Pathophysiological Mechanism of Cognitive Impairment in Obese Persons

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Cognition is a global concept encompassing various processes virtually scattered over the whole brain. Obesity itself can be viewed as a consequence of impaired energetic feedback loops or as a higher disorder of impaired reward—behavior control mechanisms. However, the adipose tissue—brain relation is much more than a simple direct bilateral communication involving virtually all metabolically active organs and a plethora of messengers.

obesity | overweight status | cognitive dysfunction

1. Introduction

One of the most significant public health problems is obesity. Cognitive decline is linked to excess adipose tissue, especially when it is distributed centrally. Indeed, obesity has been linked to several negative changes in the brain's structure and function that can be identified using neuroimaging methods. These alterations caused by obesity might cause cognitive dysfunction [1].

Classically, obesity has been described as an increased body mass index (BMI) starting from the value of 30 kg/m^2. While it is a parameter still in use today and is easy to apply in any clinical setting, it does not offer enough information to quantify the metabolical risk of patients (e.g., persons with a high muscle tissue percentage who have an increased weight but a reduced percentage of adipose tissue). Therefore, it is recommended to be used in conjunction with another anthropometric measurement, the waist-to-hip ratio (WHR). Nowadays, the definition of obesity involves both the BMI value above 30 kg/m^2 and the WHR. WHR is also a major criterion for the metabolic syndrome based on the harmonizing definition [2][3].

2. Pathophysiological Mechanism of Cognitive Impairment in Obese Persons

Cognition is a global concept encompassing various processes virtually scattered over the whole brain. Obesity itself can be viewed as a consequence of impaired energetic feedback loops or as a higher disorder of impaired reward—behavior control mechanisms. However, the adipose tissue—brain relation is much more than a simple direct bilateral communication involving virtually all metabolically active organs and a plethora of messengers. Although most of the research has focused on the hypothalamus and the hippocampus, wider abnormalities in the

central nervous system were found to correlate with obesity. White matter diffuse damage and focal white matter abnormalities [4], connectivity loss [5], and cortical and subcortical gray matter atrophy [6][7][8] were found in human imagistic studies in obese subjects, and the pattern of grey matter atrophy is similar to the one found in neurodegenerative diseases [9]. As multiple factors influence results, sometimes correlations can appear conflicting—e.g., obesity correlates with abnormal brain perfusion in subjects with normal cognition and mild cognitive impairment but not in subjects with Alzheimer's disease. In the same study, white matter integrity in the corpus callosum, superior longitudinal fasciculus, inferior fronto-occipital fasciculus, fornix, and cingulum negatively correlated with BMI in the cognitively healthy sample but not in subjects with mild cognitive impairment (MCI) or Alzheimer's, while gray matter's volume negative associations with obesity were more extensive in the cognitively healthy group than in the MCI group [10].

The direct mechanism and causality of obesity in relation to neuronal structural, functional, and cognitive parameters is still unclear, and whether association implies causality remains to be established. Abnormal impulse control and obesity share anomalies in motivation and reward-related brain centers. The generally accepted mechanisms for obesity-related CNS dysfunction are inflammation [11], vascular abnormalities (with endothelial dysfunction as an essential actor) [12][13], and, in a less definite manner, neuronal energy homeostasis (due to mitochondrial dysfunctions [14]) or direct influence of adipose tissue signals in the brain. Nutritional factors that are less specifically tied to these processes could also play significant parts—minerals such as zinc in particular, with zinc supplementation improving cognitive performances in obese women independently from weight loss [15]. Aside from "traditional" cellular and soluble factors, adipose tissue can secrete extracellular vesicles that can serve as mediators to communicate with other peripheral tissues, such as the liver and skeletal muscles. In a recently published study, the authors show that specific miRNAs are significantly upregulated in participants with obesity and diabetes and can be transferred via extracellular vesicles from the adipose tissue to the hippocampus. Among upregulated miRNAs, miR-9-3p showed a coherent upregulation trend in the hippocampus of mice fed with a high-fat diet and in the extracellular vesicles of humans with diabetes, inducing synaptic damage and cognitive impairment in both [16].

In obese persons, adipose tissue initiates a local immune response by activating multiple immune cells. An increased volume of adipocytes may be the first step in attracting macrophages and triggering their activation (shift to M1 state), beginning local immune accumulation [17]. The activated immune cells then may interact with CNS immune system cells or glial cells through various transmitters or may circulate and pass through the blood–brain barrier (BBB), maintaining a global inflammatory state. Systemic inflammation echoes in the brain, at least partly due to BBB dysfunction [14][18] and abnormal activation of CNS residents and peripheral immune system components. CNS inflammation is associated with functional and structural abnormalities of the brain. A high-fat diet induces memory impairments in mice as soon as three days after the initiation and depression-like behavior after five days, possibly explained by very prompt BBB dysfunction from the first day. However, in the same study, BBB permeability returned to normal at two weeks and increased again after four weeks—supporting the conclusion that various mechanisms contribute to cognitive abnormalities and that CNS aggression is most likely multifaceted [14].

Decreased neuronal and increased non-neuronal cell numbers and densities in the hippocampus and increased non-neuronal cells in the frontal cortex and hypothalamus of obese mice suggest a tight connection between inflammation and neurodegeneration [19]. Dystrophic hypothalamic microglia (and, to a lesser extent, astroglia) were found in obese brains when compared to normal-weight individuals [20].

Adipose tissue also produces messengers that exert their effects remotely. Leptin, a peptidic hormone synthesized mainly by white adipose tissue, appears to have various effects on central nervous system structures, mostly related to energy regulation. Normal neurodevelopment of hypothalamic structures such as the arcuate nucleus seems to require specific patterns of leptin intervention in terms of timing and duration, with potential enduring consequences in the case of abnormal stimulation [21]. Leptin is increased in obesity [22]. Its effects in the brain depend mainly on leptin receptors found not only in the hypothalamus but also in the hippocampus, amygdala, and cerebellum. In the hippocampus, leptin facilitates synaptic efficacy of both excitatory and inhibitory synapses, potentially inducing either long-term potentiation or long-term depression and is likely to have procognitive actions related to learning and memory processes and memory consolidation [23]. Leptin may have protective actions against the acute and chronic synapto-toxic effects of amyloid β, promote amyloid β clearance, and enhance neurogenesis [23]. In a populational study, higher levels of leptin and resistin (but not adiponectin) were associated with a reduced risk of dementia in overweight/obese persons and not in persons with a BMI of 25 kg/m^2 [24]. In another study, leptin levels were significantly higher and adiponectin significantly lower in obese patients. The same research has shown that while high levels of adiponectin were associated with neurodegenerative dementia and high levels of resistin with vascular dementia, leptin levels did not differ significantly in demented patients as compared to normal subjects [25]. Decreased sensitivity to leptin (“leptin resistance”) may be due to receptor abnormalities, impaired transport across the BBB, or increased activity of its negative regulators [26]. Obesity might be caused by chronic metabolic inflammation in the hypothalamus, possibly as a direct neuronal response to chronic overnutrition (local oversupply of glucose or lipids) [27]. In another neurotoxicity paradigm, leptin can inhibit neural stem cell expansion by specific receptor-mediated (via ERK/cyclin D1 pathway) apoptosis of neuronal precursors in vitro models. Whether cognitive impairment (and possibly Alzheimer’s disease) associated with obesity is due to leptin resistance (similar to cognitive deficits in leptin-deficient models) is still an uncertainty [28].

In a similar manner, abnormal gut microbiota associated with obesity appears on one side to generate inappropriate activation of the immune system and on the other side to release in circulation substances that can pathologically interact with the BBB and the CNS immune system (of whom lipopolysaccharide (LPS) is probably the most researched) [29][30]. Obesity due to a high-fat diet in wild mice was associated with gut dysbiosis—decreased relative abundance of *Faecalibaculum* and increased relative abundance of *Dubosiella* [31]. The authors found increased cognitive deficits and white matter lesions in obese mice subjected to reduced cerebral flow and attributed these to increased inflammation triggered by lipopolysaccharide (LPS) through a TLR4-dependent mechanism. Intestinal permeability, plasma LPS levels, and levels of proinflammatory cytokines IL-6 and IL-1β were significantly greater among HFD mice. In the corpus callosum, significantly higher LPS levels, TLR4 expression, activated microglia, reactive astrocytes, oxidative stress, and BBB permeability markers were found, while tight junction protein occludin was downregulated [31]. In another study in humans, obesity was associated with an increase in the *Prevotella*/*Bacteroides* (P/B) ratio as well as with an increased centrality of the nucleus

accumbens (reflecting the ability to affect the signal of connected structures) and a decreased centrality of brainstem structures involved in food intake regulation, as well as a decrease in fecal tryptophan [32]. In another study, the scores of all memory domains were associated with altered plasma levels of tryptophan, tyrosine, and phenylalanine and their catabolites, but memory-related alterations in tryptophan metabolism were only observed in individuals with obesity [33]. In the same study, common species that positively associated with learning, verbal memory, and working memory belong to the *Firmicutes phylum*, while negative associations between the gut microbiota and memory scores were identified within the *Bacteroides* and *Proteobacteria* [33]. Quinolinic acid levels were significantly increased in obese compared to non-obese humans and significantly correlated with BMI [34]. Quinolinic acid is a metabolite of tryptophan, acts as a (neurotoxic) glutamate receptor agonist, and is excessively secreted by activated macrophages and adipose tissue during inflammation [35]. In humans, serum quinolinic acid levels were negatively correlated with the total cognition score of the Repeatable Battery for the Assessment of Neuropsychological Status, particularly with regard to the delayed memory index, while in obese mice, they were negatively associated with recognition memory and spatial working memory [34].

Another possible mechanism for gut microbiome to connect to immune disorders and cognitive abnormalities involves short-chain fatty acids (SCFAs) (mainly acetate, propionate, and butyrate) produced by gut bacteria from nondigestible dietary fibers. These are major cellular energy sources and appear to modulate the strength of the gut barrier, promote cellular metabolism, and have significant immunomodulatory activity [36]. Long-time early supplementation of SCFAs in murine and cellular models for neurodegenerative diseases increased neuronal resistance to oxidative damage, enhanced astrocyte–neuron communication, and alleviated the cognitive impairment by reducing Aβ deposition and tau hyperphosphorylation [37]. However, the neuroprotective effect of SCFAs remains to be clarified—i.e., in another mouse model for Alzheimer's disease. The administration of SCFAs increases microglial reactivity and activation and increases Aβ plaque loads [38]. The correlation between gut microbiota and obesity is inconstant in human studies, with a meta-analysis showing obese adults to have higher feces levels of SCFA but no statistically significant differences between *Bacteroides* and *Firmicutes phyla* [39]. Supplementation of butyrate in obese mice improved metabolic control and cognitive parameters, generating a number of neuroprotective effects in the frontal cortex of treated mice. Its effects were probably mediated through an increased expression of BDNF in the frontal cortex due to epigenetic regulation, thus preventing a decrease in total neurite length, number of neurite branches, dendritic arborization and complexity, and have protective effects on synaptic spine morphology and spine density [34].

Information from the gut through the vagal afferences can induce behavioral changes (promoting hippocampal-depending learning and memory processes), and gastrointestinal vagal disconnection leads to impaired memory and decreased neurotrophic (BNDF) and neurogenesis markers (doublecortin) in the hippocampus [40]. Similarly, a high-fat diet can induce by itself changes in hypothalamic microglia (both pro- and anti-inflammatory), and these changes preclude the increase in pro-inflammatory cytokine expression (supporting a direct response of microglia to diet) and appear to downregulate genes involved in sensing microenvironmental alterations. Whether this

reflects that obesity and gut microbiota changes result from a specific obesogenic neural activity or whether the central pattern of activity is the result of obesity and intestinal changes remains to be established [20].

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