Insulin resistance, dyslipidemia, and apolipoprotein E interactions as mechanisms in cognitive impairment and Alzheimer's disease

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Abstract

An increased risk for Alzheimer's disease is associated with dyslipidemia and insulin resistance. A separate literature shows the genetic risk for developing Alzheimer's disease is strongly correlated to the presence of the E4 isoform of the apolipoprotein E carrier protein. Understanding how apolipoprotein E carrier protein, lipids, amyloid β peptides, glucose, central nervous system insulin, and peripheral insulin interact with one another in Alzheimer's disease is an area of increasing interest. Here, we will review the evidence relating apolipoprotein E carrier protein, lipids, and insulin action to Alzheimer's disease and Aβ peptides and then propose mechanisms as to how these factors might interact with one another to impair cognition and promote Alzheimer's disease.

Keywords: Alzheimer's disease, apolipoprotein E, dyslipidemia, insulin resistance, cognition

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Introduction

The number of individuals with Alzheimer's disease (AD) is increasing steadily and will continue to increase as the number of Americans older than 65 doubles by 2050.[1] Age is a risk factor for developing AD, and AD is the most common of the age-related neurodegenerative diseases.[1] Several modifiable risk factors contribute to the possibility of developing AD. Diabetes, physical inactivity, and obesity are among the risk factors that share pathologic features including dyslipidemia and insulin resistance. In addition, the strongest genetic risk factor for sporadic AD, the presence of the E4 isoform of the lipoprotein carrier APOE, alters lipid physiology in the brain and periphery.[2] As a result, several diet- and metabolism-based treatments are being examined in AD patients. As the results of these studies become available, the interactions among apolipoprotein E (APOE), lipids, amyloid β (Aβ) peptides, glucose, central nervous system (CNS) insulin, and peripheral insulin seem increasingly important. In this review, we evaluate the various literatures from these disparate fields, highlighting the relations of APOE, dyslipidemia, and insulin resistance to AD. We then discuss proposed mechanisms as to how these factors might interact with one another to impair cognition and lead to the development of AD.

Alzheimer's disease

AD is a devastating disease that involves loss of memory and cognition and leads to a decline in quality of life.[3] Post-mortem autopsies reveal neuronal loss, Aβ plaques, neurofibrillary tangles, and atrophy in brain regions important in memory and processing, including the hippocampus, amygdala, and frontal cortex.[4,5] Indeed, genetic mutations in genes whose proteins are involved in the processing of amyloid precursor protein (APP) to Aβ peptides, such as those for presenilin-1 and presenilin-2, are pre-disposing risk factors for AD.[6] However, these mutations are involved only in early onset familial AD (ages 30–60) and account for less than 5% of the total AD cases. This leaves more than 95% of AD cases attributable to gene-environment interactions of risk factors such as E4 carrier status, dyslipidemia, and insulin resistance. In the next sections, we will discuss how these factors may contribute to AD pathogenesis.

Apolipoprotein E

In the peripheral circulation, APOE aids in shuttling lipids between various lipoproteins. In the brain, APOE is the most abundant lipoprotein and a crucial regulator of lipid metabolism.[7] As such, CNS APOE has several important functions. APOE mediates transport of lipoprotein particles between various cell types in the brain via carriers such as the low-density lipoprotein receptor related protein-1 (LRP-1). At the blood–brain barrier (BBB), LRP-1 is involved in Aβ clearance from brain and the decrease in BBB LRP-1 levels that occurs in AD has been postulated as one reason why Aβ builds up in the brain (Figure 1(b)).[8–10] This protein

is primarily produced by astrocytes[11] and is responsible for neuronal maintenance and repair. APOE is also important in repairing the BBB after injury,[12–14] and dysfunction of the BBB has been considered to be both a cause and a consequence of AD.[15]

In humans, there are three alleles of *APOE*: E2, E3, and E4. Compared to carriage of the E3 allele, carriage of one E4 allele increases the risk of AD by 3-43–4 fold, and two alleles by up to 20-fold, making it the most potent genetic risk factor for developing sporadic AD.[2,16] The structure of the APOE4 protein has several important functional consequences. For example, the APOE4 protein is folded into a more compact structure compared to the other APOE isoforms, leading to a decreased ability to bind lipids and a higher likelihood of cleavage into neurotoxic fragments.[17] Perivascular removal of Aβ is hindered with the expression of E4, which was shown in many *in vitro* studies as well as in mice expressing human E4.[10,18] This decreased drainage, in turn, leads to decreased clearance of Aβ peptides and increased amyloid plaques, as well as other pathophysiologic features such as alterations in the neurovascular unit and BBB function.[12,14,19–22]

APOE is involved in preserving the integrity of the BBB. An *in vitro* model of the BBB was leakier when the brain endothelial cells were derived from *APOE4* knock-in mice.[23] Furthermore, *APOE4* knock-in mice had higher levels of BBB breakdown in response to injury, via upregulation of the proinflammatory cyclophilin A pathway in pericytes.[12] The role that APOE plays in transport and clearance of molecules also depends on the APOE isoform, and these transport differences may be related to differences in receptor utilization for the isoforms, with APOE4-Aβ complexes using the very low-density lipoprotein (VLDL) receptor and the other isoforms using LRP-1.[24] These isoform specific differences may also affect how the BBB transports insulin, free fatty acids (FFAs), and other metabolites involved in cognitive processes.

In addition to AD risk, E4 carrier status is correlated with increased LDL and triglyceride levels, and an increased risk of heart disease.[25] These lipid abnormalities seen in E4 carriers strongly suggest that AD can be characterized by a state of dyslipidemia. Vascular risk factors appear to be synergistic with E4 carrier status in contributing to AD pathogenesis.[26] Indeed, dyslipidemia itself, and the associated disorder of insulin resistance, are both risk factors for AD as we will discuss in the next sections.

Insulin resistance

Insulin resistance occurs when insulin-sensitive peripheral tissues respond suboptimally to circulating insulin, eventually leading to increased levels of blood glucose. Many human and experimental animal studies have confirmed a link between peripheral insulin resistance and cognitive impairment and risks for AD.[27–29] For example, the Rotterdam study identified that diabetes alone increases the risk for AD two-fold.[30] There is a close association between lipid homeostasis and glucose regulation. Elevated lipid levels can chronically impact insulin secretion by the β-cell in the pancreas.[31,32] Insulin resistance is also correlated with an increase in circulating non-esterified fatty acids, leading to increased plasma cholesterol and ultimately systemic inflammation.[33] There is substantial involvement of inflammation in AD pathogenesis.[34] Dyslipidemia and insulin resistance act in a vicious cycle to promote pathologic processes known to be involved in AD (Figure 1(b)).

Insulin also has targets in the brain and this raises the question of whether CNS insulin resistance occurs in AD, particularly in those who have chronic peripheral insulin resistance or dyslipidemia. Areas within the brain that have high levels of insulin receptors, such as the hippocampus and frontal cortex, play an important role in memory and cognition.[35,36] Work in the SAMP8 mouse, a model of AD, showed that blockage of the Aβ region of APP with an antisense oligonucleotide changed expression of several insulin-related genes in the hippocampus.[37] CNS insulin action is impaired in people with AD, and chronic peripheral hyperinsulinemia serves to reduce transport of insulin into the brain.[38,39] There have been many post-mortem brain studies showing decreases in key insulin signaling proteins in the brains of people with AD.[40–43] In addition, Talbot *et al.*[44] showed an impaired response to insulin in post-mortem brain regions including the cerebellar cortex and hippocampal formation compared to healthy controls who did not have evidence of insulin resistance at peripheral tissues.[44] This study was critical to show a functional impairment in response to insulin in the CNS, but not necessarily the peripheral tissues, in people with cognitive impairment. People with AD also have a lower cerebrospinal fluid (CSF) to plasma ratio for insulin with increased plasma insulin levels and decreased CSF insulin levels compared to healthy age-matched adults, particularly those with advanced AD or those who are E4 non-carriers.[45,46] Given these findings, intranasal insulin therapy is being investigated as a potential treatment for AD.

Intranasal insulin improves cognition

Intranasal delivery offers benefits over standard routes of delivery, such as intravenous or oral paths, including allowing direct access to the CNS, decreasing exposure to the periphery to reduce systemic side effects, and negating degradation in the blood.[47,48] Intranasal administration has been used to deliver a variety of peptides to the brain including galanin-like peptide (GALP),[49,50] pituitary adenylate cyclase-activating peptide (PACAP),[51,52] and glucagon-like peptide-1 (GLP-1).[53]

When administered to patients with AD, mild cognitive impairment, and even to those who are cognitively intact, intranasal insulin has shown marked improvements in a number of cognitive tests including the delayed story recall and the Dementia Severity Rating Scale.[54–59] Some substances delivered to the cribriform plate by intranasal administration are able to enter the brain by bypassing the BBB.[47] This is particularly useful in the delivery of proteins and peptides for the potential treatment of CNS disorders.

Work in animal models continues to support the link between brain insulin resistance and AD pathogenesis. In the SAMP8 mouse, insulin was shown to reach the brain after intranasal administration and to improve cognition.[60]

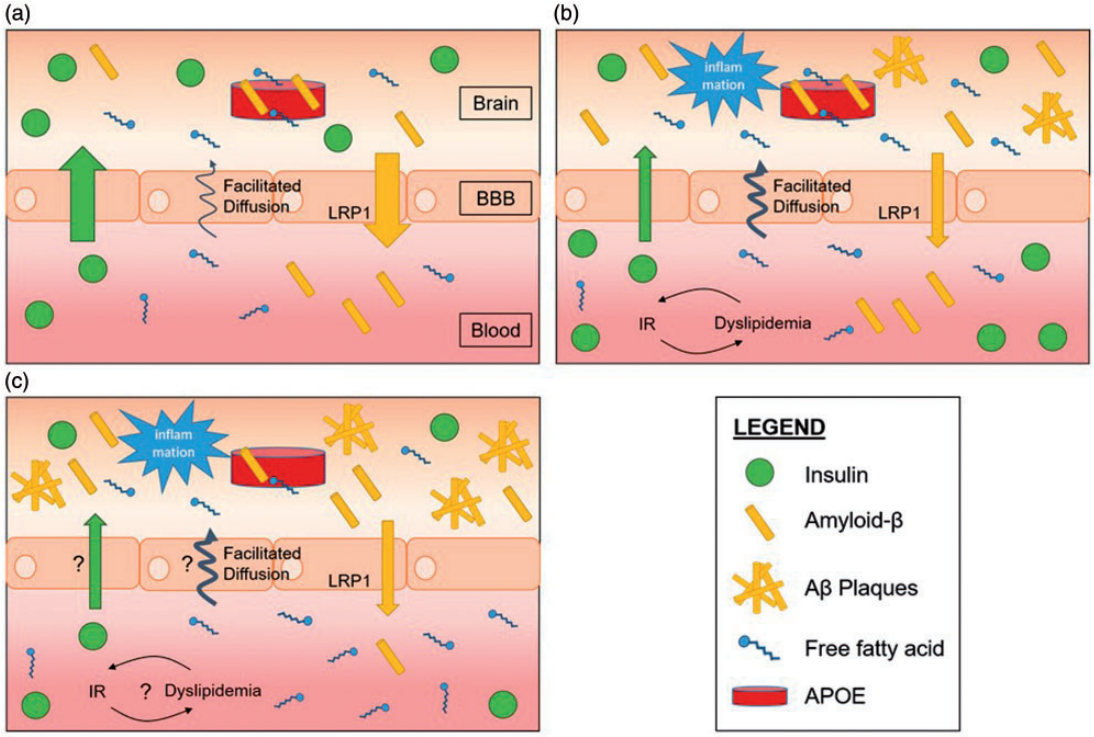

Figure 1 Schematic of metabolic factors involved in E4 status and cognitive impairment. (a) In the healthy state, insulin (green arrow) and FFA (curvy arrow) cross into the brain at a normal rate. In brain, FFA are incorporated into APOE, and APOE assists in clearing Aβ, via BBB transporters such as LRP1 (yellow arrow). Perhaps by modulating these mechanisms, brain insulin promotes cognitive health. (b) Both peripheral and central insulin resistance (IR) are associated with AD. Peripheral IR is associated with inflammation, elevated triglyceride levels, and obesity and the latter with decreased transport of insulin across the BBB. Dyslipidemia can exacerbate IR and vice versa in a vicious cycle. Central IR and elevated triglyceride levels are associated with cognitive impairments. Inflammation decreases the clearance of Aβ by LRP-1 and could contribute to formation of Aβ plaques. (c) The APOE4 protein isoform binds lipids less well and E4 carriers with AD have decreased levels of brain insulin. These variances in E4 carriers could lead to interference with Aβ binding, resulting in decreased clearance from the CNS and an increased Aβ burden compared to E4 non-carriers. Because these relationships among insulin, triglyceride, and amyloid clearance in the E4 state are speculations, they are marked with a ''?''

In the 3 × Tg-AD mouse, intranasal insulin was shown to restore insulin signaling in the brain through the activation of the canonical insulin-signaling pathway.[61]

One mechanism for how improving insulin signaling improves cognition may involve Aβ. *In vitro* work has shown that Aβ impairs neuronal insulin signaling, and insulin attenuates the toxicity of Aβ oligomers.[27] Decreased CNS insulin levels can inhibit Aβ efflux, leading to increased brain aggregation.[62] In the 3 × Tg-AD mouse model discussed above, along with the restoration of insulin signaling, the authors showed a reduction in the level of Aβ40.[61] Human studies support this insulin-Aβ link as well. An autopsy cohort showed that high plasma glucose and insulin levels correlated with increased Aβ plaques in the brain.[63] An oral glucose load increased plasma Aβ levels in adults with AD, and a high saturated fat diet which is a known risk factor for insulin resistance increased plasma and brain levels of Aβ in mice.[64,65] These studies imply that peripheral insulin resistance can influence AD pathology through central mechanisms involving insulin and Aβ.

APOE and insulin interactions

Although both E4 carriers and non-carriers with AD have low concentration of insulin in the CSF and evidence of brain insulin resistance,[44,45] the relationship between CNS and peripheral insulin in the E4 carriers is not as strong as in non-E4 groups (Figure 1(c)).[45,66] AD patients who were E4 carriers showed poorer responses to intranasal insulin treatment compared to AD patients who were E4 non-carriers.[55,67,68] This is a phenomenon observed not only with normal insulin, but also with the rapid-acting insulin, which has been shown to have enhanced effects on cognition in patients with AD.[69] It is interesting that whereas short-acting insulin was ineffective in E4 carriers, the longer acting insulin detemir produced cognitive improvements in E4 carriers, which was accompanied by an improvement in peripheral insulin resistance.[70] Another acute study of short-acting intranasal insulin in E4 carriers showed that plasma insulin decreased after one dose, although no memory improvements were noted.[69] In summary, these studies suggest possible differences in how central insulin regulates cognitive processes, memory, peripheral insulin, and other metabolic hormones in E4 carriers compared to non-carriers. Another possibility includes a potentially higher degree of brain insulin resistance in E4 carriers that requires a longer acting insulin agent to effect changes in brain insulin metabolism.

The relation between Aβ and insulin resistance is also modulated by E4 carrier status. In epidemiologic studies,

only E4 non-carriers showed a relation between CSF Aβ and the CSF to plasma ratio for glucose,[66] and only this group showed memory improvement and a reduction in plasma APP in response to an insulin infusion; E4 carriers had no changes in memory and their plasma APP increased in response to insulin.[71] We recently published that while E4 non-carrier adults with normal cognition showed an increase in plasma Aβ42 after a high-fat meal compared to a high carbohydrate meal, those who had mild cognitive impairment, and those who were E4 carriers, demonstrated higher plasma Aβ after the high carbohydrate meal.[72] We speculate that individuals at risk for AD may have a different relation between diet, fat, and amyloid regulation (Figure 1(c)). Specifically for E4 carriers, their unique lipid profiles in the periphery and in the brain may dictate different physiologic responses to fat versus carbohydrate diets, which in turn differentially affect AD biomarkers.

Dyslipidemia

In addition to insulin resistance, dyslipidemia has also been implicated in cognitive impairment and AD pathogenesis. Dyslipidemia can be a result of genetic and diet factors, and several lipid subgroups, including fatty acids (saturated or unsaturated), triglycerides, cholesterol, and phospholipids, are altered in AD.[58,73,74] Hypertriglyceridemia is the main dyslipidemia linked to metabolic syndrome, a syndrome that also includes obesity and insulin resistance. Indeed, studies investigating the role of lipids in the brain have revealed abnormal lipid metabolism as an important pathophysiological process in the development of AD.[75,76] Diets consisting of an increased consumption of saturated and trans-fats incur an increased incidence of AD, while diets rich in healthy fats are protective.[72,77] Excess saturated fat intake increases circulating lipids, including FFAs, and inflammatory cytokines and requires a redistribution of the lipid content within cells. The increased level of lipids can affect important cellular functions involved in AD including cell membrane flexibility, reduction-oxidation potential, and Aβ aggregation (Figure 1(b)).[78] Lipid metabolism is closely associated with the processing of APP, which results in increased production of Aβ.[79] E4 positive individuals have more exaggerated plasma lipid changes after high-fat diet intake.[80]

In addition to the above mechanisms, obesity and dyslipidemia resulting from diet may act on the brain through insulin resistance. Animal studies have shown diets high in saturated fats or cholesterol increase levels of Aβ and decrease brain insulin levels.[81–83] Also, increased consumption of hydrogenated and saturated fats is associated with insulin resistance. Indeed, AD and obesity share pathophysiological mechanisms, including insulin resistance.

Triglycerides alter insulin and other peptide uptake to the brain

Studies have assessed the role of triglycerides on the transport of peptides across the BBB,[84–86] focusing on peptides which are important in metabolic syndrome and obesity. These studies examined transport in lean and diet-induced obese mice under normal, fasting, and starved conditions for insulin, leptin, and ghrelin, three substances shown to have cognitive effects. One characteristic of obesity is hypertriglyceridemia, which is the classic dyslipidemia of the metabolic syndrome. Triglycerides are known to decrease with fasting and increase with starvation.

Triglycerides can alter a peptide's ability to cross the BBB. In a study examining insulin transport in obese, thin, or starved obese mice, it was observed that starvation and triglycerides reversed the obesity-induced decline in insulin transport at the BBB.[85] Insulin showed decreased transport across the BBB in diet-induced obese mice and increased transport in a state of starvation. In addition, this study demonstrated that the transport of insulin is influenced by the level of triglycerides. Insulin in the brain acts as a satiety factor. It does this through a number of mechanisms including reducing appetite and decreasing body mass. Changes in the ability of the brain to respond to insulin, therefore, could influence body weight and peripheral insulin response. By extension, a decline in the passage of insulin across the BBB could contribute to body weight gain and peripheral insulin resistance through the induction of obesity. Similar results have been observed with ghrelin, where its transport across the BBB was decreased with obesity and increased with triglycerides.[86] Ghrelin is also known to have an effect on cognition.[87]

Triglycerides do not enhance all peptide transport across the BBB. In a study examining leptin transport during starvation and diet-induced obesity, it was observed that leptin transport was decreased in both conditions.[84] A commonality between these two states is the increased levels of triglycerides in circulation. The findings of this study were novel in that they identified triglycerides as a factor inhibiting leptin transport during starvation. Also, the authors showed that increasing triglyceride levels with diet or fasting in normal or obese mice had an inverse effect on leptin transport; and that lowering triglycerides using gemfibrozil reversed the impairment in leptin transport. These results demonstrate that triglycerides are involved in peripheral leptin resistance observed during starvation and obesity.[84] Leptin has been shown to play an important role in memory and learning by influencing the synaptic plasticity of hippocampal neurons as well as long-term potentiation and depression.[88,89] Leptin levels have also been shown to be inversely correlated with AD risk and increased leptin appears to be protective against dementia in adults.[90,91]

Triglycerides affect brain processes

There are a number of peptides in the brain that have been shown to stimulate ingestive behavior; for example, the over-consumption of food, which leads to the development of obesity. These peptides include galanin (GAL), the opioid peptides enkephalin (ENK) and dynorphin (DYN), and the orexins (ORX). Investigation of these peptides demonstrates that they are highly responsive to changes in diet and nutrients. Studies have shown that endogenous gene and protein expressions for GAL, ENK, DYN, and ORX in the periventricular nucleus and perifornical lateral

hypothalamus are closely related to dietary fat, showing a positive correlation with the amount of fat consumed.[92] The mechanisms causing these changes in gene expression have yet to be determined. As these changes occur in normal weight animals and not in response to calories alone, it is believed that they are not associated with hyperphagia or with obesity induced by high-fat diet.[93,94] Since these increases in peptide expression exist, it is hypothesized that circulating factors could contribute to their rise.

A major consequence of increased fat consumption is an increase in circulating levels of lipids, including triglycerides, and fatty acids. These metabolites increase proportionately to the amount of fat consumed. The hydrolysis of triglycerides leads to the release of fatty acids, which have been shown to affect neuronal activity and gene expression in the brain.[95] While it is well established that dietary fat causes an increase in gene expression of these neuronal peptides, further experimentation was completed to provide direct evidence for an effect of circulating lipids on peptide-synthesizing neurons. A study was completed using intralipid, a lipid emulsion, to examine the effect of circulating lipids on the neuronal peptides GAL, ENK, and ORX.[92] The study demonstrated that intralipid increased the expression of certain hypothalamic peptides and activated neurons that synthesize these peptides. These results provide definitive support for the role of circulating lipids in modulating central mechanisms controlling food intake and body weight.

Little if anything is known about how E4 status might modulate the relation between triglycerides and the aforementioned appetite hormones. One group found that food-restricted rats showed differential patterns of APOE protein expression in the hypothalamus.[96] However, it is unknown whether E4 carrier status influences regulation and transport of these peptides and other hormones that simultaneously regulate appetite and cognition.

Triglycerides and cognition

As mentioned above, obesity is correlated with cognitive impairment.[97] The mechanism(s) by which obesity leads to cognitive decline have not been defined. Some hypothesize that the cognitive impairment is a result of hyperglycemia, hyperinsulinemia, and vascular damage to the CNS.[98] The direct role of dyslipidemia in cognitive dysfunction is not as well defined, but animal models are helping to elucidate these mechanisms. In an effort to delineate the role of triglycerides on cognitive impairment associated with obesity, a study was completed using aged CD-1 mice in an array of hippocampal and non-hippocampal-dependent memory tasks.[99] This study demonstrated that cognitive impairments occurred with diet-induced obesity in these mice. These cognitive impairments could be reversed by treating mice with gemfibrozil, to lower triglyceride levels, and induced by the triglyceride, triolein. Altering diet has also been shown to affect cognitive function. In a recent study examining cognitive impairment in chronic high-fat diet fed mice, they showed a rescue of cognitive function associated with a switch to low-fat diet feeding in these mice.[100] These findings suggest that the dyslipidemia of elevated triglycerides is a potential mechanism by which obesity can lead to cognitive impairments.

Triglycerides, cognition, and APOE status

We previously showed that APOE in E4 carriers is less lipidated in the CSF,[101] which *in vitro* and *in vivo* increases the toxicity of the APOE4 isoform.[10] Paradoxically, the negative association between high-fat diets and AD is predominantly limited to E4 non-carriers in some studies.[102,103] We recently published work showing that in older adults, E4 carriers actually showed cognitive improvements on some tasks after ingesting a high-fat meal, compared to a high carbohydrate meal.[72] We speculate that because of the lipid deficit in the E4 carrier brain, high fat feeding may benefit E4 carriers acutely. In addition, others have suggested that high carbohydrate feeding, which serves to increase insulin transport into the brain, could prevent crucial FFA delivery to astrocytes.[104] As mentioned above, E4 carriers respond differently to insulin therapeutics. These differences in brain lipid metabolism may explain why the E4 state simultaneously exacerbates vascular risk factors for AD yet modulates brain-specific treatments including lipid- and insulin-based therapeutics.

E4 status has been shown to modulate responses to other metabolic-related treatments for AD. For example, a trial of a medication which induced mild peripheral ketosis improved cognitive scores but only in E4 non-carrier participants.[105] These findings were not readily explained by differences in peripheral ketone body levels, and the authors speculated that the findings could be related to differences in brain transport of ketone bodies or their utilization.[106] E4 carriers have decreased cytochrome oxidase activity in the posterior cingulate, which could indicate compromised mitochondrial integrity that might not be able to respond to metabolic treatments such as ketone bodies or intranasal insulin.[69]

Conclusions

In summary, we have reviewed evidence that dyslipidemia and insulin resistance are risk factors for AD. Several different mechanisms for how these metabolic derangements might influence neurocognitive processes, which suggest different therapeutic strategies. In addition, carrier status of the E4 allele of the lipid carrier APOE is a strong risk factor for developing AD. However, E4 carriers appear to differ from non-E4 carriers in several important ways in terms of the relations among insulin, lipids, and neurodegenerative processes. Epidemiologic studies show a weaker connection between insulin resistance, dyslipidemia, and AD in E4 carriers, and this group responds differently to glucose and lipid-based interventions. Possible mechanisms for why E4 carriers would respond differently include differences in peripheral insulin metabolism, lipidation status, Aβ burden, and BBB functions. Understanding the mechanisms by which dyslipidemia and insulin resistance contribute to AD, and how they may differ from other groups at risk for AD, will be important as we continue to develop treatments for this devastating disease.

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