Obesity and Dementia

Subjects: Neurosciences

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Obesity is a growing worldwide health problem, affecting many people due to excessive saturated fat consumption, lack of exercise, or a sedentary lifestyle. Leptin is an adipokine secreted by adipose tissue that increases in obesity and has central actions not only at the hypothalamic level but also in other regions and nuclei of the central nervous system (CNS) such as the cerebral cortex and hippocampus.

Keywords: obesity ; Dementia

1. Introduction

When focusing on dementia, it is worth noting that the separating line between normal and pathological aging is not adequately defined. Therefore, it is difficult to determine where each phenomenon begins and ends and to distinguish the common deficiencies and individual differences within these phenomena [1]. This narrow line that separates the normal from the pathological is where researchers must intervene to minimise the symptoms the disease produces, making an early diagnosis of dementia necessary. The difficulty is even greater taking into account that the aging process itself can produce negative effects on general health and cognitive function in particular. Similarly, aging is linked to an increase in body weight, adiposity, and variations in hormones and adipokines, showing an altered pattern with age [2][3]. Similarly, both in murine and human models, an increase in microglial reactivity and inflammation with age has been described [2][3]. Researchers discuss how this altered pattern is a factor that predisposes to obesity and dementia, such as Alzheimer's disease (AD).

Procedures have been developed over time to identify patients with early onset dementia, a concept that has evolved into the current term, mild cognitive impairment (MCI). Ronald Petersen developed the concept of MCI through the Mayo Clinic. The concept was an improvement in its attempt to identify people who may progress to dementia, as the cognitive aspects were introduced to the pre-existing aspects of memory. Currently, the fundamental objective of dementia research is to find markers that provide an early diagnosis and thus enable action to be taken before the disease evolves [1]. MCI is an example of this.

Today, obesity is growing in the global population due to multiple causes: lifestyle, stress, nutrition, genetic background, and lack of exercise. In obesity, white adipose tissue (WAT) not only stores excess energy but also disturbs endocrine function. WAT secretes a group of substances called adipokines that exert autocrine, paracrine, and endocrine effects at the systemic level and also centrally in the central nervous system (CNS) [4][5][6]. Obesity has been linked to cognitive deficits, impaired long-term potentiation and synaptic plasticity, and a smaller brain volume, increasing the probability of developing Alzheimer's disease (AD) and other dementias [7]. Thus, obesity is established as a risk factor for dementia. Furthermore, obesity causes a state of low-grade chronic inflammation in adipose tissue that leads to the dysregulation of homeostatic systems, which in turn leads to the development of various diseases, including those related to neurodegeneration. During this process, adipose tissue produces an increase in pro-inflammatory adipokine levels (interleukin 1 beta (IL-1β), interleukin 6 (IL-6), and tumoural necrosis factor alfa (TNF-α), and leptin) and a decrease in anti-inflammatory adipokine levels, such as adiponectin [4][6]. Yet another essential component of these complex interrelationships between obesity and brain status is the gut microbiota. In fact, meticulously detailed in a review by authors [8], it is explained how an altered intestinal microbiota pattern (or dysbiosis) can lead to a permanently altered physiological pattern, which can lead to cognitive impairments due to alterations in the gut-brain axis. In addition, it indicated that the administration of pre- and probiotics can restore this dysbiosis, enabling a return to an adequate homeostatic balance.

Leptin, a pro-inflammatory adipokine secreted by WAT and found to be increased in people with a high body mass index, acts centrally at the level of the hypothalamic region through anorexigenic proopiomelanocortin (POMC)/cocaine- and amphetamine-regulated transcript (CART) neurons and orexigenic neuropeptide Y (NPY)/agouti-related peptide (AgRP) neurons, controlling food intake and energy expenditure.

2. Obesity and Dementia

Obese individuals are at greater risk of developing age-related cognitive decline, vascular dementia, MCI, and AD [4], as well as other neurodegenerative pathologies such as Parkinson's [9][10] and Huntington's disease [10][11]. In this section, researchers give an overview of obesity as a risk factor for dementia based on adipose tissue measurement indices, brain structural changes, and cognitive impairment measurements. The purpose is to identify modifiable risk factors that allow an early diagnosis and treatment.

Obesity can be defined as an excessive accumulation of adipose tissue which generates a low-grade inflammation state, whereas AD can be defined as a progressive neurodegenerative disease whose distinctive histopathological characteristics are the extracellular amyloid plaques and intracellular neurofibrillary tangles.

A parameter used as a measure of adiposity is the body mass index (BMI). However, its use has not been free from difficulties. That is why the waist circumference and the waist-to-hip ratio (WHR) have also been used to evaluate excess fat [12]. In fact, in the work by Beyer et al. (2019) [12], it is suggested that the WHR, as part of a metabolic obesity profile, is a determining factor that plays a role in grey matter volume reductions, which might lead to reduced cognitive functions, that have a weaker association when using the BMI [12][13]. Nevertheless, BMI is the most widely used adiposity index [14][15][16]. Thus, an association between BMI and dementia has been described, although this relation is controversial [14][15][16][17]. Firstly, it has been suggested that being overweight and obese in middle age is related to a higher risk of dementia in old age. Nevertheless, a high BMI in late life is associated with better cognition [6][16][17]. Secondly, other studies have described contradictory outcomes, where a lower risk of dementia was observed for very obese people (BMI > 40 kg/m2) while underweight people (BMI < 20 kg/m2) display a higher dementia risk than heavyweight people [18]. There are different epidemiological studies that relate obesity and dementias, such as the more frequent AD, but, in general, these studies find a positive correlation between obesity and cognitive impairment, with a possible U-shaped curve. In this context, a reverse relation has been described between obesity and grey matter and whole brain volume [19][20][21][22][23][24][25], even though a minor number of publications did not find such a relation [26][27].

As mentioned above, obesity generates a chronic low-grade inflammation state, which is characteristic of a variety of other chronic conditions, such as metabolic syndrome, non-alcoholic fatty liver disease, type 2 diabetes mellitus, and cardiovascular disease [28][29], as well as neuroinflammation [30][31][32], a hallmark of neurodegenerative diseases such as AD [33][34][35]. Following this line, different animal studies have confirmed the connection between obesity and cognitive mismatches and/or impairment. Thus, different works point to an altered cognitive function when administering a less-healthy diet. A high-fat diet (HFD) rich in saturated fatty acids can result in obesity as well as deficits in hippocampal-dependent learning and memory functions [36][37]. Male Wistar rats fed with a HFD showed impaired memory, an effect that was augmented with a longer duration of HFD consumption [38] while, similarly, rats fed with a high-fructose-high-coconut oil diet experienced impaired hippocampal-dependent learning and memory processes, as evaluated through the Morris water maze task [39]. In another study [40], HFD-induced brain insulin resistance and cognitive impairment were observed. Molecular changes, such as a significant decrease in tyrosine phosphorylation of the insulin receptor and increased serine phosphorylation of IRS-1, which are signs of insulin resistance, might be the cause of the cognitive impairment in this mouse model. These molecular changes were accompanied by inflammatory signalling (NFκB, JNK) and stress responses (p38 MAPK, CHOP) in whole brain lysate. In a transgenic rat model of pre-AD and MCI, impaired special learning and memory has been described in the Morris water maze when rats received a high-caloric diet [41]; at the same time, some parameters of brain inflammation, such as microgliosis, were also found. Moreover, activated OX-6+ microglia were detected, as well as GFAP+ astrocytes located predominantly in the white matter, and the synaptic density in the CA1 and CA3 hippocampal subregions was lower in this high-calorific diet. In a triple transgenic AD mice model (3xTg-AD), an impairment in the cognitive function has been shown when administering a HFD, and this diet was able to induce enhanced oxidative stress and aggravated neuronal apoptosis via inactivation of the Nrf2 signalling pathway [42]. So, numerous animal studies indicate the relation between obesity and AD and other forms of dementia that affect cognitive function.

Overall, obesity seems to be a risk factor for different forms of dementia, where researchers can find long-term memory and attention impairment, and executive function deficits. They have reviewed how cerebral structural and functional changes in obese people occur, and how a high saturated fat diet can affect cognitive function, including brain inflammation as a hallmark of this process.

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