mitochondrial DNA or nuclear mitochondrial genes, changes in dynamics of the mitochondria, changes in size and morphology, ROS production, and apoptosis [69,72].

There is evidence that excessive consumption of nutrients affects the function of mitochondria [73]. In this context, studies have shown that obesity is related to mitochondrial dysfunction [10,11,74,75]. All cells can be affected by mitochondrial dysfunction [69]. However, when it comes to obesity, some tissues were most studied (adipose tissue, muscle, and liver). Excess nutrient intake leads to high concentration of free fatty acids, hyperglycemia, increased mitochondrial ROS production, and cause adipocyte mitochondrial dysfunction [69]. Compromised mitochondrial function reduces mitochondrial biogenesis and mitochondrial DNA content and decreases the rate of β-oxidation. Then adipocyte pathways are altered, such as adipogenesis, lipolysis, fatty acid esterification and adipocyte-derived adiponectin production. These alterations contribute to changes in insulin sensitivity [69]. A study showed decreased mitochondrial biogenesis in adipose tissue of obese rodents [76]. A study in humans has also identified mitochondrial dysfunction of adipocytes in obesity, since it showed that the mitochondrial oxidative capacity (oxygen consumption rates) of adipocytes was reduced in obese individuals [75]. Another study in humans has identified reduced biogenesis and mitochondrial oxidative activity in adipose tissue in obesity [11]. The downregulation of mitochondrial biogenesis in obesity is associated with metabolic alterations, insulin resistance, and low-grade inflammation [11]. In skeletal muscle, it was reported a relationship between obesity and reduction of mitochondrial function and mass [10,74]. Jheng and colleagues [77] showed smaller and shorter mitochondria and increased mitochondrial fission in skeletal muscle of obese mice (genetic obesity and diet-induced obesity), indicating that altered mitochondrial fission is associated with...
mitochondrial dysfunction and insulin resistance in skeletal muscle. Altered mitochondrial function in muscle tissues leads to reduced fatty acid oxidation and the inhibition of glucose transport, indicating that insulin-stimulated glucose transport is reduced [65]. In liver, it has also been described that mitochondrial function is impaired by diet-induced obesity, as well as fission processes are increased [10]. Holmström and colleagues [78] showed decreased mitochondrial respiratory capacity and protein expression, including peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α), in the liver of obese diabetic (db/db) mice, consistent with increased mitochondrial fission.

The decline in the number and biogenesis of mitochondria are related to mitochondrial dysfunction in obesity. In addition to mitochondrial biogenesis, mitochondrial dynamics (the balance between mitochondrial fusion and fission) also regulate mitochondrial functions [66,72]. The regulation of mitochondrial dynamics is a complex process involving different dynamin-related GTPases that maintain a balance between mitochondrial fusion and fission. Alterations in this balance can involve oxidative stress, mitochondrial dysfunction and metabolic alterations [79]. Obesity can also impair mitochondrial dynamics [66,72]. The detailed mechanisms underlying alterations in mitochondrial dynamics in obesity remain unclear, but alterations in fusion/fission processes and the excess of ROS are probably involved [66,72]. It was reported increased mitochondrial fission in skeletal muscle of obese mice, indicating that disruption of mitochondrial dynamics may underlie the pathogenesis of muscle insulin resistance in obesity [77]. In addition, alterations in the activity of the proteins involved in mitochondrial dynamics, e.g. altered expression of optic atrophy gene 1 (OPA1) and decreased expression of mitofusin 2 (Mfn2), may participate in the reduced mitochondrial function present in obesity [10,74]. Quirós and colleagues [80] identified that loss of mitochondrial protease OMA1 alters the processing of the dynamin-related GTPase OPA1 and lead to alterations in metabolic homeostasis, increased adipose mass, and decreased energy expenditure. Sebastián et al. [81] showed that Mfn 2 deficiency causes enhanced hydrogen peroxide concentrations, greater ROS production, and mitochondrial dysfunction in the liver and in the muscle. In addition, Liu and colleagues [82] showed that the dynamic behavior was impaired in high-fat diet-induced obese mice (there is a molecular shift from fusion toward more fission), accompanying with disturbed mitochondrial respiratory function and decreased ATP content in skeletal muscle [82]. Therefore, the evidence suggests that a shift toward fission processes is linked to mitochondrial dysfunction in the skeletal muscle and in the liver in obesity [10,83].

Typically, less than 5% of the oxygen collected by mitochondria is released as ROS. However, impairment of the mitochondrial function, as seen in obesity, may increase the production of these unstable molecules, and thus result in damage to mitochondrial and nuclear nucleic acids, lipid membranes and proteins, and especially to enzymes of the mitochondrial respiratory chain [67].

Dysfunctional mitochondria can be removed via mitophagy. By removing dysfunctional mitochondria, mitophagy plays a crucial role in preventing the vicious cycle of oxidative stress and mitochondrial damage [84]. However, removal of mitochondria through mitophagy could reduce mitochondrial number, resulting in decreased substrate oxidation, further aggravating lipid accumulation [85]. The mitochondrial processes of mitophagy in obesity need more clarification.

The mitochondria of obese individuals are different from those of lean individuals. In contrast to lean individuals, mitochondria in obese individuals have lower energy generation capacities, less defined internal membranes, and reduced oxidation of fatty acids [65]. In addition to these alterations, other metabolic abnormalities have been identified in obesity, and they include decreased fat oxidation and increased glucose dependence for ATP synthesis, as well as low basal ATP concentrations. Mitochondrial dysfunction is also involved in some signs and symptoms of obesity, including low energy expenditure, chronic ingestion of excess foods, and the presence of inflammatory markers. These changes not only favor the development and progression of obesity, but also have implications for its treatment [67].

Furthermore, excessive consumption of nutrients, generally seen in obesity, causing mitochondrial dysfunction and abnormal metabolism of lipids and glucose [70], may also lead to the induction of the inflammatory cascade [56]. The process that binds excessive consumption of foods with inflammation starts with the mitochondrial overload of fatty acids and glucose, which results in an increase in acetyl-CoA production. High acetyl-CoA levels result in an increase in NADH generated from the Krebs cycle, which increases the availability of electrons to the complexes of the mitochondrial respiratory chain, consequently resulting in an increase of ROS within the cell. Oxidative stress can activate numerous transcription factors, including NFκB, which is the main mediator of the inflammatory response. NFκB, in turn, will mediate the release of inflammatory cytokines, which relates excessive food consumption to inflammation [56].

The availability or ingestion of nutrients is also related to the regulation of cell death [65]. Bioenergetic failure is often fatal to cellular function [68]. Mitochondria are the major sources of cellular energy, but also play a central role in apoptosis [12]. The organelle contains several pro-apoptotic molecules that activate cytosolic proteins for the execution of apoptosis [65,68]. The regulation of cell death by mitochondria is linked to their role as source of ROS. Mitochondria-generated ROS play an important role in the release of cytochrome c and other pro-apoptotic proteins, which can trigger caspase activation and apoptosis [86].

Apoptosis is a programmed cell death mechanism. Cellular apoptosis is mediated by an intracellular signaling program involving a variety of signaling molecules and cellular organelles, including caspases (the proteases which execute cell death), adapter proteins (caspase activators), Bcl-2 family proteins and Inhibitor of Apoptosis Proteins (IAPs) [87]. There are two main apoptotic pathways, namely the extrinsic pathway (receptor-mediated or cytoplasmic death) and the intrinsic pathway (mitochondrial, usually involving cytochrome c release) [68,87,88].

Mitochondrial homeostasis requires a balance between mitophagy and mitochondrial biogenesis [89]. Extensive mitophagy can lead to bioenergetic failure whereas excessive mitochondrial biogenesis can generate harmful levels of ROS and promote apoptosis [89,90].

The nutritional imbalance seen in western diets, usually with a high caloric intake, leads to mitochondrial dysfunction and increased the susceptibility of the cell to apoptosis [12,65]. The excess food intake impairs respiratory capacity and prepares mitochondria for apoptosis [12,65]. High caloric intake decreases levels of PCG-1α and Mfn2 leading to reduced mitochondrial fusion and compromising organelle functions [12]. In obesity, apoptotic pathways proteins are upregulated and increased apoptosis has been reported in adipocytes. This cell death is strongly dependent on mitochondria. Other cell lines, e.g. stem cells, might also suffer mitochondrial dysfunction during obesity and become more susceptible to apoptosis [12].

The apoptotic protein levels and cell death are increased in adipocytes of obese rodents and humans [12,65,91]. Tinalhones and colleagues [13] showed that increased body fat is associated with a pro-apoptotic state in adipose tissue of obese patients. A study of Keuper and colleagues [92] suggested that macrophages further drive the inflammatory process by inducing insulin resistance and apoptosis of adipocytes.

However, adipose tissue is not the only site affected. Lu and colleagues [93] have identified that a high-calorie and high-cholesterol diet induced apoptosis in endothelial cells of the thoracic aorta of mice. They also identified swollen mitochondria and extended endoplasmic reticulum (ER) in endothelial cells of obese mice. The mitochondrial swelling can enhance substrate oxidation and elevated ROS production, while the extended ER is an indication of ER stress. Apoptosis can be induced by excessive oxidative and ER stress [93].

In the brain, a study conducted by Moraes and colleagues [19] have shown that exposure to saturated fatty acids, which leads to the
activation of pro-inflammatory pathways in the CNS, can lead to apoptosis in hypothalamic rodent neurons. Rivera and colleagues [94] have reported a relationship between a diet high in saturated fat and the presence of apoptosis in the rats hippocampus.

Considering the above, it can be inferred that all the pathophysiological mechanisms present in obesity addressed in this review, such as inflammation, oxidative stress, and mitochondrial dysfunction are interrelated and may in some way lead to cellular apoptosis, as illustrated in Fig. 2. This phenomenon may occur in both peripheral tissues and brain.

In addition, necrosis is another pathway of cell death related with accumulation of ROS and is dependent on functional mitochondria [95]. We observed a lack of studies correlating obesity and necrosis. Yin et al. [96] showed that necrosis and apoptosis were induced by hypoxia in 3 T3-L1 adipocytes. Since ATP production in mitochondria was reduced by hypoxia, they suggested that the loss of ATP supply may have been responsible for cell necrosis and apoptosis. Necrosis occurs if the ATP supply was unable to meet the minimal demand for cell survival. If the cells are able to maintain the minimal ATP supply, they can either survive or become apoptotic [96].

7. Conclusion

Based on the above narrative review, it can be concluded that many intracellular alterations occur in obesity, and they involve mitochondrial dysfunction, oxidative stress, and inflammation. The inflammatory process present in obesity can lead to oxidative stress, which, in turn, can cause mitochondrial dysfunction. In addition, excess nutrient supply per se can affect the mitochondrial function and lead to oxidative stress, a process that may contribute to the onset and aggravation of the inflammatory process. All these changes can lead to cellular apoptosis.

Moreover, studies have shown that all body cells, from peripheral tissues to brain tissue, can be affected by the alterations caused by obesity. In this context, the CNS arouses concern, since intracellular alterations can compromise brain performance, especially the important functions exerted by the hypothalamus and hippocampus (brain structures that have appeared as the most affected by obesity).

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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