Leptin's Role in Obesity as a Dementia and Alzheimer's Disease Risk Factor

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Abstract

Numerous people are affected by obesity, which is a widespread health issue caused by excessive ingestion of saturated fats, inactivity, or a sedentary lifestyle. Leptin is an adipokine that is released by adipose tissue and rises in obesity. It has central activities in the cerebral cortex, hippocampus, and other areas and nuclei of the Central Nervous System (CNS), in addition to the hypothalamus. These regions are the first to experience chronic neurocognitive deficits including mild cognitive impairment (MCI) and Alzheimer's disease because they express the long form of the leptin receptor LepRb, which is the only leptin receptor capable of conveying complete leptin signals (AD). As leptin resistance is usually linked to obesity, which is a chronic low-grade inflammatory condition, and obesity is thought to be a risk factor for AD, we examine various leptin resistance mechanisms in this review that may be responsible for raising the chance of developing AD. SOCS3, PTP1B, and TCPTP, whose signaling is associated with inflammation and may be exacerbated in AD, are important leptin resistance players. However, certain results are debatable, and further research is required to understand the pathogenic processes that cause AD and how altered leptin signaling influence those processes.

Keywords: Obesity • Leptin • Inflammation • Leptin resistance • Alzheimer's disease

Introduction

It is important to note that the distinction between healthy aging and pathological aging is not well defined when discussing dementia. It is therefore challenging to pinpoint the starting point and ending point of each phenomenon as well as to separate the common flaws and unique characteristics within these phenomena [1]. Early detection of dementia is essential because it allows us to minimize the symptoms the disease causes by intervening at this fine line between the normal and the pathological. The challenge is compounded by the fact that aging itself can have detrimental impacts on both general health and cognitive performance. Similar to this, aging is associated with an increase in body weight, adiposity, and changes in hormones and adipokines, which exhibit an altered pattern with aging. Similarly to this, it has been reported that microglial reactivity and inflammation rise with age in both murine and human models. In this review, we talk about how this changed pattern contributes to the risk of obesity and dementia, including Alzheimer's Disease (AD). Over time, methods for identifying patients with early-onset dementia a concept that has since changed into the phrase Mild Cognitive Impairment—have been created (MCI). Through the Mayo Clinic, Ronald Petersen created the MCI concept. As the cognitive features were added to the pre-existing aspects of memory, the notion was an improvement in its attempt to identify those who may develop dementia. Finding markers that allow for an early diagnosis so that action can be taken before the disease progresses is currently dementia research's main goal. MCI is an illustration of this. Obesity is on the rise in the world's population today for a variety of reasons, including lifestyle, stress, nutrition, genetics, and inactivity. White Adipose Tissue (WAT) in obese people not only stores extra energy but also interferes with endocrine function. A set of chemicals known as adipokines are secreted by WAT, and they have central effects on the Central Nervous System (CNS) as well as autocrine, paracrine, and endocrine actions at the systemic level. Obesity increases the risk of acquiring Alzheimer's Disease (AD) and other dementias because it is associated with cognitive impairments, decreased long-term potentiation and synaptic plasticity, and a lower brain volume. Thus, obesity has been identified as a dementia risk factor. Additionally, obesity results in a state of low-grade chronic inflammation in adipose tissue, which disrupts homeostatic mechanisms and results in the emergence of several illnesses, including those linked to neurodegeneration. Interleukin 1 beta (IL-1), Interleukin 6 (IL-6), Tumor Necrosis Factor Alfa (TNF-), and leptin are pro-inflammatory adipokines that are produced by adipose tissue during this process, while anti-inflammatory adipokines such adiponectin are decreased [2,3]. The gut flora is another crucial element of these intricate interactions between obesity and brain health. It is well outlined in a review by authors how modifications in the gut-brain axis might cause cognitive deficits by permanently altering physiological patterns as a result of altered intestinal microbiota patterns (or dysbiosis). Additionally, it showed that pre- and probiotic treatment can reverse this dysbiosis, allowing recovery to a sufficient homeostatic equilibrium. Leptin, a pro-inflammatory adipokine secreted by WAT and found to be elevated in individuals with a high body mass index, acts centrally at the level of the hypothalamic region through orexigenic neuropeptide Y (NPY)/agouti-related peptide (AgRP) neurons and anorexigenic Proopiomelanocortin (POMC)/Cocaine-and Amphetamine-Regulated Transcript (CART) The development of inflammation in the body is thought to be how leptin connects dementia and obesity, according to the literature. Therefore, as a potential pathogenic mechanism underlying neurodegenerative disorders like Alzheimer's disease and other dementias, we will examine the data on inflammation-induced leptin resistance that develops during obesity.

Obesity and Dementia

Obese people are more likely to acquire neurodegenerative diseases including Parkinson's and Huntington's, as well as other neurodegenerative disorders such as vascular dementia, MCI, and AD [4]. Based on assessments of adipose tissue, structural changes in the brain, and cognitive impairment, we provide an overview of obesity as a risk factor for dementia in this section. Our goal is to find modifiable risk factors so that they can be treated and diagnosed early. While AD is a progressive neurodegenerative disease with extracellular amyloid plaques and intracellular neurofibrillary tangles as its distinguishing histopathological features, obesity is characterized as an abnormal accumulation of adipose tissue that results in a low-grade inflammatory state. Body mass index is a metric used to determine adiposity (BMI). However, there have been some issues with its use. To assess extra fat, waist circumference and the Waist-To-Hip Ratio (WHR) have also been utilized. It is suggested that the WHR, as part of a metabolic obesity profile, is a determining factor that contributes to grey matter volume reductions, which may result in diminished cognitive functions, in the work by Beyer et al. (2019), which have a weaker association when using the BMI. However, BMI is the adiposity indicator that is most frequently utilized. The relationship between BMI and dementia has therefore been described, however, it is debatable. First off, it has been hypothesized that obesity and being overweight during middle age are linked to an increased risk of dementia in old age. However, a high BMI in old age is linked to improved cognition. Second, contradicting findings have been reported by other research, with very obese individuals (BMI>40 kg/m^2) showing a decreased risk of dementia while underweight individuals (BMI 20 kg/m^2) show a higher risk of dementia than heavyweight individuals. Numerous epidemiological research links obesity to dementias, including the more common AD, but generally speaking, these studies discover a positive correlation between obesity and cognitive impairment, with a potential U-shaped curve. Although a small number of studies did not uncover such a relationship, a reverse association between obesity and grey matter and whole brain volume has been described in this area. As was already mentioned, obesity causes a state of chroniclow-grade

inflammation that is typical of several other chronic illnesses, including metabolic syndrome, non-alcoholic fatty liver disease, type 2 diabetes mellitus, and cardiovascular disease, as well as neuroinflammation, a defining feature of neurodegenerative diseases like AD [4]. Along these lines, numerous research on animals has supported the link between obesity and cognitive dysfunction. Therefore, various studies indicate that administering a less-healthy diet will change cognitive performance. Saturated fatty acid-rich High-Fat Diets (HFD) have been linked to obesity and deficiencies in hippocampal-dependent learning and memory. When given an HFD, male Wistar rats displayed poor memory, which was exacerbated with longer consumption, and when given a high-fructose, high-coconut oil diet, rats displayed impaired hippocampal-dependent learning and memory processes, as measured by the Morris water maze experiment. HFD-induced brain insulin resistance and cognitive impairment were seen in a different study. The cognitive impairment in this mouse model may be due to molecular alterations, such as a considerable reduction in the tyrosine phosphorylation of the insulin receptor and an increase in the serine phosphorylation of IRS-1, which are indicators of insulin resistance. Inflammatory signaling (NF-B, JNK) and stress responses (p38 MAPK, CHOP) were present along with these molecular alterations in the whole brain lysate. Impaired specific learning and memory have been reported in the Morris water maze in a transgenic rat model of pre-AD and MCI when rats were fed a high-calorie diet. At the same time, various markers of brain inflammation, such as microgliosis, were also discovered. Activated OX-6+ microglia and GFAP+ astrocytes, which are primarily found in white matter, were also found, and this high-calorie diet resulted in reduced synaptic density in the CA1 and CA3 hippocampus subregions [5]. An HFD was able to cause increased oxidative stress and worsened neuronal death by inactivating the Nrf2 signaling pathway in a triple transgenic AD mice model (3xTg-AD), which has been proven to impair cognitive performance. Therefore, several research on animals has shown a connection between fat and AD and other types of dementia that impair cognitive ability. Overall, obesity appears to be a risk factor for many types of dementia, where we might discover deficiencies in executive function, long-term memory, and attention. We have discussed how a high-saturated-fat diet might influence cognitive performance, including brain inflammation as a characteristic of this process. We have also covered how cerebral anatomical and functional alterations in obese persons occur.

Obesity and Leptin

The establishment of a signaling and functional connection between the peptides released by the peripheral organs is necessary for energy homeostasis and the maintenance of body weight. Adipocytes produce and secrete adipokines that have pleiotropic effects in different tissues and control a variety of physiological processes to do this. Leptin will be the main topic of this review because it controls how much food we eat and how much energy we spend. We'll also look at how it affects dementia and how it relates to obesity. Plasma leptin levels have been observed to fluctuate in body fat mass, and this can be used as a measure of adiposity. Its levels are affected by several variables, including sex, BMI, famine, and calorie levels, making its study challenging. Leptin levels peak between midnight and dawn, and it also exhibits a circadian pattern and is influenced by other hormones and cytokines. The ob (obese) gene produces the 16 kilodaltons (kDa) peptide hormone leptin. Class I cytokine receptors are leptin receptors. The leptin receptor gene encodes six isoforms, including four short forms (LepRa, LepRc, LepRd, and LepRf), one long form (LepRb), and an extracellularly released soluble form (LepRe). In addition, LepRa-LepRd and LepRf, two of the six isoforms, share extracellular and transmembrane domains, while LepRe, the soluble form, only has an extracellular domain. While the other isoforms appear to be involved in leptin transport from the periphery to the CNS through the Blood-Brain Barrier (BBB), the long-form LepRb has intracellular domains and proline-rich regions known as box1, box2, and box3 that are associated with Janus kinase (JAK) and Signal Transducer Activators Of Transcription (STAT) signaling activation. The body has leptin receptors expressed all over it. The Arcuate Nucleus (ARC), the Dorsomedial Hypothalamus (DMH), the Ventromedial Hypothalamus (VMH), the Lateral Hypothalamus (LH), the Mediobasal Hypothalamus (MBH), and the paraventricular nucleus all express leptin receptors in the central nervous system. Additionally, they have been discovered in the cerebellum, medulla, substantia nigra, ventral tegmental region, cerebral cortex, and hippocampus [6]. Furthermore, LepRa and LepRc short isoforms have been shown to mediate leptin transport in the BBB, and dysfunctional receptors can result in leptin resistance. The LepRa and LepRc short isoforms are expressed in the brain microvessels that make up the BBB, suggesting that these receptors may be associated with leptin transmission are also essential for the establishment and stabilization of hippocampus memory during these processes. Leptin and glutamate receptors N-methyl D-aspartate (NMDA) and amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA receptors) are thus important participants in these processes at the level of the hippocampus. Leptin receptors have been discovered in neuronal and non-neuronal cells in the hypothalamus, cerebral cortex, dentate gyrus, and the CA1 and CA3 regions of the hippocampus, lending credence to this evidence [7]. This conclusion is crucial since these regions are crucial for cognition and memory. Recent research suggests that the leptin-dependent homeostatic regulation of body weight necessitates the involvement of NMDA receptors. Leptin improves NMDA receptor performance by increasing the efficacy of excitatory synaptic transmission at Schaffer-collateral (SC)-CA1 synapses in the hippocampal nucleus and enabling the transformation of short-term potentiation into long-term potentiation (LTP). Therefore, it is not surprising that leptin-insensitive obese mice (db/db) and leptin receptor-deficient rats (fa/fa) show LTP and LTD defects. Leptin, therefore, enhances hippocampus-dependent memory. Accordingly, it was discovered in the review by McGregor and Harvey that leptin enhanced performance in contextual, fear-conditioned, and object recognition tasks in transgenic mouse models of Alzheimer's disease (CRND8). Additionally, animals prone to accelerated senescence (SAMP8) that have higher levels of the -amyloid peptide (A) performed better on hippocampal-dependent memory tasks. Leptin can control how neurons are arranged [8,9]. In different parts of the brain, the amount of grey matter has been linked to plasma leptin levels. Congenitally leptin-deficient people recover from structural brain abnormalities with exogenous leptin administration, while ob/ob mice recover from defects. Intriguingly, Annweiler's research reveals a connection between U-shaped cognition and circulating leptin levels. Their findings point to leptin as a modifiable risk factor and imply that older persons with low or high circulating leptin concentrations are particularly susceptible to cognitive impairment. We can therefore conclude that leptin provides neuroprotective effects that enhance memory and cognitive function through its actions in the peripheral or CNS. Therefore, activities that encourage neurodegeneration can be triggered by its malfunction brought on by a deficiency in signaling pathways, a drop or modification in its levels, or leptin resistance [10].

Conclusions

Obesity is a risk factor for AD and other dementias, so it's important to find effective markers to stop negative effects and start comprehensive preventative initiatives. Indeed, there are biochemical similarities between AD and obesity. As a result, adipokines, which are released by adipose tissue and communicate with the CNS, contribute to the development of AD and other dementias. Leptin, one of these adipokines, exerts neuroprotective effects at the CNS level. To correct the malfunction of these pathways and thereby enhance the prognosis of AD, it is essential to correctly identify the changes in the signaling pathways triggered by leptin and its receptor, LepRb. In reality, a variety of leptin resistance mechanisms have been identified, including those mediated by SOCS3, PTP1B, and TCPTP. In an animal model of AD, changing expression levels of SOCS3 and PTP1B disrupt leptin signaling. Therefore, research should concentrate on developing inhibitors or related mechanisms to lessen this leptin resistance. In reality, it is possible to create inhibitors for protein tyrosine phosphatases, and it has also been proposed to employ ATR inhibitors to lower SOCS3 expression. The development and progression of neurodegenerative illnesses like AD, PD, or HD are significantly influenced by CNS inflammation or neuroinflammation, and inflammation can disrupt leptin-triggered signaling, resulting in leptin resistance. Therefore, using anti-inflammatory medications along with those that lower leptin resistance may be beneficial.

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