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REVIEW

The Potential Crosstalk Between the Brain and Visceral Adipose Tissue in Alzheimer's Development

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Abstract

The bidirectional communication between the brain and peripheral organs have been widely documented, but the impact of visceral adipose tissue (VAT) dysfunction and its relation to structural and functional brain changes have yet to be fully elucidated. This review initially examines the clinical evidence supporting associations between the brain and VAT before visiting the roles of the autonomic nervous system, fat and glucose metabolism, neuroinflammation, and metabolites. Finally, the possible effects and potential mechanisms of the brain-VAT axis on the pathogenesis of Alzheimer's disease are discussed, providing new insights regarding future prevention and therapeutic strategies.

Keywords Alzheimer's disease · VAT · Crosstalk · Brain · Visceral adipose tissue

Introduction

Obesity is defined as an increase of fat mass that adversely affects health and is an underlying promoter of systemic metabolic dysfunction. According to the CDC, obesity is a public health issue and a major risk factor for chronic diseases, including type 2 diabetes and heart disease. In addition, accumulating evidence shows it has deleterious effects on the central nervous system (CNS), some of which are not limited to the classical metabolic circuits in the brain [1]. The impact of obesity on the numerous pathways linking the CNS with the abdominal organs remains the most widely studied [2]. As a result, many new concepts and underlying mechanisms regarding the brain-gut-microbiota axis [3], brain-pancreas axis [4], brain-liver axis [5], gut-brain-liver axis [6], and brain-spleen axis [7] have emerged, all of which have greatly enriched and sublimated people's understanding of neurological diseases.

Excessive fat accumulation contributes to adipose tissue dysfunction resulting in elevated free fatty acids (FFA) and systemic dyslipidemia [8]. There are two major types of adipose tissues in humans: white adipose tissue (WAT) and brown adipose tissue (BAT). BAT is a heat-producing tissue typically appearing in supraclavicular and paravertebral regions during puberty [8]. WAT is composed of many adipocytes and stromal components, such as undifferentiated preadipocytes, fibroblasts, inflammatory cells, blood vessels, nerves [9]. Visceral WAT (VAT) and subcutaneous WAT (SAT) possess considerable energy storage capacities. SAT resides under the skin of the hip, thigh, back and anterior abdominal wall accounting for about 80% adipose tissue by mass. In obesity, excess VAT is closely linked to metabolic complications, such as insulin resistance and type 2 diabetes

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[10]. VAT concentrates around the abdominal organs in six depots, including the perirenal, gonadal, epicardial, retroperitoneal, omental and mesenteric [9, 11].

It's been proposed that obesity is an independent risk factor for AD and vascular dementia [12]. Intriguingly, many studies indicate that the incidence of AD is higher in obese individuals with insulin resistance [13]. Insulin influences the clearance of amyloid β peptide and phosphorylation of tau (the major neuropathological hallmarks of AD) via modulation of vascular function through effects on vasoreactivity, lipid metabolism, and inflammation [14]. Moreover, structural evaluation of brain networks involving analyses of gray matter volume, cortical thickness, and surface area by Zsido et al. revealed that increased visceral fat was potentially associated with accelerated brain aging in adults and the elderly [15]. Furthermore, Holland et al. showed that reduced brain melanocortin signaling promotes white adipose tissue expansion via signals conveyed by efferent innervation of the vagus nerve [16] (Fig. 1).

Second, only to adipose tissue, the brain is the most lipid-rich organ in the body. Cerebral lipids constitute a major part of neuronal cell membranes. Situated within the membranes are multifunctional lipid rafts that can foster the formation of Aβ aggregates and hyperphosphorylated tau protein [17]. Exposure of membrane lipids to said aggregates can lead to peroxidation and altered fatty acid (FA) composition via reactive oxygen species (ROS) [18]. The FAs most vulnerable to ROS attack are polyunsaturated fatty acids which accumulate in the CNS, as do the resultant peroxidation by-products. Some of these products have been investigated as potential biomarkers for AD and other neurodegenerative diseases. For example, increased F2-dihomo-isoprostanes (F2-dihomo-IsoP) levels in the brain and CSF of AD patients [19] were found to correlate with disease progression, and the increase could be differentiated from normal controls with 100% accuracy [20]. In addition, lowering brain F2-IsoPs levels caused a significant decrease in

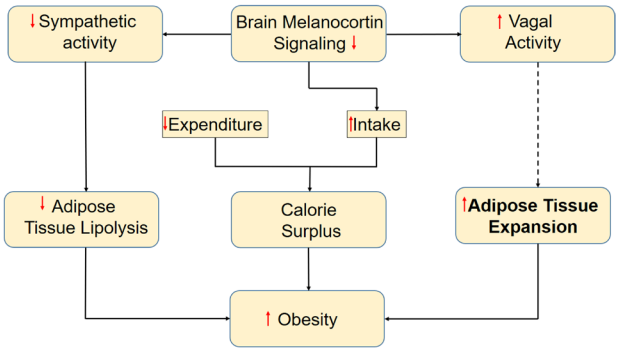

Fig. 1 Brain-melanocortin signaling controls fat mass indirectly by regulating energy balance and by direct control of lipid mobilization from adipose tissue via sympathetic nervous system activity

Aβ deposition and plaque formation in the βAPP/PS1 mice [21], suggesting elevated F2-IsoPs may serve as an early biomarker of lipid peroxidation in AD patients prior Aβ depositions [22]. Another by-product found in the CSF and brains of AD patients is F4-NeuroPs [23]. Studies involving subjects with mild cognitive impairment (MCI) and AD showed elevations for F4-NeuroP, as wells IsoP 8,12-iso-iPF2α-VI, HNE, MDA and acrolein [24, 25], suggesting oxidative damage and lipid peroxidation are early events in AD [26].

To date, most VAT clinical studies have focused on its associations with metabolic syndrome, inflammation, peripheral insulin resistance, and obesity [27–29]. However, interactions and the underlying mechanisms regarding AD and VAT have yet to be elucidated. This review examines the clinical evidence supporting VAT and brain associations before addressing the potential effects on the brain and vice versa. Finally, the possible impact and mechanism of VAT on the pathogenesis of neurodegenerative disorders are discussed.

Neuroimaging Studies Supporting Brain-VAT Associations

An emerging body of evidence suggests that physical activity (PA) could benefit cognitive and brain health during pre-adolescence [30]. For example, in a recent study by Logan et al., PA interventions in obese children prevented further deterioration of P3 event-related brain potential (ERP) amplitude compared with the control group. In normal-weight children, PA interventions resulted in VAT reduction accompanied by faster task performance and elevated amplitude P3 event-related brain potential (ERP) [31]. Elevated VAT volumes can also influence adolescent structural brain integrity and potential development. Research by Schwartz et al. demonstrated that in a community-based sample of 970 adolescents, increased VAT volume was independently associated with the high signal intensity of white matter, white/gray matter signal ratio, and standardized magnetization transfer ratio (MTR) of white and gray matter. In addition to VAT, other fat depots were also independently associated with adolescent brain structure, suggesting adiposity-related variations in phospholipid in cerebral lipids and potential for long term effects on neurotransmission and plasticity [32].

Over the last decade, numerous neuroimaging studies have highlighted the direct and indirect roles of VAT in the association between obesity and adolescent brain structures [33]. For example, among 15–18 years olds, the total cerebral cortical thickness was significantly correlated with the ratio of VAT to total body fat (via MRI measurements) independently of BMI [34]. In addition, a recent study also found that a mutation close to the DHCR24 gene was associated with the changes in white matter microstructure and

peripheral lipid metabolism, providing supporting evidence for a potential link between VAT and brain microstructure [35]. Another factor that may influence adolescent brain structure is low-grade peripheral inflammation. A recent study revealed that VAT related peripheral inflammation in adolescents was associated with the changes in white matter microstructure and decreased cognitive function [36], with 4 of the 64 tested glycerophosphocholines (GPCs) associated with both VF and serum C-reactive protein (CRP).

Accumulation of visceral adiposity can disrupt the brain's sensitivity to interoceptive feedback, leading to food cravings and impulsive eating. In a study involving 75 adults and the utilization of a 60-point scale based on the body composition analyzer (a score of 1–12 indicates normalized VAT levels, 13–59 signifying visceral obesity), researchers showed that the VAT score was associated with connectivity changes among different regions of the brain [37]. Negative associations were located in the middle-dorsal insula with a cluster involving the bed nucleus of the stria-terminalis and the hypothalamus, whilst positive associations among the rostral insula and the right amygdala, the middle-dorsal insula with the middle frontal gyri, and the middle-dorsal insula with the right intraparietal cortex) were reported. Likewise, a higher VAT mass (assessed by dual-energy X-ray absorptiometry (DXA) fan-beam technology) was associated with reduced white matter connectivity in military pilots, even though the correlation between the total body fat and white matter connectivity was of positive significance [38]. Before lifestyle intervention, increased cerebral insulin sensitivity was associated with decreased body total fat and VAT volume, respectively [13, 23]. The strong responsiveness of the hypothalamus was most closely associated with reduced VAT, but not SAT [13]. In middle-aged adults, SAT and VAT volumes showed no correlation with total brain volume via CT measurments [39], whilst a negative correlation between VAT and brain volume was demonstrated [39], suggesting high VAT levels may have a harmful effect on brain gray matter as well.

In the elderly, VAT volumes were associated with significant changes in the structural regions of the cerebellum (involved in motor processing) and cerebrum (engaged in cognitive and emotional processing). Another study also showed a bigger VAT area was significantly associated (irrespective of sex) with thinner parietal cortexes, temporal, cingulate, insular lobes. It should be noted that none of the regional cortical thicknesses significantly differed between individuals with the highest and middle levels of the subcutaneous fat area [40]. Moreover, VAT area was correlated with the peak height of MTR of gray matter and white matter, even though BMI, hypertension type 2 diabetes mellitus, smoking and statin influenced this correlation [41].

Present understanding of cerebellar functions encompasses motor and cognitive processes [42]. The cerebellum shows significant glucose metabolism and a greater reduction in cerebral blood flow following satiation in obese subjects, being structurally responsive to leptin levels involved in the neurobiology of obesity [43, 44]. Interestingly, the cerebellum shows pathological changes in most cases of AD [45]. An interesting study revealed a significant VAT–age interaction for cerebellar structure and connectivity [46] (Fig. 2). The human brain shrinks with age, and this shrinkage is differential and selective [47], whereas both cerebellar grey and white matter show accelerated structural decrease [48].

The research presented so far suggests that VAT might be a better indicator of obesity-induced cortical thinning than BMI in the elderly [49, 50]. Yet a recent study showed the volume ratio of thigh muscle/VAT was positively correlated with the volume of cognition-related brain regions (e.g., left entorhinal cortex, right temporal pole, and inferior temporal gyrus) and motor function-related brain regions (e.g., cerebellum and right globus pallidus), whilst, the correlation between VAT and temporal lobe volumes was less significant [51] implying that cerebellum and pallidum volumes could be influenced by physical activity. In addition, another study showed a significant inverse association of the cingulate gyrus and hippocampus GM volume and hepatic fat fraction, but no significant association with BMI, VAT, or pancreatic fat content [52]. Taken to together, these reports suggest liver-specific fat depots and muscle/VAT ratios may be better risk markers for neurodegenerative processes than VAT alone, with potentially important implications for early-stage lifestyle interventions regarding the older populous.

Imaging Studies Supporting White Matter and VAT Associations

There are such studies revealed that brain parenchymal lesions were able to be associated with VAT. The VAT area was significantly higher in the white matter lesions (WMLs)-positive group than in the WMLs-negative group, and high VAT area and insulin resistance were the independent predictors of WMLs in patients with type 2 diabetes mellitus, respectively [53]. In addition, an area of VAT (≥ 100 cm^2) was associated with WMLs and silent lacunar infarction (SLI) independent of age, cardiovascular risk factors, waist circumference and BMI in subjects without a history of symptomatic cerebrovascular disease [54]. Waist-to-hip ratio (WHR), a marker of visceral obesity, was predominantly related to higher deep white matter hyperintensities (WMH) and higher deep-to-periventricular WMH ratio [55], in which the elevated IL-6 is probably acting as a mediator showed by the mediation analyses [55]. In subjects free of cerebrovascular disease, WMH had higher VAT area, BMI and waist circumference than those without WMH, and the

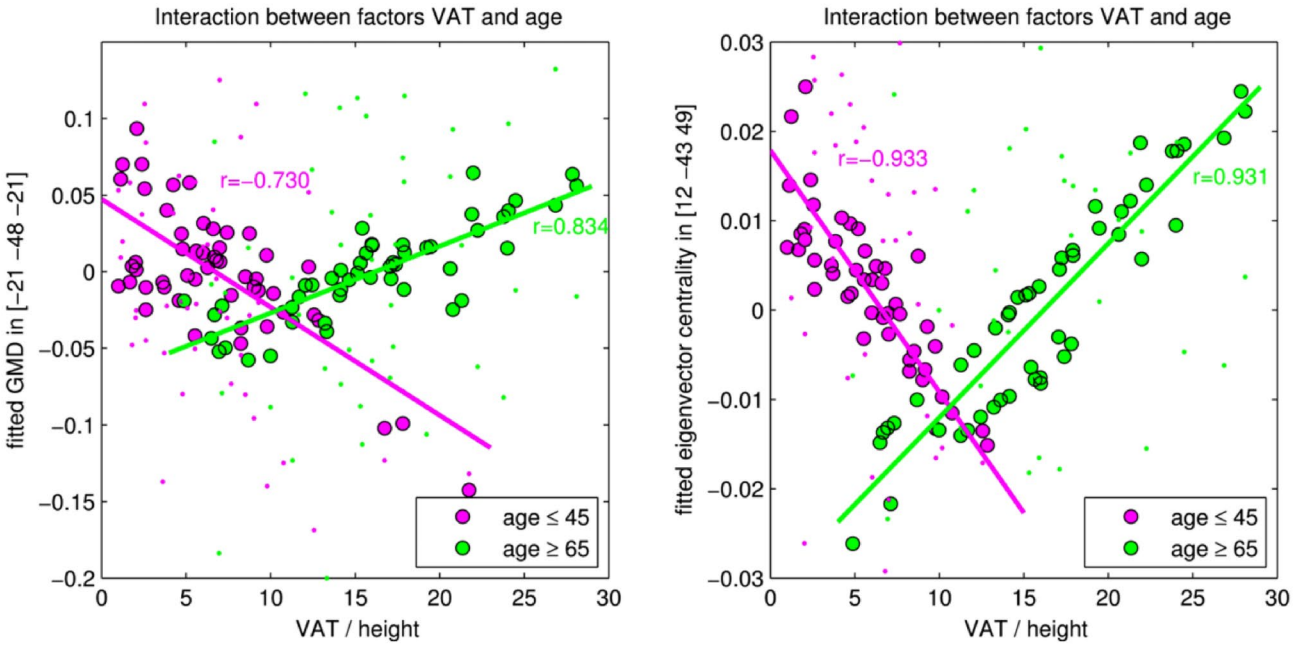

Fig. 2 Interaction between the factors visceral adipose tissue (VAT) and age in the left cerebellum with changes of grey matter density (GMD, left plot) and eigenvector centrality (EC, right plot). The young-to-mid-age participants are shown with violet dots; older participants are shown in green colour. Circles with black edge show the fitted GMD/EC values with computing the interaction between VAT and age; the smaller dots show the normalized GMD/EC values including the error term of the general linear model. Thus, the dots show original GMD/EC values adjusted for confounds that were used in the model [46]

VAT area was an independent risk factor of cerebral WMH after adjusting for age, sex, diabetes, hypertension, smoking and alcohol [56]. Similar comparison and regression analysis results were also observed in VAT and lacunar infarct [49]. It was shown that a higher VAT/SAT ratio was an independent predictor of cerebral microbleeds (CMBs) in neurologically healthy people [57] and this ratio was also independently associated with the presence of ischemic changes, cerebral artery stenosis or occlusion, and cervical plaque in apparently healthy adults [58].

Interaction and Potential Mechanism of Brain and Visceral Adipose Tissue

Effects of the Hypothalamus on Visceral Adipose Tissue in Murine Models

Murine model evidence indicates the deleterious effects of excess VAT may extend beyond metabolic dysregulation and impact cognitive function and brain health, impairing tasks requiring cognitive control. Early experiments involving the long-term infusion of brain-derived neurotrophic factors(BDNF) in mice showed reductions in food intake, body weight, SAT and VAT, and serum triglyceride levels [59]. The authors attributed the partial mediation of BDNF and enhanced lipolysis to the activity of the corticotrophin releasing hormone-urocortin-corticotropin releasing hormone-receptor 2 (CRH-urocortin-CRH-R2) in the paraventricular nucleus and its connection to hypothalamic regions [59]. Interestingly the ablation of tanycytes, a kind of radial glial cells located in the arcuate nucleus and median eminence of the hypothalamus, induced the marked growths of VAT distribution and insulin insensitivity in male mice, without significant influence on either food intake or bodyweight [60]. Furthermore, by acting on adjacent adipocyte mesenchymal cells via the β2-adrenergic receptor, sympathetic nerve endings could modulate glia-derived neurotrophic factor expression and the innate lymphoid cell group 2 (ILC2) in gonadal fat, further regulating energy metabolism, insulin resistance and propensity to obesity [61]. This sympathetic aorticorenal circuit could also be regulated by the higher-order brain regions, including the paraventricular nucleus of the hypothalamus [61]. In addition, afferent signaling via the hepatic branch of the vagus nerve inhibited lard intake, induced VAT deposition, and modified plasma metabolite levels in a diabetic rat model [62]. In such a case, restoration of glucose energy homeostasis may be achieved via long-term central perfusion of adiponectin, which could decrease VAT mass and may increase energy consumption by activating hypothalamic leptin and insulin signaling pathways [63].

Effects of Visceral Adipose Tissue on the Brain

Visceral obesity may result from a neuroendocrine disorder associated with hypothalamic-pituitary axis(HPA) dysregulation and sympathetic nervous system activation. Initial experiments with the rats fed a high-fat diet showed brain mitochondrial dysfunction, increased brain apoptosis, impaired hippocampal plasticity, and decreased learning and memory ability, all of which were reversible via intraperitoneal fibroblast growth factor injection [64]. As a result, there has been a growing interest in analyzing the relationships among body composition, physical fitness, and brain function. Several brain imaging studies have shown an association between adiposity and decreased global brain volume [65], as well as a reduced volume of grey matter [66] (GM) and white matter [67] (WM). The accumulated evidence has demonstrated that obesity raises the risk of cognitive decline and dementia related to this topic, and the accumulation of VAT may hamper brain connectivity (Fig. 3). However, according to Cárdenas et al., VAT may enhance brain connectivity and probably affect overall brain health [38].

Recent research by Kang et al. highlighted the neuroprotective benefits of endurance exercise against high-fat diet-induced hippocampal neuroinflammation in rats. Compared with the sedentary controls, rats fed with a high-fat diet and subject to long-term treadmill exercise (TE) periods exhibited up-regulated expression of anti-apoptotic protein B-cell lymphoma-2 (bcl-2) in the hippocampus, decreased glial fibrillary acidic protein in the cerebral cortex and the hippocampal dentate gyrus. Resulting in the alleviation of proinflammatory cytokine production via inhibition of toll-like receptor 4 (TLR-4) signaling pathway [68]. Another murine model study involved supplementing a high-fat diet with unsaturated fatty acid Omega-3. Compared to the high-fat control group, rats fed the supplemented diet presented reduced VAT mass, attenuation of mitochondrial respiratory chain complex inhibition, partial neuroinflammatory and oxidative damage reversal in the brain [69]. In addition, VAT was shown to promote the migration of peripheral macrophages into the hypothalamus [70]. Whilst the permeability of the blood–brain barrier (BBB) was increased, tight junction protein expression was decreased in VAT-removed mice [71]. In rats undergoing transient middle cerebral artery occlusion (MCAO), those whose VAT was removed before surgery showed reductions in ischemic cerebral infarction volumes, BBB permeability and brain proinflammatory cytokine levels compared with those without VAT-removal, although the behavioral results were not significantly different [71].

Brain-VAT Axis and Alzheimer's Disease

Current studies regarding the correlation between VAT and AD are small in quantity and low in evidential strength, and prospective cohort studies with large sample sizes are insufficient. However, genetic analysis has shown that several potential pathogenic genetic risks in AD patients are closely related to lipid metabolism [72, 73]. Clinical studies also revealed that estradiol and VAT were associated with adults' brain networks and memory ability [15]. The accumulation of VAT was associated with mild cognitive impairment, especially non-amnestic mild cognitive impairment, among elderly Japanese women from a single community [74]. Among healthy elderly adults, VAT was negatively correlated with nonverbal memory and attention, while the increase of VAT was related to reduced hippocampal volume and an increase in ventricular volume. Participants with 25% more VAT also had the smallest hippocampal volume, even after adjusting for age, gender, hypertension and BMI [75]. In cognitively normal adults, a higher VAT level corresponded to memory decline and volume reductions in subcortical gray matter and hippocampal; moreover, the correlation gradually increased with age [76]. All the findings suggest a clear relationship between BVA and cognitive impairment.

It was found that VAT of APP/PS1 transgenic mice had a deposition of brain-derived Aβ by ELISA [77]. Besides, the peritoneal dialysis reduced the levels of Aβ in the brain and blood of APP/PS1 mice significantly and increased the level of Aβ in VAT markedly (about 3.2 times higher than the control group) [77]. These results suggest that VAT (e.g., the greater and lesser omentum) may reduce cerebral Aβ burden via the direct uptake of Aβ in the blood.

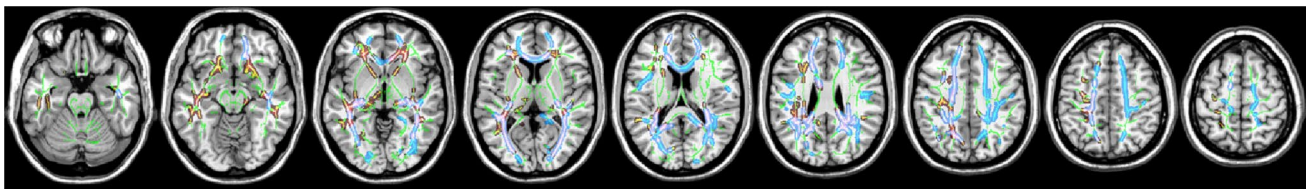

Fig. 3 White matter cluster showing both negative and positive correlation between visceral adipose tissue/total fat mass-respectively and fractional anisotropy. Significant areas are represented in blue for visceral adipose tissue (VAT) and red for total fat mass, indicating higher VAT was associated with lower fractional anisotropy [38]

VAT contains a variety of immune cells. For example, milky spots (MSs) are unique structures found in the greater omentum, consisting of leukocyte aggregations embedded among the adipocytes composed of VAT-related CD4+ regulatory T cells (Tregs), which can express chemokine receptors (CCR)-1 and CCR-2 [78, 79], both of which belong to a family of G-protein-coupled receptors with seven transmembrane domains. Notably, post mortem examination confirmed that the levels of CCR-1 in the hippocampus and cerebral cortex of AD patients were highly correlated with the degree of cognitive impairment, and CCR-1 was mainly distributed in the neurite where the senile plaques with higher Aβ42 levels were located [80]. These findings suggest that VAT may affect Aβ metabolism via Tregs-derived CCR. In addition, the changes in obese and aging VAT are partly driven by a chronic local inflammatory state, characterized by immune cells that typically adopt an inflammatory phenotype during metabolic disease, which may be age-associated VAT dysfunction in AD development (Table 1).

It has been reported that peripheral adipose tissue insulin resistance could change hippocampal synapses' lipid composition and function [89]. There are more natural killer T (NKT) cells in VAT (greater omentum) than other lymphoid tissues [90]. Mice lacking NKT cells gained body weight significantly after a high-fat diet, with significant increases of inflammatory macrophages in adipose tissue and induced insulin resistance [91, 92]. However, some animal experiments have shown that the insulin sensitivity of VAT can be increased by blocking IL-33 receptors that consume VAT-related Tregs [83]. As previously inferred, insulin influences Aβ clearance and tau phosphorylation affecting AD's pathogenesis through various ways (e.g., enhancing synaptic transmission and dendritic spine formation, promoting neurotransmitter metabolism, regulating lipid metabolism and neuroinflammation) [93]. All the above findings suggest that VAT has the potential of affecting Aβ metabolism and AD pathogenesis by regulating insulin resistance.

The resident macrophages (GATA6+) specific to VAT MSs can express retinal dehydrogenase (RD)-2 [94] at a high level, which is the critical enzyme for retinoic acid (RA) synthesis in vivo. Interestingly, animal experiments have found that RA could regulate the nuclear transcription factor (NF)-κB signaling pathway to reduce the expression of β amyloid cleaving enzyme-1 (BACE-1) [6]. Therefore, exogenous supplementation of RA receptors could improve learning and memory abilities, increase insulin-degrading enzyme (IDE) expression, reduce brain Aβ burden, and reduce the level of inflammatory factors in the hippocampus of AD

Table 1 Alterations in the visceral adipose tissue (VAT) immune cells during aging and AD development

Factor	Significant effects	Models	References
Innate immune cells			
Macrophages	↑ pro-inflammatory phenotype	Mouse	[81]
	↓ proportion of M2-like ATMs		
	↔ proportion of M1-like ATMs		
	↑ proportion of CD11c- CD206- ATMs		
	↑ expression of CCR2, IL-6, MCP-1, TNFα		
	↓ expression of PPARγ		
ILC-1	↔ proportion [H]	Human	[82]
ILC-2			
Eosinophils	↔ ↓ eosinophils in VAT [M]	Mouse	[83]
Adaptive immune cells			
B2	↑ mature B2 in VAT	Mouse	[84]
	↑ circulating IgG levels		
	↑ OcaB expression in VAT		
B1	↔ ↑ numbers of B1a and B1b		[84]
	↑ accumulation of 4-1BBL+ B1a cells]	Mouse and human	[85]
ABCs	↑ accumulation of aged adipose B cells (AABs)	Mouse	[86]
	↑ in females	Mouse	[87]
CD4+	↑ in VAT	Mouse	[81]
Treg	↑ in VAT	Mouse	[81]
	↑ enrichment in males	Mouse	[88]
CD8+	↑ in VAT [M]	Mouse	[83, 81]
	↑ activation and proinflammatory cytokine secretion in females	Mouse	[88]

↑indicates increased, ↓ indicates decreased, and ↔ indicates no change or no consensus

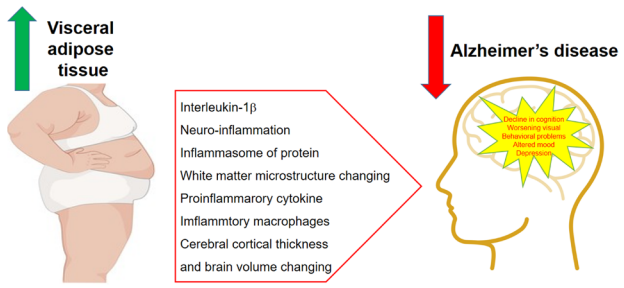

Fig. 4 Visceral adipose tissue may be associated with decreased cognitive functional and then eventually Alzheimer's disease

mice [95]. Thus, these findings suggest that VAT could reduce brain Aβ burden via RA synthesis by macrophages.

Recent studies have confirmed that MSs innervated with peripheral sympathetic fibers [95] can produce brain-derived neurotrophic factors (BDNF) and a variety of neurotrophins (NTs) [96], and able to maintain the precursors and promote the proliferation of macrophages dependent on gut microbiota [90, 97]. Notably, peripheral sympathetic excitability [98] and the gut microbiota diversity [99] changed at the early stage of AD. Thus, these findings indicate that VAT may affect the pathogenesis of AD through gut microbiota and vice versa.

The NACHT, LRR, and PYD domains-containing protein 3 (NLRP3) induced by VAT could impair the learning and memory abilities of mice through microglia activation mediated by interleukin (IL)-1 [100]. In addition, under hypoxia, mesenchymal stem cells in the peripheral adipose tissue were thought to enhance neuroinflammation in AD rats by altering the expression of Toll-like receptor (TLR)-2 and TLR-4 [89]. Thus, neuroinflammation may also mediate BVA and AD pathogenesis (Fig. 4).

Conclusion and Perspectives

As described earlier, peripheral energy metabolism and particularly lipid metabolism have been associated with AD and $A\beta_{1-42}$ deposition. In the clinical setting, total and visceral adiposity has been associated with the risk of dementia [101, 102]. VAT seems more prone to insulin resistance and low-grade inflammation related to obesity [103]. Notably, increased VAT is reported to increase the risk of AD progression in a seemingly more robust manner than general adiposity [104–106]. The overlap between brain signals and metabolic signals and VAT indicates crosstalk between brain and peripheral adipocytes; thus, the brain may play a crucial role in AD progression. Obesity-mediated signaling may evoke AD by secreting various signalling molecules, including cytokines, growth factors, immunomodulatory protein, complement and complement-related proteins, steroidogenic enzymes, leptin and adiponectin metabolic functions concerning energy homeostasis. Although VAT has emerged as a hot field of biomedical research, especially in immunity, inflammation, neurological disorders. However, the precise mechanisms promoting AD through VAT's secreted factors remain elusive. Further investigations in neuroimaging need to be conducted regarding interactions between VAT and the brain. This current study provides the groundwork for some potential mechanism of the axis and its influence on AD, providing some novel ideas for the strategies study of the pathogenesis, prevention and treatment of AD.

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Data Availability Enquiries about data availability should be directed to the authors.

Declarations

Conflict of interest The authors declare no conflicts of interest.

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