Obesity-Induced Brain Neuroinflammatory and Mitochondrial Changes

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Obesity is defined as abnormal and excessive fat accumulation, and it is a risk factor for developing metabolic and neurodegenerative diseases and cognitive deficits. Obesity is caused by an imbalance in energy homeostasis resulting from increased caloric intake associated with a sedentary lifestyle. However, the entire physiopathology linking obesity with neurodegeneration and cognitive decline has not yet been elucidated. During the progression of obesity, adipose tissue undergoes immune, metabolic, and functional changes that induce chronic low-grade inflammation. It has been proposed that inflammatory processes may participate in both the peripheral disorders and brain disorders associated with obesity, including the development of cognitive deficits. In addition, mitochondrial dysfunction is related to inflammation and oxidative stress, causing cellular oxidative damage.

high-fat diets | cognitive decline | metabolic disorders | energy homeostasis | neuroinflammation | mitochondria | hippocampus | hypothalamus

1. Introduction

Obesity is a chronic disease defined as abnormal and excessive fat accumulation, and it represents an important risk factor for many diseases and premature death. Body mass index (BMI) is a weight-for-height index commonly used to classify overweight and obesity in adults. The healthy weight range is a BMI range between 18.5 and <24.9 kg/m^2. If an individual's BMI is between 25.0 and 29.9 kg/m^2, they fall within the overweight range; if their BMI is 30.0 kg/m^2 or higher, they are considered obese. In 2015, more than 1.9 billion adults were overweight; over 600 million were obese [1][2]. Even more alarming is that child obesity affects 107.7 million children [1][2]. Changes in lifestyle in the last century (increased consumption of hypercaloric diets and sedentary behavior) are the fundamental causes of obesity epidemics.

Obesity is associated with an increase in noncommunicable diseases, including metabolic and cardiovascular diseases, some types of cancer, musculoskeletal disease, and several brain diseases, which represent the leading causes of premature mortality and disability [2][3][4]. In addition, long-term high-fat diet (HFD) consumption has been found to induce peripheral insulin resistance and cause brain insulin resistance [5][6][7].

In recent years, increasing attention has been given to the relationship of obesity and associated insulin resistance/type 2 diabetes with the development of brain diseases, including depression, neurodegenerative diseases, dementia, and vascular dementia [8][9][10]. Epidemiological studies have shown that people with a higher

BMI are at greater risk for developing Alzheimer's disease than subjects with normal BMI [11][12][13]. Moreover, some population-based studies have identified diabetes as a risk factor for dementia and metabolic syndrome, a grouping of risk factors for type 2 diabetes mellitus [14][15][16]. However, cellular and molecular mechanisms linking these conditions have not yet been fully elucidated.

2. Mitochondria Functions and Dynamics

Mitochondria are double-membrane organelles responsible for energy production and homeostasis, the regulation of intracellular calcium levels, and the regulation of apoptosis (mainly via the intrinsic pathway) [17][18]. In addition, mitochondria are responsible for generating more than 90% of the energy for the cell through oxidative phosphorylation [19][20].

To generate ATP through oxidative phosphorylation, mitochondria use an electron transport chain inserted within the mitochondrion's inner membrane (**Figure 1**) [21]. NADH and $FADH_2$ are generated by the Krebs cycle and donate electrons to complex I (NADH: ubiquinone oxidoreductase) and complex II (succinate dehydrogenase), respectively. The electrons from NADH are passed from complex I to ubiquinone (CoQ) in order to enter the Q cycle, where CoQ is reduced to ubiquinol (QH_2). This electron transfer induces the pumping of protons by complex I from the matrix into the intermembrane space. The electrons donated from $FADH_2$ are transferred from complex II to CoQ similarly to complex I, although this process is not accompanied by proton translocation [21]. Once in the Q cycle, the electrons are transferred to complex III (coenzyme Q: cytochrome c reductase) and then to cytochrome c, releasing two protons into the intermembrane space. Then, when cytochrome c is reduced, it transports single electrons from complex III to complex IV (cytochrome c oxidase), where molecular oxygen is reduced to water. At complex IV, a total of eight protons are pumped from the matrix, of which four are used to form two water molecules, and the other four are transferred into the intermembrane space [21][22].

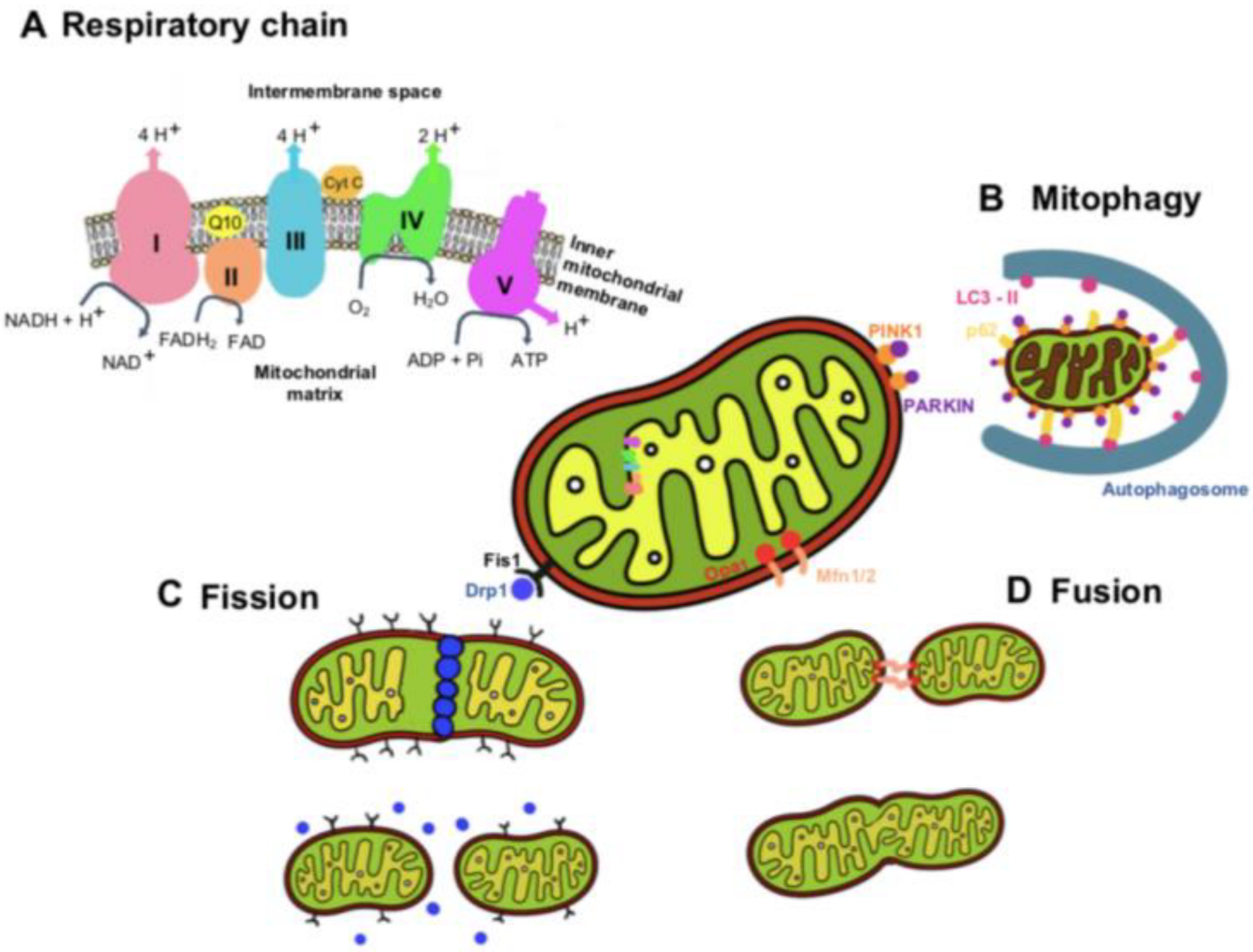

Figure 1. Respiratory chain and mitochondrial dynamics. (**A**) Respiratory chain. Electrons and protons flow through complexes of the respiratory chain in oxidative phosphorylation. (**B**) Mitophagy is mediated by PINK1, PARKIN, and P-62 proteins, which recruit the protein LC3-II and form the autophagosome for cell degradation. (**C**) Mitochondrial fission is mediated by the protein Drp1, which is recruited from the cytosol to interact with the protein fis1 in the mitochondrial outer membrane, forming constriction points that lead to mitochondrial fission. (**D**) Mitochondrial fusion requires the action of the Opa1 protein on the inner mitochondrial membrane and the action of Mfn1 and Mfn2 proteins in the outer mitochondrial membrane, promoting the fusion of juxtaposed mitochondrial membranes.

In response to electron transport, a total of ten protons are pumped from the matrix into the intermembrane space, where they accumulate to generate an electrochemical and concentration proton gradient that generates a proton motive force, essential for the activity of complex V (ATP synthase) to generate ATP [21]. A consequence of electron transfer is the generation of reactive oxygen species (ROS), which contributes to homeostatic signaling. However, when ROS are produced in excess, they cause oxidative stress and can lead to mitochondrial dysfunction and diseases [22]. Therefore, an efficient measurement of the electron transport chain function and ATP production,

using high-resolution respirometry, such as a Seahorse XF24 Extracellular Flux Analyzer and oxygraphy, can provide insight into cellular physiology and dysfunction.

Mitochondria are highly dynamic organelles that undergo a continuous cycle of fission and fusion, processes called mitochondrial dynamics (**Figure 1**). Another dynamic process of mitochondria is the selective removal of dysfunctional mitochondria, a quality-control mechanism that ensures a healthy mitochondrial population. The dynamic properties of mitochondria are critical for their optimal function in energy generation [23]. Mitophagy is a mechanism of mitochondrial quality control used to eliminate damaged mitochondria and prevent excessive ROS production, thus maintaining homeostasis in mitochondria. Mitochondrial dynamics involve the plasma membrane and organelles, such as ER and lysosomes. The contact point of ER–mitochondria is referred to as mitochondria-associated ER membranes. Some studies have suggested that the integrity of mitochondria-associated ER membranes is required for insulin signaling (for a detailed description, see the revision [24]). Studies have been carried out to investigate the effect/defect of insulin signaling on different features of mitochondrial dysfunction, focusing on dynamics, biogenesis, and mitophagy and their role in pathologies in which metabolic dysmetabolism is comorbid with neurodegeneration [25][26]. Some studies have also suggested that the protective actions of leptin may be facilitated through the regulation of mitochondrial dynamics, namely, mitochondrial fission and fusion [27][28][29][30].

Dysfunctional mitochondria are recognized by the autophagy machinery, resulting in their engulfment by autophagosomes and trafficking to the lysosome for degradation. The most common mitophagy pathways are mediated by PINK1 and PARKIN proteins. Mitochondrial fission is the process where mitochondria divide into two separate mitochondrial organelles. Fission is mediated by the interaction between the mitochondrial fission factor (Mff) and dynamin-related protein-1 (Drp1). Briefly, Drp1 is recruited from a cytosolic pool onto the mitochondrial surface, where it self-assembles into spiral structures to facilitate fission, acting similarly to endocytic invaginations of the cell membrane. Several mitochondrial-bound proteins then aid in the recruitment of Drp1 to the mitochondria, including Fis1, Mff, MiD49, and MiD51 [23][31][32].

Fusion is the process of joining two adjacent mitochondria through a physical merging of the outer and then the inner mitochondrial membranes, resulting in the content mixing of the matrix components diffusing throughout the new mitochondrion. Fusion is mediated by the proteins mitofusin-1 (Mfn1) and mitofusin-2 (Mfn2) [33][34][35], located on the mitochondrial outer membrane. Mitofusins are required for outer membrane fusion. The fusion of the inner membrane is mediated by the protein optic atrophy 1 (Opa1), which is associated with the inner membrane ([36] for a detailed description of the mitochondria dynamics, please read the review manuscript [23]).

Mitochondrial dynamics is important for growth redistribution and maintenance in a healthy mitochondria network and plays a role in disease-related processes. All the cells consume energy for their homeostasis and specific activity, and they require the support of functional mitochondria that provide ATP obtained via oxidative phosphorylation. A reduction in mitochondria respiration and bioenergetics is associated with insulin resistance [24].

Therefore, the dysfunction of mitochondrial dynamics and function could lead to disorders in mitochondria, which are greatly associated with the progression of several diseases, including obesity and metabolic and neurological conditions.

3. Obesity Induces Cognitive Decline

Obesity, as well as HFD diet consumption, and metabolic disorders, such as diabetes mellitus, are widely recognized as inducing impairments in brain structure and function in the form of memory dysfunction, as well as neurodegenerative diseases [37]. Furthermore, magnetic resonance imaging studies have demonstrated that regional brain atrophy and changes in gray and white matter are observed in patients with obesity, providing new insights into the relationship between obesity and cognitive decline from the imaging perspective [37][38][39][40]. Furthermore, a higher BMI is correlated with a lower gray matter volume in the prefrontal, temporal, insular, and occipital cortexes; thalamus; putamen; amygdala; and cerebellum, mediating the negative effects on memory performance [41].

Patients with obesity have an earlier onset of Alzheimer's, which is considered an aging disease [42]. An 18-year follow-up longitudinal study demonstrated a higher degree of overweight in older women who developed AD. No associations were found in men [42]. In the same study, the authors concluded that Alzheimer's disease risk increased by 36% for every 1.0 increase in BMI. In other studies, it has been shown that patients with a higher BMI present significantly lower scores in cognitive tests and a longitudinal decline in cognitive abilities in both men and women [37][43][44]. Changes in cognitive function can be potentiated since middle-aged adults with obesity may experience differentially greater brain atrophy [37]. The relationship between a higher BMI and reduced cognitive performance does not change with age [45] or race [46]. A high intake of fat and sugar is associated with impairments in hippocampal-dependent learning and memory in children [47] and adults [48][49], suggesting a negative impact on hippocampal function across the lifespan. In the community-based Framingham Offspring Cohort, it was observed that central obesity was significantly related to poorer performance in executive function and visuomotor skills, and no changes were observed for verbal memory [50]. Adults with overweight and obesity also have poorer executive function than normal-weight adults, without changes in performance on attention tests. Children and adolescents with overweight/obesity also present poor cognitive function on verbal, full-scale, and performance IQ; visual–spatial; and executive function tests [51][52]. A systemic review found that executive dysfunction is associated with obesity-related behaviors in children and adolescents, such as increased food intake, disinhibited eating, and less physical activity. In children and adolescents, obesity is associated with poorer cognitive competence and may affect their academic achievements [53].

Body weight and diet composition are modified risk factors for cognitive decline. Weight loss appears to be associated with low-order improvements in executive/attention functioning and memory in individuals with obesity. Moreover, a stable BMI predicts better cognitive trajectories [54]. Patients with severe obesity may obtain immediate verbal and delayed memory function benefits from Roux-en-Y gastric bypass [55][56].

Different animal models of obesity and metabolic disorders have also exhibited cognitive dysfunctions and worse performance in learning and memory tasks compared to non-obese animals [57][58][59][60][61][62]. In addition, based on studies of animal models and in vitro models, high levels of glucose and saturated fatty acids are responsible for neuroinflammation, microglia activation, mitochondrial dysfunction, neuronal loss, and impairments in synaptic plasticity (**Figure 2**) [63][64][65][66][67][68].

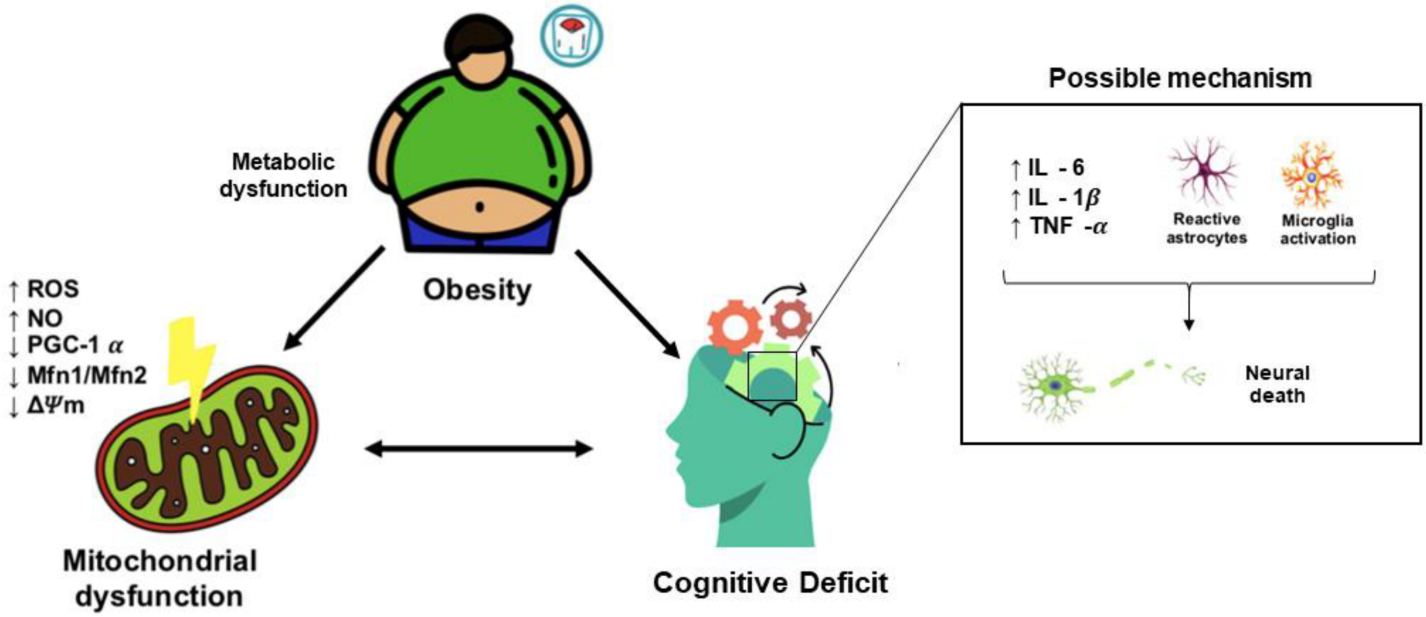

Figure 2. Obesity, neuroinflammation, and mitochondrial dysfunction. Excessive food consumption in obesity can lead to mitochondrial dysfunction characterized by increased reactive oxygen species (ROS) levels, increased nitric oxide (NO) levels, decreased protein content of PGC-1α and Mfn1/Mfn2, and decreased mitochondrial membrane potential (ΔΨm). Obesity is associated with increased levels of inflammatory cytokines in the brain and compromises neural viability.

3.1. Obesity-Induced Cognitive Decline: Role of Neuroinflammation

Obesity is a low-grade chronic inflammatory disease that increases susceptibility to the numerous conditions associated with it. During the expansion of white adipose tissue, the recruitment and infiltration of immune cells, mainly macrophages, occur [69]. The growth of adipose tissue is also associated with an increased expression of proinflammatory cytokines, particularly interleukin-6 (IL-6), interleukin-1 beta (IL-1β), and tumor necrosis-α (TNF-α) [70][71][72]. Subjects with obesity have high circulating proinflammatory adipocytokines that trigger chronic inflammation. Systemic low-grade chronic inflammation has been reported to cause neuroinflammation and changes in different brain structures, such as the cerebellum, amygdala, cerebral cortex, and hypothalamus [57][73][74][75]. Obesity-induced inflammation has been related to changes in the integrity of blood–brain barrier permeability, inducing leukocyte extravasation, along with the potential entry of pathogens and toxins into the central nervous system, which, in turn, stimulate more inflammatory responses in a vicious cycle [57]. The decrease in tight junction protein expression and the disturbed blood–brain barrier are regulated by the NF-κB pathway, which increases the expression of proinflammatory proteins, such as IL-1β, TNFα, and IL-6. The loss of the blood–

brain barrier during obesity facilitates proinflammatory cytokines to enter the brain parenchyma, thus allowing them to interact and activate glial cells (microglia and astrocytes) [76]. Activated microglia secrete more inflammatory cytokines (TNFα, IL-1β, and IL-6), perpetuating the neuroinflammation and leading to neuronal damage. NLRP3 proteins of the inflammasome secreted by visceral adipose tissue directly activate microglia through the IL1 receptor [77].

Furthermore, HFD can directly activate microglial cells, inducing morphological changes in the hypothalamus without causing microglial changes in the cerebral cortex and striatum. Moreover, HFD-induced obesity is associated with an increased entry of peripheral immune cells into the central nervous system and may contribute to the inflammatory response [78]. Fatty acid intake induces the activation of immune cells and the inflammatory response through the activation of the innate immune system through Toll-like receptors (TLRs) [63]. The binding of fatty acids to TLR4 activates nuclear factor-Kb (NF-Kb) and activator protein 1 (AP-1), which, in turn, upregulate the expression of proinflammatory cytokines and chemokines [79]. Another proposed mechanism for obesity-induced inflammation relies on the ability of an HFD to modulate the gut microbiota. Indeed, the subsequent changes in microbiota populations result in the permeabilization of the gut barrier, leading to the increased passage of bacterial endotoxins into the circulation [80][81].

Based on studies conducted on animal models of obesity, it has been proposed that inflammatory processes may participate in both the peripheral and brain disorders associated with obesity, including the development of cognitive alterations. Diet-induced obesity leads to microglia activation, which induces synaptic alterations, including impairment in hippocampal synaptic plasticity, reductions in dendritic spine density and the sites of excitatory synapses, and promoted synaptic stripping [58].

3.2. Obesity-Induced Cognitive Decline: Role of Mitochondrial Dysfunction

Diabetes and obesity are modifiable risk factors for cognitive dysfunction and dementia. Several studies have demonstrated and identified overlapping neurodegenerative mechanisms observed in these disorders, including oxidative stress, mitochondrial dysfunction, and inflammation. An excessive intake of nutrients provokes the mitochondria to become overloaded with fatty acids and glucose, leading to an increase in the production of acetyl-CoA. This then causes the production of NADH through the Krebs cycle, which promotes an increase in the electron transfer chain in the mitochondria and, subsequently, increases ROS production, leading to oxidative stress. In addition, there is evidence that the brain's energy status is decreased in obesity, although the underlying mechanisms are currently unknown. Patients with obesity have been found to have impaired cerebral energy gain upon experimentally increased blood glucose levels up to a postprandial status. This suggests that the brains of individuals with obesity cannot generate an appropriate amount of energy due to dysfunctional glucose transport or a downregulated energy synthesis in mitochondrial respiration [82].

The consumption of a western diet increases the circulating levels of palmitate, which is converted into ceramide in order to accumulate in tissues in response to obesity. Pharmacological and genetic strategies that reduce tissue ceramide levels reverse the metabolic consequences of obesity. Specifically, reducing ceramide production

protects mice from the metabolic effects of high-fat diet consumption by preventing the fragmentation of the mitochondrial network within the hypothalamus. Restoring mitochondrial function through the decreased accumulation of ceramide increases leptin sensitivity and, consequently, reduces food intake [83].

Various studies have demonstrated that diet-induced obesity and metabolic disorders induce mitochondrial dysfunction and oxidative stress in the brain, contributing to neuronal dysfunction, the dysregulation of whole-body metabolism, and cognitive deficits.

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