The Importance of Adipokines in Alzheimer’s Disease

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Abstract
Dementia and Alzheimer’s disease (AD) are characterized by disturbances in brain function and structure. Similarly, body mass index and obesity are associated with certain brain pathologies, including AD and dementia. In fact, there is mounting evidence linking metabolic dysfunction with dementia and AD. The major endocrine axes constitute links between brain and peripheral tissues, especially adipose tissue. Adipose tissue is metabolically very active and produces a variety of adipokines known to affect both peripheral and central nervous system processes. Experimental studies suggest that changes in adipokine function may contribute to the pathogenesis of AD. Herein, we review the adipokines leptin and adiponectin, which are associated with morbidities related to obesity, as well as dementia and AD.

Introduction
Metabolism is managed by the central nervous system (CNS) inputs, especially hypothalamic, and peripheral hormones, such as insulin, ghrelin, and adipokines (e.g., adiponectin and leptin). Thus, neuronal and/or vascular brain pathologies could be potentiated by metabolic risks via changes in adipokine levels and subsequent control mechanisms (1).

The hypothalamus, a key regulatory region of the brain, is often affected in Alzheimer’s disease (AD) and dementia (2). In addition, to providing a wider evidence-base for the involvement of peripheral metabolism in the healthy brain, recent findings have increasingly implicated the abnormalities in both vascular and metabolic systems in AD etiology. Considering the major endocrine axes constitute a link between brain and peripheral tissues, neuropathological changes in AD may dysregulate the axes.

Unfortunately, current treatments for AD often result in unsatisfactory outcomes. Recent reports indicate a link between metabolic dysfunction and some neurodegenerative disorders. For example, treatments administered to restore metabolic homeostasis are associated with improvements in cognitive and motor functions, as well as lifespan, in neurodegenerative disorders (3,4). However, it is still unclear whether disordered systemic metabolism is a cause or consequence of AD pathology. In this review, we focus on adiposity, obesity, and abnormal energy regulation related to AD and dementia.

Obesity and AD
Due to its high prevalence, obesity is considered by many authors to be an epidemic illness, caused by a fundamental imbalance between energy expenditure and intake consequent to complex environmental factors and/or genetics (5,6). Obesity causes many adverse health conditions and contributes to multiple morbidities and mortality (7). Moreover, this condition may also play multiple roles in brain aging, especially in subjects at risk for dementia-related pathologies. Obesity has also been shown to cause changes in brain structure and function, cognitive deficits, and has been linked to the development of dementia and AD (8-13). In particular,
obese or overweight subjects has been shown to have an increased risk of AD (14,15). Besides metabolic risk factors, studies have shown the involvement of vascular and other factors, like body mass index (BMI), in AD, implicating multiple biological processes in brain neurodegeneration.

The first study to show a relationship between AD and increased body weight was conducted on overweight women with BMIs <30 kg/m² and ≥25 kg/m² (16). Specifically, weight gain in middle-aged subjects was linked to an increased risk of mild cognitive impairment (MCI), AD, and dementia later in life (17-20). In contrast, weight loss has also been associated with an increased risk of MCI, AD, and clinical dementia (21). In 20 years, prospective observational study of 299 men and women aged 50-79 years, AD was shown to develop in 60 people who lost ≥5 kg (22). These seemingly contradictory results, however, can be delineated by the age at which weight was gained or lost, as elderly individuals with dementia were more likely to have a lower body weight or BMI than their cognitively normal counterparts (14,23). Nevertheless, in the prodromal phase, associations between body weight or BMI changes and development of dementia were insignificant (22-24).

Further studies are needed to clarify why midlife weight gain is a risk factor for AD, while weight gain in the elderly is not.

Dementia and AD are characterized by changes in brain function and structure, including accumulation of amyloid plaques and neurofibrillary tangles, decreased total gray matter volume, increased white matter lesions, reduced white matter integrity, and synaptic dysfunction (12,25-28). BMI and obesity are also associated with brain pathologies related to aging and AD, such as temporal lobe atrophy, white matter changes (12,26,29,30), and blood-brain barrier (BBB) disturbances (1,26). Furthermore, peripheral adipose tissue of obese individuals has been shown to exhibit classic AD pathologies, such as increased amyloid precursor protein (APP) production; and positive correlations between APP expression, insulin resistance, and cytokine expression in adipocytes (31).

Adiposity and Adipose Tissue Hormones

As the largest endocrine organ in the body, adipose tissue is metabolically very active and produces a variety of hormones collectively referred to as adipokines (adipocyte-derived cytokines). Total body fat is comprised of subcutaneous and internal fat. Subcutaneous fat is in larger proportion whereas adipokines come mainly from the internal fat, which is consisted of visceral and perivascular fat (32). Adipokines are known to affect both peripheral and CNS processes, and experimental studies suggest that changes in adipokine function may contribute to AD pathogenesis. The BBB is a large neurovascular interface, which controls the transport of a variety of circulating factors, such as amino acids and proteins, as well as many other molecules, like adipokines into the CNS (33-35). Herein, we reviewed two main adipokines, leptin, and adiponectin, which are associated with morbidities related to obesity, as well as dementia and AD (36-38).

Leptin

Leptin is a BBB-permeable protein hormone secreted by adipose tissue (39). Since its discovery in 1994, leptin has been shown to have many important metabolic effects, including regulation of energy expenditure, food intake, fat storage, immune system and reproductive function, insulin sensitivity, locomotor activity, bone mass, growth, adrenal and thyroid function, thermogenesis, and senescence (40-44). In addition, leptin plays a significant physiological role in neuronal activity and plasticity in the brain and has been shown to affect brain development (43,45).

Although some evidence suggests leptin may be synthesized in the brain (46), this peptide is largely produced in the periphery and readily crosses the BBB to bind specific hypothalamic receptors in order to mediate food intake, body weight, and energy expenditure (38), as well as control memory and learning processes in the hippocampus (47).

Obesity has been linked with heightened leptin levels, as well as leptin and insulin resistance (14,23). In the non-obese, food intake increases leptin production, which in turn stimulates expression of anorexigenic neuropeptides through negative feedback mechanisms in the brain. Despite these positive associations, some reports have shown that leptin levels are highly variable in adults (48), and its production is influenced by BMI and gender in humans (49).

Notably, the Framingham study showed that lower leptin levels correlated with an increased risk of AD (50). A 4 years study of 3000 subjects showed that individuals with lower leptin levels had poorer cognitive function than those with higher levels (35,36), linking altered leptin production with BMI, dementia, and...
aging. This relation may also reflect the influence of leptin on the fat brain axis and neuropathology underlying dementia. Considering the rate of leptin transport into the brain can be reduced by heightened plasma leptin concentrations, reduction of leptin in the brain may represent a pathological regulatory mechanism adapted in obese individuals (51). Leptin may even improve the structure of the hypothalamus in the earliest period of development and improve cognition (45).

In normal aging, circulating leptin levels correlate with gray matter volume in various brain regions including the hippocampus (50,52), and inversely correlate with cognitive decline (51). Leptin also reverses neurocognitive deficits and structural abnormalities in multiple brain regions in humans with congenital leptin deficiency (53,54). Thus, these findings indicate that leptin has strong effects on brain structure and function in multiple brain regions and may be deficient in AD brain.

Leptin acts through the longest isoform of leptin receptor, which contains a cytoplasmic signaling domain (55-57). Leptin receptors are expressed in the hypothalamus and hippocampus (43,58,59) and have been identified in peripheral tissues, as well. However, the major metabolic effects of this peptide hormone are on hypothalamic and hindbrain neurons, wherein leptin receptors are susceptible to AD pathology (60). Indeed, leptin is crucial for the maintenance of normal hippocampal synaptic plasticity (61,62). In hippocampal cornuammonis-1 (CA1) neurons, leptin improves pre- and post-synaptic neurotransmitter sensitivity and release (63). In addition, impaired long-term potentiation in the CA1 region of leptin receptor-deficient rodents has been shown, suggesting the involvement of leptin and/or its receptor in normal working memory (64).

Due to the requirement of leptin for normal hippocampal function, it represents a reasonable AD therapeutic target. In rodents, direct leptin injection into the hippocampus was associated with improved memory processing and modulation of long-term potentiation and synaptic plasticity (45). Leptin also improves memory in senescence-accelerated mice, which develop amyloid-β (Aβ) plaques (65).

Manipulation of leptin levels has been shown to improve AD pathology by resolving Aβ plaques (66-68), and chronic leptin treatment reduces Aβ levels in brain and serum of APP Tg mice (66,69). Leptin also reduces tau phosphorylation through inactivation of glycogen synthase kinase-3 in cultured neuronal cells and organotypic cultures (70). In AD, leptin deficiency contributes to downregulation of adenosine monophosphate-activated protein kinase signaling, increasing Aβ levels, and tau phosphorylation (67,71).

All of the aforementioned data indicate that leptin may directly regulate the behavioral and pathological progression of AD, implying AD patients are reasonable candidates for leptin replacement therapy.

**Adiponectin**

As an important adipose tissue-derived peptide hormone, adiponectin regulates food intake in the CNS, energy expenditure in the CNS and periphery, and insulin-glucose metabolism (72-75). Plasma adiponectin levels are inversely correlated with insulin resistance, metabolic syndrome, obesity, Type 2 diabetes, and cardiovascular diseases, and increases in white adipose tissue (WAT) and surrogate measures, such as percent body fat, waist-to-hip ratio, and BMI (76,77), all of which are risk factors for AD, as well (78).

Adiponectin is released from adipose tissue into the circulation as complex, multimeric, high molecular weight hexamers, and trimers. Apart from adipose tissue, adiponectin is also produced by other peripheral and CNS tissues, including the brain. Two types of adiponectin receptors (adipoR1 and adipoR2) are expressed throughout the CNS, including the hippocampus, hypothalamus, brainstem, and brain microvessels in both humans and rodents (79,80). Nevertheless, it is not clear whether adiponectin is produced peripherally and traverses the BBB (81,82) or is secreted in the brain in response to an increase of peripheral adipokines (e.g., leptin).

Some studies have shown a potential correlation between adiponectin and AD. Adiponectin exhibits neuroprotective functions in rodents and may reduce weight by increasing energy expenditure (74,80). In addition, some AD patients have elevated levels of adiponectin in both plasma and cerebrospinal fluid (83). Considering the role of obesity and BMI in AD pathology discussed above, these findings suggest adiponectin plays a role in mediating AD progression, possibly through its effects on peripheral and/or brain metabolism.

Furthermore, adiponectin may indirectly affect inflammatory signaling across the BBB and within the brain through blocking the production of interleukin (IL-6) and tumor necrosis factor-α (TNF-α). The IL-6
has been found to be elevated in AD patients while adiponectin treatment was shown to reduce IL-6 secretion in brain endothelial cells (82). Moreover, adiponectin injected into the lateral ventricle of mice was shown to alleviate neuronal damage from kainic acid-induced seizure activity in hippocampal neurons (84). Overall, these findings confirm the neuroprotective effects of adiponectin.

**Conclusion**

Although major advances in the fields of endocrinology and neuropathology have been made in recent years, the complex relationship between peripheral metabolic factors and the brain are not completely understood. Increased adipokine production by WAT in obesity mediates typical pathological processes, such as imbalanced energy metabolism, inflammation, and hypertension. These alterations may have severe implications for the etiology of several prominent neurodegenerative disorders of the brain, such as dementia and AD. Moreover, altered adipokine production and/or function might increase susceptibility to the development of pathological processes in the brain. Epidemiological studies have shown increased risk of AD and brain-related events in association with obese and overweight middle-aged individuals and to some extent in the elderly.

Peripheral signals, such as leptin and adiponectin, interact with critical brain regions associated with normal metabolic processes and brain function. Aging and metabolic susceptibility play an important role in altering the balance. Increased peripheral leptin is related to a decreased incidence of AD in non-obese elderly subjects. Leptin therapy has also been shown to improve AD-related pathology in transgenic mice. However, whether leptin resistance in the CNS associated with aging and obesity enhances amyloid plaque deposition has yet to be determined. Furthermore, few studies have focused on the relationships between adiponectin levels and normal cognitive function, dementia, and/or AD. Although adiponectin is thought to be complementary to leptin, it has little impact on AD pathology. Nonetheless, neurodegenerative therapies related to manipulation of these metabolic factors seem promising.

Other than leptin and adiponectin, some adipokines including TNF-α, IL-6, visfatin may play roles in the pathophysiology of AD. Obesity is known as a chronic low inflammatory state, which is developed via production of inflammatory adipokines such as TNF-α and IL-6 (85). In a study, it is shown that there is an increase in brain gliosis due to this inflammatory state in obese patients (86). Adipokines induced high inflammation in the perinatal session is related with neurodevelopmental and neurodegenerative diseases (87). Furthermore, IL-6 and TNF-α production in patients with obesity can cause resistance to anorexigenic signals in the hypothalamus (88). Ceramide may induce AD by producing oxygen radicals and damaging the BBB (89,90). Visfatin may increase reactive oxygen species through the NADH redox cycle which damage the BBB and enhance the inflammation (91). Eventually, ceramide and visfatin may impair the BBB together (92) and may damage the cerebral cortex and hippocampus.

However, based on mechanistic, animal, and clinical studies discussed above, successful study and treatment of neurodegenerative disorders should ideally encompass the whole body, rather than the CNS alone, as a complex network of multiple endocrine factors are likely involved in AD development. Likewise, multiple metabolic and hormonal changes associated with obesity and/or aging will certainly prove to influence the brain in both healthy and diseased states, especially considering previous studies suggest a definite link between obesity, altered energy metabolism, and AD. Moreover, whether these hormones are protective or detrimental to cognitively normal obese individuals requires further clarification. Future studies examining the relationship between adipokines and AD will help characterize and evaluate the potential for using metabolic factors to treat both metabolic and neurodegenerative disorders.

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