Visceral Adipose Tissue Metabolism and Alzheimer's Disease

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Alzheimer's disease (AD) is a progressive, neurodegenerative disorder characterized by the presence of intracellular neurofibrillary tangles and extracellular amyloid-β (Aβ) plaques in the brain. Although the accumulation of Aβ plaques is believed to be one of the factors driving AD pathogenesis, clear pathophysiology of AD delineating the contributions of each pathological protein has not been confirmed. The visceral adipose tissue (VAT) has been recognized as an endocrine organ, and VAT dysfunction could be a risk factor for AD. Epidemiological studies revealed that high adiposity is correlated with an increased risk of developing dementia, including AD. In addition, significant relationships between adipose-derived molecules, such as leptin and adiponectin, and progression of AD have been reported. Moreover, it was recently reported that the proinflammatory cytokine derived from VAT plays an important role in the pathogenesis of AD. However, the mechanism by which VAT dysfunction affects the development and progression of AD remains unclear.

adipose tissue Alzheimer's disease amyloid-β glucose metabolism

1. Current Insights

The visceral adipose tissue (VAT), which produces a wide array of bioactive peptides, has been recognized as an endocrine organ [1]. An increase in VAT mass promotes abnormal secretion of adipose-derived inflammatory cytokines or a wide array of bioactive peptides, causing VAT dysfunction [2] that could affect the brain [3]. A recent study demonstrated that VAT metabolism correlated positively with cerebral Aβ burden. This finding provides strong evidence that VAT dysfunction is related to AD development.

VAT metabolism, measured by ^{18}F-FDG PET, could be used as a surrogate marker of VAT dysfunction. Several previous studies reported that VAT metabolism, as measured by ^{18}F-FDG PET, is related to several diseases, and that ^{18}F-FDG uptake in VAT is an excellent measure of VAT dysfunction. A prospective ^{18}F-FDG PET study demonstrated that ^{18}F-FDG in the neck adipose tissue was highly predictive of cardiovascular risk in 173 patients [4]. Another ^{18}F-FDG PET study revealed that ^{18}F-FDG uptake in VAT was associated with a risk of metabolic syndrome, and it reduced with adiposity by exercise [5]. Additionally, a recent ^{18}F-FDG PET study reported that ^{18}F-FDG uptake in VAT was positively correlated with adiponectin levels and inversely with insulin resistance, suggesting that VAT metabolism could be a proxy of VAT dysfunction [6]. VAT metabolism is expected to represent not only metabolism of the adipocyte itself, but also several complex biological processes, such as energy storage, insulin resistance, lipolysis, and adipose inflammation [6], because the VAT contains not only adipocytes, but also other cell types that contribute to its physiology and pathophysiology, including preadipocytes, mesenchymal stem

cells, vascular cells, and inflammatory cells [7]. An increase in VAT mass disrupts the homeostasis of the adipose-derived molecules, such as leptin, adiponectin, apelin, and inflammatory cytokine, causing VAT dysfunction [2], and the dysregulation of these bioactive peptides could affect the brain [3]. Recently, growing evidence has suggested a critical role for VAT dysfunction in AD development [2][8][9]. However, in most previous studies, the degree of VAT dysfunction has been evaluated by measuring the bioactive peptides [10][11][12], which was not sufficient to accurately assess the degree of VAT dysfunction due to limitations in which the origin of the bioactive peptides is not clear. Interestingly, the present research showed that VAT metabolism was negatively correlated with BMI. This finding agrees with that of a previous research with cardiovascular patients that reported a negative correlation between BMI and the metabolism of the neck adipose tissue [4]. The discrepancy between BMI and VAT metabolism is consistent with the phenomenon known as the "obesity paradox", in which a higher BMI in elderly subjects decreases the risk of AD [13]. This means that BMI is not regarded as the optimal surrogate marker for pathological obesity, as it could not differentiate between body fat and lean muscle [14]. In this context, non-invasive evaluation of VAT metabolism using ^{18}F-FDG PET may be an optimal alternative for evaluating the degree of VAT dysfunction.

A recent study reported that there was a significant association between VAT metabolism and cerebral Aβ burden. Although ^{18}F-FDG PET/CT was not used to measure VAT metabolism, several previous studies revealed the relationship between VAT dysfunction and AD pathology. A previous whole-body magnetic resonance imaging (MRI) case-control study revealed that AD patients had more volume of VAT than CU individuals, and increased leptin levels were correlated with lower CSF $A\beta_{1-42}$ [15]. A recent clinical study reported that serum adiponectin was higher in AD patients than in MCI patients, and adiponectin CSF levels were positively correlated with $A\beta_{1-42}$ and cognitive function, suggesting that higher serum adiponectin in AD patients constitutes a strategy to compensate for possible central signaling defects [16]. Another study with a murine model of high-fat-diet-induced VAT dysfunction reported that both adipose tissue and brain from animals fed a high-fat diet had elevated amyloid precursor protein (APP) levels localized to macrophage/adipocytes and neurons, respectively [17]. Another recent animal study demonstrated that adipocyte-specific and mitochondria-targeted APP overexpressing mice had increased body mass and reduced insulin sensitivity, along with VAT dysfunction due to a dramatic hypertrophic program in adipocytes [18]. Thus, it is postulated that APP, which is expressed in both neurons and adipocytes, plays an important role in VAT dysfunction affecting AD pathology.

Although the underlying mechanism of VAT dysfunction and AD pathology is still unclear, it can be explained by dysregulation of adipokines from the VAT. VAT dysfunction causes dysregulation of adipokines, including hyperleptinemia and hypoadiponectinemia, which may contribute to AD development [19]. Leptin, which positively correlates with BMI, has been found to display neurotrophic, antiapoptotic, and neuroprotective effects [20]. Furthermore, leptin could inhibit the transport of APP by reducing beta-secretase 1 activity [21], and also facilitates the formation and motility of hippocampal dendritic filopodia, leading to enhanced synaptogenesis [22]. Thus, it is postulated that hyperleptinemia and subsequent leptin resistance are linked to AD development [18]. In addition, adiponectin, which negatively correlates with BMI, counteracts insulin resistance and exerts anti-inflammatory effects by inhibiting the expression of IL-6 or tumor necrosis factor alpha (TNFα) [23]. Since hypoadiponectinemia has been linked to several vascular risk factors, including hypertension, coronary artery disease, heart failure,

cerebrovascular disease, and type 2 diabetes [24], it is presumed that hypoadiponectinemia shares a vascular risk factor and causes AD with leptin resistance [3].

Another possible mechanism to induce AD pathology by VAT dysfunction is chronic low-grade VAT inflammation, which can influence the occurrence of cerebral inflammation via circulating inflammatory mediators to increase the risk of AD development [3]. Immune dysregulation in the adipose tissues results in a chronic low-grade inflammation characterized by increased infiltration and activation of innate and adaptive immune cells, such as macrophages, dendritic cells, mast cells, neutrophils, B cells, and T cells [8]. In particular, macrophages, the predominant inflammatory cell type in VAT, are polarized into proinflammatory M1 macrophages, which secrete many proinflammatory cytokines, such as IL-6 and TNFα capable of developing chronic low-grade systemic inflammation [25]. Furthermore, VAT inflammation could induce adipocytes to produce various cytokines and chemokines, such as C-reactive protein, plasma monocyte chemoattractant protein-1, macrophage migration inhibitory factor, plasminogen activator inhibitor-1, and retinol-binding protein-4 [26]. These proinflammatory signals from the VAT may penetrate the blood–brain barrier [27] and exacerbate AD neuropathology, increasing the activity of various tau protein kinases and promoting cerebral Aβ accumulation [19][28]. A recent in vivo study with an obesity mouse model showed that a high-fat diet was associated with activation of inflammatory, endoplasmic reticulum stress, and apoptotic signals in the hippocampus [29].

2. Conclusions

VAT metabolism is associated with AD pathology in older subjects. VAT dysfunction could contribute to the development and progression of AD. Further longitudinal studies with larger sample sizes and histopathological confirmation are necessary to evaluate the contribution of VAT dysfunction to AD development.

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