REVIEW

Alzheimer's disease and type 2 diabetes mellitus are distinct diseases with potential overlapping metabolic dysfunction upstream of observed cognitive decline

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Abstract

Alzheimer's disease (AD) and type 2 diabetes mellitus (T2DM) are highly prevalent aging-related diseases associated with significant morbidity and mortality. Some findings in human and animal models have linked T2DM to AD-type dementia. Despite epidemiological associations between the T2DM and cognitive impairment, the interrelational mechanisms are unclear. The preponderance of evidence in longitudinal studies with autopsy confirmation have indicated that vascular mechanisms, rather than classic AD-type pathologies, underlie the cognitive decline often seen in self-reported T2DM. T2DM is associated with cardiovascular and cerebrovascular disease (CVD), and is associated with increased risk of infarcts and small vessel disease in the brain and other organs. Neuropathological examinations of post-mortem brains demonstrated evidence of cerebrovascular disease and little to no correlation between T2DM and β-amyloid deposits or neurofibrillary tangles. Nevertheless, the mechanisms upstream of early AD-specific pathology remain obscure. In this regard, there may indeed be overlap between the pathologic mechanisms of T2DM/"metabolic syndrome," and AD. More specifically, cerebral insulin processing, glucose metabolism, mitochondrial function, and/or lipid metabolism could be altered in patients in early AD and directly influence symptomatology and/or neuropathology.

INTRODUCTION

The purpose of this article is to describe potential aspects of distinction and commonality between type 2 diabetes mellitus (T2DM) and Alzheimer's disease (AD). T2DM is a chronic metabolic disease characterized by hyperglycemia, insulin resistance (IR), and loss of pancreatic β-cell function (137). The majority of diabetes cases worldwide are T2DM. Between 1980 and 2014, the global prevalence was reported to have risen from 108 to 422 million (108). T2DM typically presents with increased thirst, fatigue, frequent urination, and delayed wound healing (137). Major complications of T2DM include retinopathy, kidney failure, heart disease, cerebrovascular disease (CVD), neuropathy, and limb amputation (137).

AD is a neurodegenerative disease with an insidious onset and progressive course (23). It is the most common form of dementia a contributing factor in approximately 70% of all dementia cases (23). The neuropathologic hallmarks of AD are extracellular β-amyloid peptide deposits, which are recognized as "amyloid plaques," and intracellular hyperphosphorylated tau deposition which forms neurofibrillary tangles (NFT) when occurring in nerve cells (11). The typical course of AD is characterized by impairment of various cognitive domains including memory, executive function, and often comorbid psychiatric changes, ultimately culminating in death (23). While speed of progression varies, the average life expectancy after diagnosis is approximately nine years (148,185).

In this review, discussion will initially focus on existing evidence that T2DM related cognitive decline is not associated with increased AD-type neuropathology, but is instead mediated by cerebrovascular pathology. Next, we address the emerging role of glucose, mitochondrial, and lipid metabolism abnormalities as upstream components of AD clinical and neuropathological features. The review will finish by discussing hypothesized causes of cognitive decline in T2DM patients, with or without comorbid AD.

T2DM ASSOCIATION WITH CLINICALLY AND PATHOLOGICALLY DEFINED AD

T2DM is associated with the clinical features of cognitive decline and AD-type dementia

Cognitive dysfunction is a relatively poorly understood complication of T2DM; see Figure 1. Multiple epidemiological studies link T2DM to cognitive decline and clinically diagnosed AD (27,117,119,145,187,198,208), however, not all studies demonstrate this association (see below). While there may be an association between T2DM, cognitive decline, and AD-type dementia, most of these studies lack correlation with neuropathology, ie, autopsy confirmation. A 2013 systemic review and meta-analysis evaluated published studies to better delineate the relationship between T2DM and AD (190). The meta-analysis identified 15 studies conducted between 1998 and 2012. Nine studies found a statistically significant correlation between T2DM and AD with risk estimates ranging from 0.83 to 2.45. Five of these studies evaluated the interaction between T2DM and Apolipoprotein E epsilon 4 allele (*APOE* ε4), and three of these five studies demonstrated significant association with odds ranging from 2.4 to 4.99. While there is a reported epidemiological risk association between T2DM and clinical AD, Vagelatos and Eslick noted that this association has a major confounder—cerebral infarcts (190). They found that infarcts are more common in patients with T2DM and were associated with the development of clinical AD. Based on neuropathological examination, the authors concluded: (1) cerebral infarcts are more common in T2DM than AD neuropathology is; (2) Patients with clinical dementia have both infarcts and AD-type neuropathology on post-mortem exam; (3) Cerebral infarcts reduce the number of AD-type lesions needed to cause clinical dementia but do not necessarily interact synergistically with AD-type pathology. Additionally, a recent review evaluated the association between T2DM and clinical AD diagnoses, and highlighted the complexity of the related scientific literature (94). The authors examined studies since 2015 and included a total of 10 articles. According to the authors, only 2 of 10 studies found that T2DM was independently related to cognitive decline in AD dementia.

From a neuropathological standpoint, T2DM cognitive decline is not associated with AD lesions

The large majority of autopsy (neuropathologic) studies report no association between T2DM and amyloid plaques or NFTs (2,10,13,35,67,76,109,110,126,140,176). A recent multi-center study evaluated 2365 autopsied patients with >1300 patients having available cognitive data (1). The authors concluded that T2DM status is associated with altered likelihood of being diagnosed during life with clinical "Probable AD"; yet, at autopsy, there was no association between T2DM and AD pathology. The authors utilized logistic regression modeling to evaluate the association between diabetes, CVD pathology, Braak NFT stage, and neuritic amyloid plaque score. The presence of T2DM was associated with increased odds of brain infarcts (OR = 1.57), specifically lacunae (OR = 1.71). T2DM with infarcts was associated with lower cognitive scores at end of life

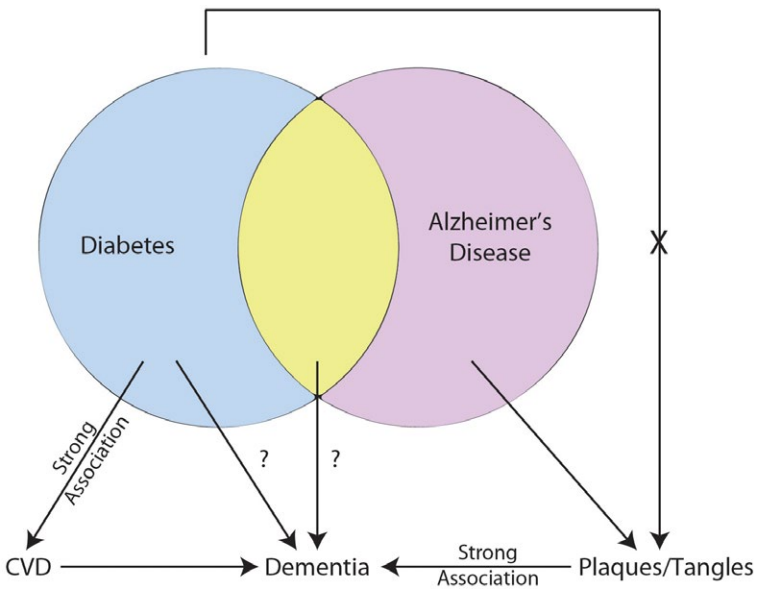

Figure 1. Relationship between T2DM and AD and cognitive decline. Diabetes, specifically T2DM, has a strong association with CVD that causes dementia through generation of subcortical and cortical infarcts. T2DM has been linked with dementia and AD, however, the mechanism(s) are uncertain. Amyloid plaques and neurofibrillary tangles have a strong association with cognitive status and to date, T2DM has not been associated with increased levels of plaques and tangles. *T2*DM, *type 2 diabetes mellitus;* CVD, *cerebrovascular disease;* AD, *Alzheimer's Disease.*

relative to T2DM without infarcts. Studies that have arrived at the conclusion that T2DM is associated with AD pathological hallmarks are few in number and characterized by subgrouping to determine a "positive" association. Overall, in dozens of papers, the null hypothesis—T2DM is not associated with AD-type pathology—has been tested repeatedly, and has been strongly supported.

Cerebrovascular disease contributes to cognitive decline in T2DM

T2DM is a known risk factor for CVD (81). T2DM is associated with acute cerebral infarcts and increased stroke/brain infarction risk (44,71). Many clinical–radiological studies report that cerebral infarcts are significantly associated with increased odds of developing dementia (38,189,193). This association may help account for the reported epidemiological association between T2DM and dementia (181).

Multiple mechanisms underlie CVD in T2DM. In terms of large-vessel pathologies, vascular complications of T2DM are mediated at least partly through chronic hyperglycemia and production of reactive oxygen species (ROS) that apparently damage the vessel endothelium, and lead to atherosclerosis. Insult to vascular endothelium activates thrombotic cascades and recruits T-cells, macrophages, and mononuclear leukocytes, impairing vascular integrity (211). From autopsy studies, T2DM is associated with cortical and subcortical atherosclerosis, and intracranial vascular stenosis is more common in those with T2DM than those without (8,85,111). Therefore, it is likely that T2DM association with cognitive decline is partly mediated through accelerated atherosclerosis in large blood vessels.

While microinfarcts are invisible to most radiological and gross examination techniques (by definition), they are well described in neuropathological literature and are often detected during post-mortem microscopic examination. The location of microinfarcts (ie, cortical vs subcortical) correlates with disease subtypes. Cortical microinfarcts have been associated with cerebral amyloid angiopathy (CAA), subcortical microinfarcts with hypertensive encephalopathy, and periventricular microinfarcts with normal pressure hydrocephalus (3,6,37). Microinfarcts are often located in subcortical areas in diabetics; however, cortical infarcts and lacunes have also been described (1,10,146,176). T2DM-associated microinfarcts often coexist with AD neuropathological changes, however, the number of microinfarcts is not necessarily related to the severity of AD neuropathology (9,129,165). The typical reported microinfarct size is 0.2 mm, however, they range from 0.2 to 2.9 mm (9,136). Several prospective cohort autopsy-based studies evaluated the associative effect(s) of microinfarcts on cognition (9,19,60,61,120,129,165,177,180,189,201). According to these studies, microinfarcts are present in 18%–40% of persons, while four studies found that the prevalence of microinfarcts was higher in those with dementia than those without dementia (9,165,177,180). These studies concluded that microinfarcts are independent predictors of dementia.

CLASSIC HALLMARKS OF AD: CORRELATION WITH COGNITIVE STATUS AND THE QUESTION OF "UPSTREAM" FACTORS

Before focusing in on the possible overlapping pathogenetic mechanisms of AD and T2DM, an important concept to address is the AD-specific lesions themselves—β-amyloid plaques and NFTs. There has been some controversy about whether β-amyloid and NFTs are deleterious, whether they should be considered "disease-defining," and/or whether these lesions are specifically associated with cognitive impairment (25,125,173,175). Numerous factors have contributed to this confusion, including the strong influence of impactful "mixed" and non-AD pathologies, some of which (eg, TDP-43 pathology) were only relatively recently discovered (128), and others of which (eg, small vessel pathologies) have only recently been appreciated to have an association with cognitive impairment independent of other brain lesions (74,78,97). There also are notable biases in terms of the research volunteers that are drawn from dementia clinics (124,164), and limitations associated with studying elderly individuals without carefully documented antemortem cognitive status. Furthermore, the dichotomous approach of "dementia yes/no" (and even the corresponding dichotomous assessment of pathologies) is prone to bias as the results are dependent on the application of imperfect and arbitrary diagnostic thresholds. Over the past several decades, new research contributions have come from large community-based autopsy series with a new standard of cognitive assessments and longitudinal follow-up; from biomarker (neuroimaging and body fluid) studies in clinical series; and, from genetic studies with large sample sizes and carefully assessed phenotypes. These approaches have led to an improved appreciation of, and insights into, the heterogeneity and complexity of what occurs in the aged human brain. The direct "toxicity" of β-amyloid and NFTs still remains to be definitively proven, and autopsy evaluation is intrinsically cross sectional. However, to summarize recent studies: an evolving scientific literature has provided strong support for the hypothesis that β-amyloid and NFTs are a part of a devastating organic disease within the complex milieu of the aged human brain, with strong adverse impact on brain function (125). For these reasons, these classic hallmarks still constitute the "gold standard" for disease instantiation and severity.

Even if one accepts the concept that β-amyloid and NFTs "define" AD, there remain critically important questions: what occurs upstream of plaques and tangles? Can a person have the AD disease "phenotype" even before the pathologies are present? Are there common, clinically impactful features of AD that are parallel and separate from plaques and tangles? These questions get to the critical issues of causative "upstream" factors. Clearly, there is a strong genetic component to AD risk, involving *APOE* and other genes (163), but the exact genotype/phenotype mechanisms are still incompletely understood. To date,

the association(s) between specific environmental factors and AD risk is even more controversial. Developing study designs to address those uncertainties in human studies is challenging because any influence that negatively impacts cognition increases the chance of diagnosis of AD-type dementia, whether or not AD pathologies are the factors that underlie the symptoms. Here, we attempt to explore how the upstream biochemical pathways that contribute to AD-type dementia may overlap with T2DM, with the important caveat that classical AD pathologic hallmarks may be irrelevant to some of these pathways.

GLUCOSE AND METABOLIC DYSREGULATION IN AD

While there is a wealth of information about AD pathophysiology, the initial events upstream of NFT formation and β-amyloid deposition are still unclear. Metabolic dysregulation has been shown to be a possible contributory factor for AD neuropathology. Alterations in cerebral glucose metabolism, mitochondrial function, and lipid metabolism may be upstream triggers for NFT and β-amyloid deposition. The next section will focus on these topics and describe the links between metabolism and AD.

AD and glucose metabolism

Studies that used fluorodeoxyglucose (FDG) positron emission tomography (PET) imaging has been interpreted to indicate likely glucose metabolism abnormalities, and/or synapse loss, in patients at risk of AD, well before symptom onset. This FDG PET neuroimaging modality has indicated that cerebral glucose metabolism may be impaired early in the adult life of persons at genetic risk for developing AD. While the exact mechanism(s) underlying this phenomenon are currently unknown, deficits in FDG PET tracer uptake begin decades before clinical onset of symptoms and—perhaps more importantly—well before the age range where abundant plaques and tangles are observed (5,155,160,162).

There has been some controversy about the pathophysiologic implications of FDG PET studies. Since the radiolabeled FDG is taken up by cells but not metabolized, its uptake is largely dependent on its partitioning in the blood stream (ie, on blood flow), and hence it does not necessarily provide direct information on glucose metabolism per se, except to the extent that that affects blood flow. This neuroimaging modality also does not provide direct information on synapse loss. There are additional technical questions related to the FDG PET modality, since the observed phenomena in individuals at risk for AD may be attenuated by partial volume correction (73,206). Knopman et al. addressed this concern by increasing the power of their study and utilizing a larger patient cohort. His group found that there was a modest age-related reduction in cerebral glucose metabolism, and the presence of at least one *APOE* ε4 allele was associated with lower glucose metabolism measured in the posterior cingulate, precuneus, and/or lateral parietal regions (87). These results are similar to those found by Reiman et al. as indicated above (156).

Complementing the studies of preclinical disease, other studies have provided additional evidence that were interpreted to indicate that persons with AD-type dementia have substantially reduced rates of cerebral glucose metabolism in posterior cingulate, parietal, temporal, and prefrontal cortices (112–114,174). This phenomenon was demonstrated in studies conducted by Herholz et al. and Loessner et al. and was later confirmed by others (68,130,155,156). Additional studies found that levels of glucose transporters in brain microvessels, frontal cortex, hippocampus, caudate nucleus, parietal, and temporal lobes were reduced in AD patients when compared with controls on autopsy studies (79,170). A recent study using the Baltimore Longitudinal Study of Aging autopsy cohort provided further evidence supporting the hypothesis that glucose metabolism is affected early in AD (5). The authors found that higher brain tissue glucose concentrations (neural insulin resistance) and lower GLUT3 levels were associated with severity of AD neuropathology and AD clinical presentation. From these studies, the possibility emerges that glucose dysmetabolism is somehow correlated with AD-type pathologies per se, either as a causative factor or otherwise as part of the syndrome.

Mitochondrial dysregulation in AD

Alterations of mitochondria in AD were reported as early as the 1960s (52); See Figure 2. Subsequently, studies have reported that mitochondrial structure was altered, oxygen consumption reduced, and mitochondrial-localized enzyme activities were affected in AD (51,53,57,77,142,202). Furthermore, mitochondrial mass, size, and copy number were shown to be reduced in AD brains, and this was linked to mitochondrial interaction with β-amyloid peptide deposits (12,40). Cardoso et al. demonstrated that ρ0 cells were protected from β-amyloid peptide exposure, supporting the hypothesis that β-amyloid peptide is detrimental to mitochondrial function (24). Others have shown that β-amyloid peptide is capable of interacting with β-amyloid peptide-binding alcohol dehydrogenase (ABAD) and cyclophillin D (42,103). Interactions of β-amyloid peptide with ABAD deform the enzyme and prevents its interaction with nicotinamide adenine dinucleotide (NAD). When β-amyloid peptide interacts with cyclophilin D, this causes increased mitochondrial membrane permeability. The detrimental effects of β-amyloid peptide on the mitochondria may cause a compensatory response by increasing mitochondrial fission. The actions of mitochondrial-shaping proteins (OPA1, MFN1, MFN2, DRP1, FIS1) play a vital role in shaping and modifying mitochondrial structure during fusion and fission (210). Specifically, mediators of mitochondrial fusion (OPA1, MNF1, and MFN2) were reduced in degenerating neurons and mediators of mitochondrial fission (FIS1, DRP1) were increased (106,195–197). While these studies are important for elucidating the effect

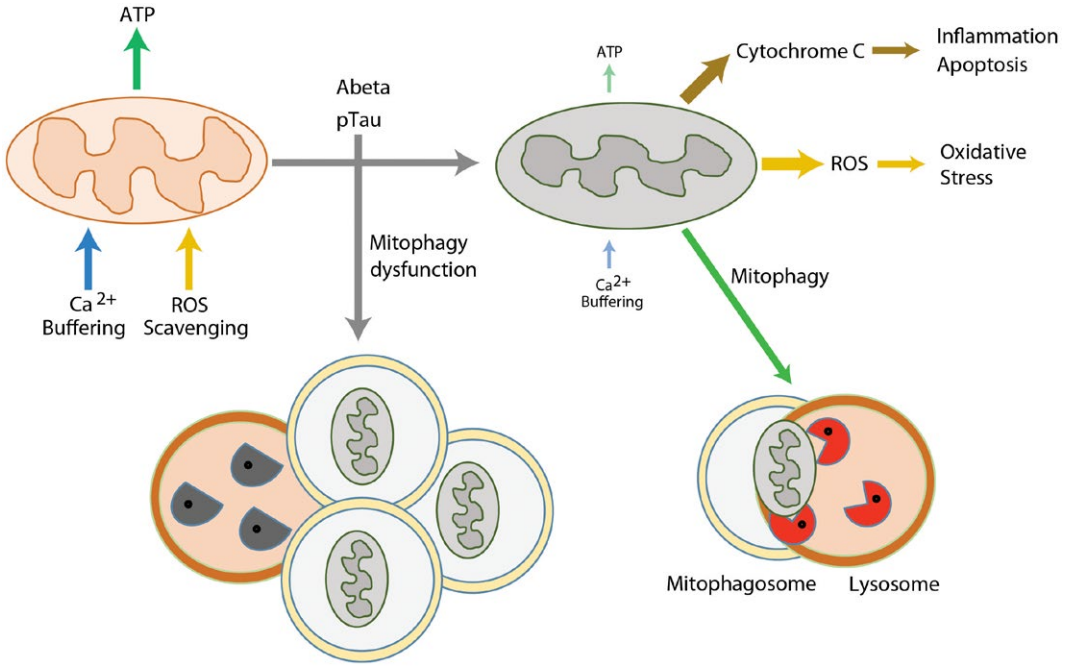

Figure 2. Mitochondrial autophagy in AD. Mitochondrial dysfunction could play key roles in AD pathogenesis. Damaged mitochondria not only compromise the production of cellular energy and lose the capacity for Ca2+ buffering, they also release harmful ROS and cytochrome C resulted in activation of destructive pathways. Mitophagy is a mechanism for removing aged or damaged mitochondria, however, this mechanism is impaired in AD. Functionally defective mitochondria and insufficient clearance of the damaged organelles and macromolecules may synergistically intensify the detrimental pathways of AD. ATP, *adenosine triphosphosphate;* ROS, *reactive oxygen species*.

of β-amyloid peptide on mitochondrial metabolism and dynamics, they do not necessarily imply a reciprocal effect—they do not prove that mitochondrial dysfunction promotes β-amyloid peptide deposition.

The potential for mitochondrial metabolism to affect β-amyloid peptide production was demonstrated when cultured SH-SY5Y cell lines expressed AD- and wt-mtDNA (83). These AD-mtDNA "cybrid" cell preparations generated increased intracellular and extracellular levels of β-amyloid peptide relative to controls. This result suggests that AD-mtDNA causes functional changes which may potentiate Aβ plaque formation. Additionally, another study found that when COS cells undergo glucose deprivation, levels of α-secretase-derived APP product increase (56). This alteration is perhaps relevant because AD patients have reduced rates of cerebral glucose metabolism in posterior cingulate, parietal, temporal, and prefrontal cortices (112–114,174), as stated above. These data may indicate how reduced glucose metabolism is linked to AD phenotype though dysregulation of mitochondria, which, as indicated in the prior paragraph, may be a self-propagating cycle with increasing β-amyloid peptide production and worsening mitochondrial dysfunction.

Mitochondrial autophagy in AD

Both neurodegeneration and diabetes are associated with oxidative stress and inflammatory conditions in the CNS that may be mediated partly by mitochondria dysfunction. Dysfunctional mitochondria may be compromised in the production of cellular energy and lose the capacity for buffering intracellular Ca2+, and they also can release harmful ROS. Uncontrolled oxidative stress triggers the discharge of cytochrome C and activates the pro-death apoptotic cascade (115). Increased oxidative stress also results from an imbalance in production of ROS and cells' ROS scavenging systems from defective mitochondria. The inhibition of the clearance of damaged mitochondria, accompanied by the concurrent oxidative stress and inflammatory condition, may synergistically affect the health of neurons in AD and other conditions.

In healthy cells, mitochondria are turned over—damaged mitochondria are selectively identified, ubiquitinated, and degraded via an autophagy pathway termed "mitophagy." This pathway is particularly important in long-lived (post-mitotic) cells such as neurons. Mitophagy selectively sequesters abnormal mitochondria to form autophagosomes and subsequently deliver the cargo to lysosomes for degradation. Mitophagy plays a key role in mitochondrial quality control and is an essential mechanism in tissue maintenance and cellular homeostasis, and the literature that pertains to autophagic dysregulation in AD may also be germane to mitophagy. Dysregulation of autophagy has been associated with AD pathogenesis. Nixon et al. reported the accumulation of immature autophagic vacuoles (AVs) in dystrophic neurites of AD brains (133). Later reports conflicted on how autophagy flux was affected in AD and what specific stages were

dysregulated in human brains (134). Recently, Bordi et al. assessed the autophagy pathways and autophagy flux by performing microarray and immunochemical analyses of hippocampal CA1 neurons in post-mortem tissue samples from AD subjects at different stages of disease (18). This study revealed that autophagy is upregulated and lysosomal biogenesis is increased in the early stage of AD (~10 years before clinical AD diagnosis). Additionally, autophagic flux was obstructed due to the impairment in the clearance of autophagic substrates. These studies indicate that the regulation of mitophagy plays important roles in mitochondrial homeostasis, however, how those molecular pathways interact with β-amyloid and pTau remains mostly unknown.

Lipid metabolism dysfunction in AD

Lipid dysmetabolism is a component of the metabolic syndrome that occurs in many T2D patients, and multiple lines of evidence have implicated perturbations in lipid biochemistry in AD. The brain is one of the most lipid-enriched organs and is partly composed of a variety of lipids such as glycerophospholipids (GPs), sphingolipids, and cholesterol (17). The involvement of lipid metabolism in the pathogenesis of AD was suspected when brains of AD patients were examined post-mortem and found to contain "adipose inclusions" or "lipid granules" (48). Alois Alzheimer originally described this finding in his milestone study of the brain of Auguste Deter (4).

After the discovery that *APOE* ε4 allele is the strongest genetic risk factor for late onset AD, interest in lipid metabolism gained added momentum (15,32). One copy of the *APOE* ε4 allele increases the risk of developing AD by 2–3 fold, but two copies of *APOE* ε4 alleles increase the risk to ~12 fold (14,158). The APOE protein regulates cholesterol metabolism and mediates uptake of lipoprotein particles via low-density lipoprotein (LDL) receptor related protein (LRP) (22). The APOE E4 isoform at least somewhat selectively binds β-amyloid peptide, modulating its aggregation and clearance (22). The *ε4* allele is associated with higher cholesterol levels (47,99).

Studies demonstrated that cholesterol modulates β-amyloid peptide levels by affecting secretase function (100). Additionally, the involvement of cholesterol has been implicated in pathogenesis of AD in epidemiological studies (22,84). When membrane cholesterol levels are decreased, the activities of β-secretase (BACE1) and γ-secretase are reduced, leading to lower β-amyloid production (46,169,194,207) (Figure 3A). In addition, the inhibition of cholesterol synthesis enzymes (3-hydroxy-3-methylglutaryl-CoA-reductase and 7-dehydro-cholesterol-reductase) is able to reduce intracellular and extracellular β-amyloid levels (46,153,169).

Under normal conditions, free intracellular cholesterol is esterified to form cholesteryl-esters by sterol

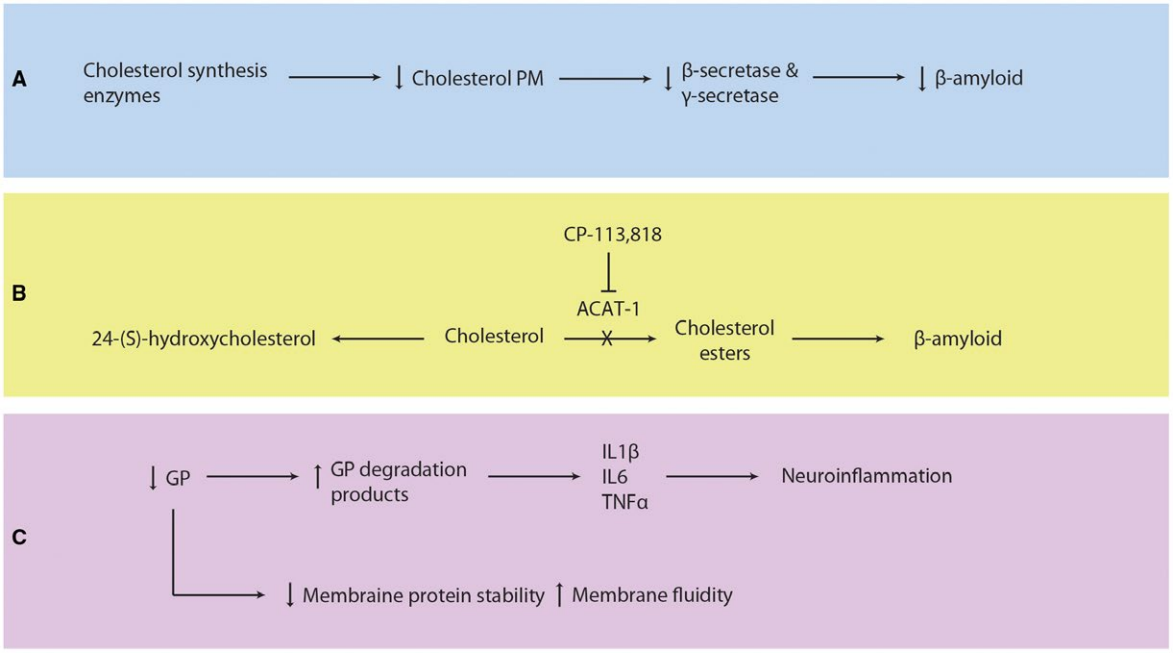

Figure 3. Lipid metabolism dysfunction in Alzheimer's Disease. A. Inhibition of cholesterol synthesis enzymes decreases plasma membrane cholesterol levels, β-secretase and γ-secretase activities, and β-amyloid production. B. Cholesterol can be converted to 24-(S)-hydroxycholesterol or cholesteryl ester by CYP461A or ACAT-1, respectively. Increased ACAT-1 activity causes production of cholesteryl esters and increased β-amyloid levels. Inhibition of ACAT-1 by CP-113,818 reduces β-amyloid. C. Glycerophospholipids (GP) stabilize plasma membrane proteins such as ion channels and affect plasma membrane fluidity. Lower levels of GP are found in AD as evidenced by increased levels of GP degradation products, which are proinflammatory. Recruited astrocytes and microglia release IL1β, IL6, and TNFα and cause subsequent neuroinflammation. CYP*461A, 24-hydroxylase;* ACAT-*1, sterol O-acyltransferase 1;* GP *glycerophospholipids;* AD*, Alzheimer's Disease;* IL*1*β*, interleukin-1*β*;* IL*6, interleukin-6;* TNFα *tumor necrosis factor alpha.*

O-acyltransferase 1 (ACAT1) (Figure 3B). In cultured cells, it was demonstrated that when cholesteryl ester concentration was increased, there was a proportional rise in β-amyloid levels (147). When ACAT1 activity was inhibited, there was a significant reduction in β-amyloid peptide (72). Genetic deletion of *ACAT1* has been shown to reduce β-amyloid peptide and cognitive impairment in AD mouse models, supporting its role in AD pathology (21). In addition to formation of cholesteryl-esters by ACAT1, cholesterol can be metabolized by the brain-specific enzyme, 24-hydroxylase (CYP46A1), into 24-(S)-hydroxycholesterol (cerebrosterol) that can cross the blood–brain barrier (21). When ACAT1 activity is reduced (either genetically deleted or antagonized using a small molecular inhibitor), levels of 24-(S)-hydroxycholesterol are increased and β-amyloid pathology in the brain is decreased (21). Studies have found that persons with early stage AD have higher levels of 24-(S)-hydroxycholesterol in peripheral circulation and CSF relative to normal controls (88,104). This increase in 24-(S)-hydroxycholesterol suggests that cholesterol metabolism is affected early in AD and 24-(S)-hydroxycholesterol is produced as a byproduct or as part of a compensatory mechanism. Furthermore, peripheral levels of 24-(S)-hydroxycholesterol could be used as a blood biomarker for detection of early AD (82,104). Collectively, these studies suggest that the balance between free cholesterol and cholesteryl-esters can alter amyloidogenesis in AD.

Lipids other than cholesterol—GPs and sphingolipids—have been implicated in AD pathogenesis. Normally, GPs interact and bind to membrane proteins and ion channels, helping them maintain correct position in the plasma membrane (139) (Figure 3C). When GPs are reduced in cell plasma membranes, the membranes become more fluid and permeable (69). Interestingly, lower levels of GPs have been reported in AD (64,143). Further, higher levels of GP degradation products were found in the brains of AD patients (121). GP degradation products are pro-inflammatory, and may act as signals to activate astrocytes and microglia (45). This leads to additional release of interleukin-1β, interleukin-6, and TNFα, producing a cascade of additional neuroinflammation (64,143), which can result in local tissue damage and neuron cell death.

Sphingolipids make up the largest structural lipid component of CNS membranes and are highly expressed in the myelin sheath. There are different subtypes of sphinolipids, for example, ceramides are the simplest, while sphingomyelins and glycosphingolipids (eg, cerebrosides, sulfatides, and gangliosides) are more complex (101). Sulfatides play important roles in the nervous system and are abundant in the myelin sheath and in oligodendrocytes (183). In AD brains, sulfatide levels are reduced and when sulfatides are degraded, ceramide byproducts are formed (65). Sulfatides were shown to be depleted up to 93% in gray matter and up to 58% in white matter of AD brains, while other major classes of lipids were not affected (65). Also, ceramide levels were increased more than three fold in AD brains (36,65,66). Low levels of sulfatides are specific for AD and do not occur in patients with Parkinson's disease, Lewy body dementia, frontotemporal dementia, or multiple sclerosis (29,101). The exact mechanism of sulfatide deficiency or how the loss of sulfatides contributes to AD neuropathology is currently unknown; however, it has been suggested that it is unlikely to be mediated directly by β-amyloid peptide accumulation (29). A later study by the same group was inconclusive in elucidating a mechanism of sulfatide deficiency in AD (28); however, they proposed several explanations for the relationship between sulfatides and AD pathology. It was suggested that APOE mediates sulfatide depletion, sulfatides enhance β-amyloid binding to APOE, and sulfatides enhance uptake of β-amyloid peptides into the cell, leading to abnormal β-amyloid accumulation in lysosomes (63). We conclude from the prior literature on lipid neurochemistry in AD that the findings are complex and, as far as we know, the various experimental "story lines" have not been reconciled together nor tied directly to T2DM. However, there appears to be compelling data in support of the hypothesis that changes in lipid biochemistry occurs early in the course of AD pathogenesis.

T2DM-RELATED PATHWAYS THAT MAY AFFECT THE BRAIN

While CVD is a likely pathologic substrate of cognitive decline in T2DM, evidence exists for other mechanisms that may contribute in parallel or separately. The following section will discuss the impact of hyperglycemia, insulin resistance, inflammation, hypercorticolism, and amyloid accumulation as non-mutually exclusive mechanisms that cause or exacerbate cognitive decline in T2DM and AD.

Hyperglycemia and cognitive decline

The relationship between blood glucose levels and degree of cognitive dysfunction in T2DM patients has been extensively evaluated. Yaffe and colleagues studied a population of 1,983 women and found that participants with HbA1c levels >7.0% had a four-fold increase in probability of developing cognitive impairment (203). Intriguingly, this study only included "non-diabetic" women. These findings again support the hypothesis that glucose dysregulation is associated with cognitive impairment. Other studies also found an inverse relationship between HbA1c and working memory, executive function, learning, and/or psychomotor performance in T2DM patients (123,141,152,159). While impaired glucose control in the context of T2DM is associated with declining cognitive function, studies have found that impaired glucose tolerance without a formal diagnosis of diabetes ("pre-diabetes") is also a risk factor for cognitive dysfunction (35,80,90,191). Despite the strong evidence that supports the link between impaired glucose regulation with cognitive dysfunction, it is important to note that not all studies to date demonstrate this relationship (49,89,98,167).

Many of the prior studies that directly connect hyperglycemia with AD-relevant pathways were performed in

animal models. The direct relevance of these studies to the human conditions (T2DM and AD) is not firmly established. In some of these studies, hyperglycemia causes tissue damage and alters cellular function through increasing polyol pathway activation, which causes the formation of advanced glycation end products (AGEs), and protein kinase C (PKC) activation (16,20,86,188). For example, streptozotocin-treated rats were found to have increased sorbitol in cranial nerves, cerebrum, and retina. When animals were subsequently treated with tolerstat, an aldose reductase inhibitor, the accumulation was reduced (178). Another study found that when sorbinil, an aldose reductase inhibitor, was given to streptozotocin-treated rats, it reduced brain levels of sorbitol and corrected cognitive dysfunction. However, more information is needed to definitively state whether this pathway contributes to cognitive decline in humans with T2DM.

Another potential mechanism of cognitive decline due to hyperglycemia is the formation of AGEs and receptors for AGE (RAGEs). While there may be an association between AGEs, RAGEs, and cognitive decline in T2DM, currently there is not enough evidence to support this mechanism. While animal studies demonstrated increased RAGE expression and damage to white matter and myelin, human studies on this topic produced conflicting results (188,205). Several studies using human tissue demonstrated that patients with diabetes and AD have increased N-carboxymethyllysine (a type of AGE) staining on postmortem analysis (58). However, another study failed to replicate this association (67). Little firm evidence exists for the role of PKC in relation to T2DM and cognitive decline. While some animal studies have found that PKC is highly expressed and has increased activity in diabetic animal models, other studies did not support this data (151,168).

Some animal studies have elucidated molecular changes that occur in hippocampal neurons in response to hyperglycemia. For example, in streptozotocin-induced diabetic rats, the NMDA currents and NMDA protein levels were reduced in the hippocampus (54). Furthermore, CA3 neurons underwent remodeling in response to hyperglycemia. This remodeling includes apical dendrite retraction and simplification. There is also an associated decrease in presynaptic vesicles (105). Another study using the streptozotocin-induced diabetic model found evidence of apoptosis in hippocampal neurons. Cognitive deficits were associated with DNA fragmentation, positive TUNEL staining, and increased caspase-3 levels (95).

Insulin resistance, inflammation, hypercorticolism, and amyloid accumulation

There is a growing body of evidence linking IR, a component of T2DM, to the pathogenesis of AD (116,118,127). Several studies have reported that the incidence of clinically diagnosed AD is 1.2–1.7-fold greater in patients with T2DM and IR (34,35,90,93,138,140,203). Also, IR is reported to occur more frequently in patients with AD (76). IR has been found to impair central cholinergic activity, and diabetic animal models have reduced production and release of acetylcholine (ACh) (199,200). Remarkably, the administration of intranasal insulin rescued memory deficits in a subset of research volunteers with clinical AD (7,33,135,154).

Exactly how IR exerts its effects on cognitive function is not clear. However, several mechanisms have been proposed to help explain how IR contributes to cognitive decline in T2DM. The first mechanism is based on inflammatory markers, such as C-reactive protein (CRP) and IL-6 that are increased in T2DM and metabolic syndrome and are associated with reduced cognitive function (26,102). Further, inflammatory reactants and proinflammatory cytokines have been found in CSF and β-amyloid plaques (43,62,75). A study conducted by Singh-Manoux et al. evaluated IL-6 and CRP in 5,217 people and found that elevated IL-6 in midlife can predict subsequent cognitive decline (171). The authors concluded that pro-inflammatory molecules can influence cognition by inducing a prothrombic state. For example, inflammatory signals can trigger local thrombotic vascular events leading to brain infarction. Other studies have also demonstrated that persons with metabolic syndrome and elevated inflammatory markers have impaired cognitive function (107,203).

Another hypothesized mechanism by which IR could contribute to cognitive impairment in T2DM involves dysregulation of the HPA axis, leading to higher cortisol levels. Humans and animals with T2DM have increased serum cortisol levels (92,157,186) and several studies found that high serum cortisol is associated with cognitive decline and dementia, an effect independent of *APOE* genotype. There is experimental evidence supporting the detrimental effects of cortisol on cognitive performance (131,132). For instance, healthy individuals treated with dexamethasone, corticosterone, or hydrocortisone performed worse on memory tests, and, additionally, patients with active Cushing's disease (and thus high blood cortisol levels) also demonstrate decreased performance on working memory, reasoning, and attention tests relative to controls (50,150,184). However, not all studies agree on the association between increased levels of cortisol and cognitive impairment (30,91,166).

CONCLUSION

T2DM is a risk factor for cognitive decline, although the exact mechanism(s) mediating this relationship are unclear. Multiple studies have found that CVD is more common in patients with T2DM than in non-diabetics. CVD is a rather broad term, encompassing a combination of macroscopic and microscopic vascular lesions, which together contribute to cognitive impairment by impairing blood flow.

Alterations in glucose metabolism, mitochondrial metabolic dysfunction, mitochondrial autophagy, and alterations in lipid metabolism are all additional potential contributing factors to cognitive decline in T2DM. The mechanisms

and processes that are occurring in aged brains still remain imperfectly characterized, and may involve the polyol pathway, formation of AGEs, PKC activation, IR, inflammation, and dysregulation of HPA axis.

Upstream events responsible for eventual β-amyloid peptide deposition and NFT formation are also still not well understood. However, recent literature has found that metabolic dysregulation is linked with clinical and pathological AD. Abnormalities in cerebral glucose metabolism, mitochondrial function, and lipid metabolism have been reported in persons at risk for developing AD. Deeper understanding of how metabolic perturbations contribute to AD-type pathology may help in developing new preventative and/or treatment strategies.

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