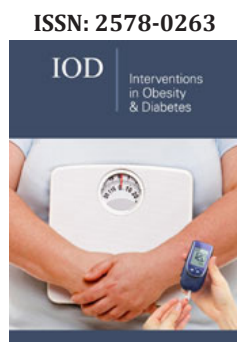


Cross-Talk Between Obesity and Central Nervous System: Role in Cognitive Function

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
Abstract

Obesity is a world health problem. Excess of white adipose tissue (WAT) might lead to development of neurodegenerative disorders. WAT contributes to low-grade inflammation leading to the enhancement of pro-inflammatory adipokines, such as TNF- α , leptin and IL-6, which will lead to a peripheral inflammation that affects central nervous system functioning. Pro-inflammatory adipokines are enhanced in obesity, while anti-inflammatory, such as IL-10 and adiponectin, are reduced. Obesity seems to be related to cognitive decline and the development of neurodegenerative diseases, such as dementia and Alzheimer, through the production of pro-inflammatory adipokines with a consistent reduction of adiponectin and IL-10.

Keywords: Obesity; Inflammation; Leptin; Brain regions; Cognitive performance

Abbreviations: WAT: White Adipose Tissue; TNF- α : Tumor Necrosis Factor Alpha; IL: Inter Leukin; CNS: Central Nervous System; BBB: Blood Brain Barrier

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Introduction

Obesity is a health problem in western societies being usually associated with low-grade inflammation [1]. White adipose tissue (WAT) accumulation contribute to an increased risk of obese subjects develop several related diseases, such as type 2 diabetes and neurodegenerative diseases [2-4]. Obesity is associated to mild cognitive impairment, and increased risk of developing dementia and Alzheimer's disease [5,6]. Obesity-induced neuroinflammation has shown to affect brain areas related to cognitive performance and memory, such as the hippocampus, and cortex [7,8]. The expanded hazard for obese subjects to develop a CNS pathology mirrors the connectivity of WAT to the cerebrum through different pathways to affect the mind work [4-6]. It is now well established that WAT is not just a fat storage organ, as it was considered for many years, but an endocrine organ that secretes different substances called adipokines, which play a role in cognitive function [6,9,10].

Adipokines circulating levels are changed in overweight, and obesity due to the expansion of WAT [6,9]. Low-grade inflammation state is produced by the increased level of several pro-inflammatory adipokines, such as leptin, tumor necrosis factor alpha (TNF- α), and interleukin (IL)-6 [11]. The levels of circulating pro-inflammatory mediators can affect the central nervous system (CNS) through lymphatic vessels, coroid-plexus and blood brain barrier (BBB) [1]. The mechanism of affecting CNS occurs due to the development of a peripheral inflammation that leads to the elevation of these pro-inflammatory adipokines, such as TNF- α , leptin and IL-6, which are able to cross the BBB, and might contribute to the development of brain inflammation and insulin resistance [10,12,13]. Intracellular signaling mediated by pro-inflammatory adipokines and insulin resistance are the main mediators of obesity-associated cognitive decline because they will disturb synaptic plasticity, induce oxidative stress and neuroinflammation interfering in the learning processes [7,10,14,15]. On the other hand, anti-inflammatory adipokines are diminished in obese individuals, such as IL-10 and adiponectin [6].

Leptin resistance in obesity affects learning and memory

Neurophysiological functions have also been attributed to leptin, another adipokine secreted by WAT that can cross the BBB, which is involved in brain development, neurogenesis, neuronal survival, and behavior [16,17]. In the absence of leptin in early life, even for a short period of time, will favor a poor development of arcuate nucleus neural projection [18]. Leptin also influences reproduction and metabolism acting on the hypothalamus to suppress food intake [16]. Leptin acts as a potential psychological enhancer as it stimulates the cell events involving learning and memory in hippocampi [17]. Leptin responses are diminished in obesity, aging, and neurodegenerative disorders, contributing to insulin resistance and inflammation, and leading to cognitive decline [6]. When leptin is reduced in the organism, we call this physiological change of leptin resistance.

TNF- α is a strong mediator of neuroinflammation and cognitive decline

Microglial cells and astrocytes are the main TNF- α producers in human body [19]. Neuroinflammation is strongly mediated by microglial and astrocyte cells activation with consequently secretion of TNF- α [20-22]. Learning and memory failure are associated to inflammation and changes in insulin signaling in the brain [15,23]. Brain regions involved in cognitive decline show exacerbated microglial and astrocyte expression [5,10,24]. Higher expression of TNF- α with activation of stress kinases are the main features for defective neuronal insulin signaling and, consequent, cognitive decline [10,25]. Interestingly, blockade of TNF- α in mouse models leads to an improvement in insulin sensitivity and glucose homeostasis rescuing synaptic plasticity, short and long-term memory [10,26,27].

IL-6 is associated with cognitive decline

It has been shown that obesity leads to brain atrophy, reducing volume in a number of brain regions [28,29]. Thus, peripheral inflammation might contribute to cognitive decline and memory loss [5]. A recent meta-analysis showed that increased plasma levels of IL-6 and C-reactive protein are main features of obesity that are associated with an increase in dementia [30]. However, a recent study revealed that IL-6 blockade increased cholesterol levels, and visceral adipose tissue was not reduced even under physical exercise training [31]. Thus, IL-6 is needed for exercise in order to reduce visceral adipose tissue mass and also play an undefined role in cognitive decline [30,31].

IL-10 reduces neuronal degeneration

Termination of neuroinflammation has the participation of anti-inflammatory adipokines, such as IL-10 [32]. It has been shown that the level of IL-10 in different areas of the brain increases in several conditions and diseases, thereby promoting survival of neurons [33-35]. Associations between cognitive decline, memory loss and pro-inflammatory adipokines have been showed and the oppose actions to these mechanisms by IL-10 have also been

proved in a recent meta-analysis [35]. It can be suggested that anti-inflammatory cytokines, such as IL-10, develop an important role in conditions of memory impairment, since IL-10 is also synthesized in the central nervous system [32-35].

Adiponectin reduction is related to memory impairment

Adiponectin is responsible for the increasing in insulin sensitivity in liver and muscle [36]. Adiponectin develops several anti-inflammatory activities, such as suppression of macrophage activation, in peripheral tissues [37]. It inhibits, *in vivo* and *in vitro*, microglia pro-inflammatory profile [38]. Plasma levels of adiponectin are decreased in obesity and contribute to insulin resistance being also linked to cardiovascular diseases [39]. Low levels of adiponectin are also related to cognitive decline, although the specific role in brain functioning related to learning and memory is not completely clarified yet.

Conclusion

Obesity is a world health problem that has been linked to a reduction in cognitive performance. Obese subjects present an increased risk to develop neurodegenerative disorders, such as type 2 diabetes, dementia, and Alzheimer. Excess of white body fat tissue seems to lead to neuroinflammation through activation of different adipokines affecting cognitive performance and memory. The ability of adipokines, pro and anti-inflammatory, to modulate learning and memory emphasizes the special properties of the WAT not only in obesity.

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