Lipid metabolism, aging and cognitive dysfunction

The role of altered lipid metabolism in the pathogenesis and progression of Alzheimer’s disease

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Outline

- Introduction
- Major Lipid Classes and Functions in the Brain
- Apolipoprotein E and the Pathogenesis of AD
- Role of Cholesterol Metabolism in AD Pathogenesis
- Role of Sphingolipid Metabolism in AD Pathogenesis
- Concluding Remarks
Introduction

- Lipids are abundant in the brain.
- Lipids play crucial roles in cell signaling and various physiological processes, especially in the brain.
- Impairment of lipid metabolism in the brain has been implicated in neurodegenerative diseases, such as Alzheimer’s disease.
- Although the potential link between cholesterol and AD pathogenesis has been intensively studied, growing evidence suggests that other lipids, such as sphingolipids and glycerophospholipids, also play important roles.
Major Lipid Classes and Functions in the Brain

**Cholesterol:**
- Major component of cellular membrane, essential for membrane structural integrity and protein function;
- neuronal synaptic plasticity; regeneration; lipid raft, which is important for neuronal signaling;
- lipoprotein particles; neuroinflammation; neurodegeneration
- precursors for lipid mediators and hormones

**Fatty Acids:**
- Sustain structural integrity of cellular membrane; cellular signaling; neuronal activity and plasticity;
- synaptogenesis and neurogenesis;
- neuroinflammation; neurodegeneration; oxidative stress

**Glycerophospholipids:**
- Structural integrity of neural membrane; precursors for lipid mediators; oxidative stress; neuroinflammation;
- lipoprotein particles; neuronal activity; neural cell differentiation and migration; neurodegeneration

**Sphingolipids:**
- Structural integrity of neural membrane; precursors for lipid mediators; oxidative stress; neuroinflammation;
- lipid rafts; neuronal activity; neural cell differentiation and migration; neurodegeneration
Membrane lipids
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Apolipoprotein E

- Apolipoprotein E (ApoE), a 39-kDa protein, is a major apolipoprotein in CSF, which is highly expressed in brain and is derived from the brain, not the liver.
- The CNS contains high levels of apoE, in particles the size of HDL and in abundance second only to the liver.
- ApoE is the principal cholesterol carrier in the brain, participating in cholesterol homeostasis.
- Astrocytes are the major source of ApoE followed by oligodendrocytes, microglia, and ependymal layer cells.
- ApoE is required for lipoprotein uptake into cells via the LDL family of receptors.
three major alleles (epsilon 2, epsilon 3, and epsilon 4): 

- APOE-ε2 (cys112, cys158)
- APOE-ε3 (cys112, arg158)

Aβ binding (209–255)
Apolipoprotein E polymorphism

- The ε4 allele of the apolipoprotein E (APOE) gene, on chromosome 19 → Inheritance of the e4 allele is a risk factor for developing late-onset familial and sporadic AD
- One ε4 allele: increase the chance of developing AD (3x-4x)
- Two ε4 alleles: increase the chance of developing AD (up to 12X)
- In Caucasian populations <65 years of age, APOE ε3 is the most common allele (75 %), followed by ε4 (15 %) and ε2 (8 %).
ApoE and Alzheimer’s disease

- The primary role of apoE in AD pathology is through modulating the Aβ clearance from the brain.
- ApoE4 appears to be less efficient than the other isoforms in promoting cholesterol efflux from neuronal cells and astrocytes.
- ApoE also appears to be involved in the binding and clearance of brain Aβ, with apoE3 and apoE2 being more effective than apoE4.
Major Aβ clearance pathways in the brain: role of APOE isoforms

- Clearance through the BBB
- Clearance along the ISF drainage pathway
- Proteolytic degradation by neprilysin, IDE, etc.
- Uptake by astrocytes, microglia, and neurons
- Amyloid plaque
- Cerebrovascular artery
- LDLR-related protein 1 (LRP1)
- Cerebral amyloid angiopathy (CAA)
Roles of APOE isoforms in the healthy brain and AD pathogenesis

APOE3 binds to Aβ more strongly than APOE4, and therefore it is more efficient at mediating Aβ clearance through APOE receptors.

The primary function of APOE is to transport lipids from astrocytes to neurons, an event that is crucial for synaptogenesis, synaptic repair, dendritic spine integrity and synaptic functions.

APOE4 functions less efficiently than APOE3 in these processes.
ApoE is synthesised and secreted by astrocytes in the brain.

The cellular functions of APOE are mediated by APOE receptors, which are members of the low-density lipoprotein receptor (LDLR) family. LDLR-related protein 1 (LRP1) and the LDLRs are the two major types of APOE metabolic receptors in the brain.
Effects of cholesterol and apolipoprotein E on transport and metabolism of amyloid beta (Ab).

- 24S-hydroxycholesterol has been found to down-regulate the beta-cleavage of amyloid precursor protein amyloid with a lower production of Ab42.
- The influx of 27-OHC into the brain may have an opposite effect, and a higher uptake of 27-OHC from the circulation may contribute to amyloid deposition.
Evidence suggests that the major effect of apoE isoforms on the risk of developing AD is via its effect on Aβ aggregation and clearance, influencing the onset of Aβ deposition.
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Other genes of cholesterol metabolism linked to AD

- genes encoding **APOJ** (involved in the transport of cholesterol)
- low-density lipoprotein receptor-related protein (**LRP**, a major receptor for ApoE in the brain)
- the enzyme cholesterol 24-hydroxylase (**CYP46A1**, responsible for the catabolism of cholesterol to 24S-hydroxycholesterol)
- a member of the ATP-binding cassette membrane transport protein superfamily (**ABCA1**, involved in the efflux of cholesterol)
- the enzyme acyl-coenzyme-A cholesterol acyltransferase (**ACAT1**, responsible for the esterification of cholesterol)
High midlife total cholesterol increases risk of late-life AD

Total cholesterol measured in midlife and cognitive outcome in late-life

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study</th>
<th>Weight</th>
<th>RR</th>
<th>CI</th>
<th>p-value</th>
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<tbody>
<tr>
<td>AD</td>
<td>Notkola et al., 1998§ [27]</td>
<td>23.52</td>
<td>3.10</td>
<td>1.16, 8.25</td>
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<tr>
<td></td>
<td>Kivipelto et al., 2001## [12]</td>
<td>30.48</td>
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<td>Mielke et al., 2010### [27]</td>
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<td>Pooled</td>
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<td>1.33, 3.44</td>
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<tr>
<td>Dementia</td>
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<td>84.61</td>
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<tr>
<td></td>
<td>Beydoun et al., 2011[[21] ]</td>
<td>15.39</td>
<td>1.31</td>
<td>0.82, 2.09</td>
<td>0.06</td>
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<td>Pooled</td>
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<td></td>
<td>1.47</td>
<td>0.96, 2.27</td>
<td>0.08</td>
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<tr>
<td>AD/Dementia</td>
<td>Notkola et al., 1998 [2]</td>
<td>13.39</td>
<td>3.10</td>
<td>1.16, 8.25</td>
<td>0.02</td>
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<td></td>
<td>Kivipelto et al., 2001 [12]</td>
<td>10.66</td>
<td>3.10</td>
<td>1.18, 6.62</td>
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<tr>
<td></td>
<td>Mielke et al., 2010 [27]</td>
<td>58.61</td>
<td>2.82</td>
<td>0.94, 8.44</td>
<td>0.26</td>
</tr>
<tr>
<td></td>
<td>Beydoun et al., 2011 [21]</td>
<td>17.35</td>
<td>1.31</td>
<td>0.82, 2.09</td>
<td>0.06</td>
</tr>
<tr>
<td>Pooled</td>
<td></td>
<td></td>
<td>1.82</td>
<td>1.27, 2.60</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Meta-analysis (up to October 2016)
- 34 articles
- 17 studies
- 23,338 participants
Meta-analysis: 14 studies

A. Statins use and Alzheimer’s Disease

<table>
<thead>
<tr>
<th>Study name</th>
<th>Risk ratio</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hendrie, 2015</td>
<td>0.440</td>
<td>0.200</td>
<td>0.968</td>
<td>0.041</td>
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<tr>
<td>Chen, 2014</td>
<td>0.480</td>
<td>0.302</td>
<td>0.763</td>
<td>0.002</td>
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<tr>
<td>Ancelin, 2012</td>
<td>1.139</td>
<td>0.846</td>
<td>1.533</td>
<td>0.391</td>
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<tr>
<td>Betterman, 2012</td>
<td>0.830</td>
<td>0.613</td>
<td>1.124</td>
<td>0.229</td>
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<tr>
<td>Beydoun, 2011</td>
<td>0.300</td>
<td>0.097</td>
<td>0.926</td>
<td>0.036</td>
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<tr>
<td>Li, 2010</td>
<td>0.620</td>
<td>0.398</td>
<td>0.965</td>
<td>0.034</td>
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<tr>
<td>Haag, 2009</td>
<td>0.570</td>
<td>0.365</td>
<td>0.890</td>
<td>0.013</td>
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<tr>
<td>Arvanitakis, 2008</td>
<td>0.910</td>
<td>0.542</td>
<td>1.527</td>
<td>0.721</td>
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<tr>
<td>Sparks, 2008</td>
<td>0.330</td>
<td>0.111</td>
<td>0.983</td>
<td>0.047</td>
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<tr>
<td>Li, 2007</td>
<td>0.200</td>
<td>0.048</td>
<td>0.831</td>
<td>0.027</td>
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<tr>
<td>Rea, 2005</td>
<td>1.210</td>
<td>0.763</td>
<td>1.918</td>
<td>0.418</td>
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<tr>
<td>Zandii, 2005</td>
<td>1.190</td>
<td>0.409</td>
<td>3.462</td>
<td>0.750</td>
</tr>
<tr>
<td>Li, 2004</td>
<td>0.820</td>
<td>0.460</td>
<td>1.461</td>
<td>0.501</td>
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<tr>
<td>Reitz, 2004</td>
<td>0.880</td>
<td>0.440</td>
<td>1.760</td>
<td>0.718</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td><strong>0.719</strong></td>
<td><strong>0.576</strong></td>
<td><strong>0.899</strong></td>
<td><strong>0.004</strong></td>
</tr>
</tbody>
</table>
Model 3 was adjusted for age, sex, systolic blood pressure, fasting blood glucose, fasting insulin, body mass index, current smoking, regular exercise, cerebrovascular disease, and APOE 4 carrier.

### Model 3

<table>
<thead>
<tr>
<th>CERAD score</th>
<th>0 (n = 47)</th>
<th>1 (n = 23)</th>
<th>2 (n = 22)</th>
<th>3 (n = 55)</th>
<th>p for trend</th>
<th>p (1–3 vs 0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC, mmol/L</td>
<td>4.82</td>
<td>5.42(^b)</td>
<td>5.69(^b)</td>
<td>5.36</td>
<td>0.049</td>
<td>0.005</td>
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<tr>
<td>LDLC, mmol/L</td>
<td>3.01</td>
<td>3.53</td>
<td>3.85(^b)</td>
<td>3.50</td>
<td>0.05</td>
<td>0.007</td>
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<tr>
<td>HDLC, mmol/L</td>
<td>1.31</td>
<td>1.26</td>
<td>1.33</td>
<td>1.26</td>
<td>0.62</td>
<td>0.63</td>
</tr>
<tr>
<td>TG, mmol/L</td>
<td>1.06</td>
<td>1.25</td>
<td>1.01</td>
<td>1.15</td>
<td>0.77</td>
<td>0.49</td>
</tr>
<tr>
<td>TC/HDL C</td>
<td>3.87</td>
<td>4.58(^b)</td>
<td>4.51</td>
<td>4.50(^b)</td>
<td>0.05</td>
<td>0.009</td>
</tr>
<tr>
<td>LDL/C/HDL C</td>
<td>2.45</td>
<td>2.92</td>
<td>3.07(^b)</td>
<td>2.94</td>
<td>0.06</td>
<td>0.02</td>
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<tr>
<td>Non-HDL C, mmol/L</td>
<td>3.51</td>
<td>4.16(^b)</td>
<td>4.36(^b)</td>
<td>4.10(^b)</td>
<td>0.03</td>
<td>0.002</td>
</tr>
</tbody>
</table>
Hypercholesterolemia Accelerates the Alzheimer’s Amyloid Pathology in a Transgenic Mouse Model

**FIG. 3.** Effect of hypercholesterolemia on the mean number of CNS β-amyloid deposits. β-Amyloid deposits were visualized using monoclonal antibody 4G8, as described under Methods. Data represent mean deposit number ± SEM. *Statistical significance relative to the basal group (P = 0.019). Statistical significance was calculated using a paired t-test (two-tailed).

**FIG. 4.** Increased number of β-amyloid deposits in response to high dietary cholesterol. Serial coronal sections were immunostained with 4G8 as described under Methods. Arrows indicate β-amyloid deposits in the entorhinal cortex of mice on control (basal) and high-cholesterol diets. The photomicrograph illustrates the average density of β-amyloid deposits in the hypercholesterolemic versus basal control mice. Bar = 220 µm.
Increased Amyloidogenic Processing of APP of hypercholesterolemic Mice

- the hypercholesterolemic mice had significantly
  - decreased levels of sAPPa
  - increased levels of C-terminal fragments (b-CTFs)
- suggesting alterations in amyloid precursor protein processing in response to hypercholesterolemia.
Modulation of proteolytic processing of APP by lipids

**a** Cholesterol, GGPP, LRP

Targeting APP, BACE1 or γ-secretase into lipid rafts

γ-secretase cleavage

β-secretase cleavage

α-secretase cleavage

**b** Isoprenoids, diacylglycerol, PLC

sAPPα

+
Cholesterol Greases the Aβ Aggregation Machine

- Cholesterol-laden vesicles accelerated Aβ42 aggregation in vitro.
- Fibrils formed in the presence of cholesterol were structurally similar to those formed without cholesterol.
- Increased cholesterol levels in the lipid bilayers enhance Aβ conformation changes from a helix-rich to a beta-sheet-rich structure, which facilitates amyloid accumulation.
- Cholesterol sped up nucleation of Aβ42 monomers into oligomers.
Cholesterol in the brain

- Cholesterol is an essential component of cell membranes
- It plays key roles in the development and maintenance of neuronal plasticity in the brain
- The CNS accounts for only 2% of the total body mass of cholesterol, but contains up to 25% of the total body’s unesterified cholesterol
- Essentially all (> 99.5%) cholesterol is unesterified
  - believed to reside in two different pools
    1. by the myelin sheaths (i.e. oligodendroglia) (~70–80 %)
    2. plasma membranes of astrocytes and neurons
Turnover of brain cholesterol

- Cholesterol synthesis is relatively high in the developing CNS, low in adults
- Efficient recycling of cholesterol
- The turnover of brain cholesterol is relatively low compared to that within the periphery with a half-life estimated to be 4–6 months in rodents and 5 years in human

M Maulik, D Westaway, JH Jhamandas, S Kar - Molecular Neurobiology, 2012 - Springer
BBB is impermeable to circulating cholesterol

- Experimental work in both animals and humans has indicated that brain cholesterol is largely independent and unaffected by the serum levels, as the blood–brain barrier (BBB) is impermeable to circulating cholesterol.
Oxysterols

- In contrast to cholesterol, the side-chain oxidized oxysterols, 24-hydroxycholesterol (24-OHC) and 27-hydroxycholesterol (27-OHC), have the ability to cross lipophilic membranes into and out of the brain.
- 24-OHC may favor the non-amyloidogenic pathway.
- 27-OHC may enhance production of Aβ42 by upregulating APP and BACE1.
Passive transport 24S-hydroxycholesterol across BBB
Cholesterol synthesis and metabolism in the brain

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Metabolic pathways of sphingolipids

Sphingomyelin

Gangliosides

GalCer

GlcCer

LacCer

Gangliosides

Ceramide

Sulfatide

GalCer

Ceramide
Ceramide and beta amyloid

- Ceramide stabilizes the APP cleaving enzyme 1 (BACE1), promoting A beta biogenesis
- Reduction of ceramide levels leads to reduced secretion of APP and A in human neuroblastoma cells

Patil et al., 2007; Puglielli et al., 2003
Elevation of ceramides at the earliest stage of AD

- The mass content of ceramides in white matter from subjects with very mild AD was dramatically elevated (over 3 fold) relative to the controls in all examined brain regions including cerebellum.

- The mass content of ceramides in white matter from subjects at the more severe stages of AD decreased in comparison with that at CDR 0.5, but was still substantially higher than that found in white matter of age-matched cognitively normal subjects.

Serum sphingomyelins and ceramides are early predictors of memory impairment

- 100 women enrolled in a longitudinal population-based
- six visits over 9 years

Fig. 1. Kaplan–Meier survival graph showing baseline total SM, in tertiles, and incident HVLT-delayed memory impairment.

Fig. 2. Kaplan–Meier survival graph showing baseline ceramide C22:0, in tertiles, and incident HVLT-delayed memory impairment.
Peripheral ceramides may be associated with AD

CSF and brain ceramides

Amyloid-beta pathology → Neurodegeneration → Alzheimer’s disease

BBB (Blood-Brain Barrier)

Peripheral ceramides

Atherosclerosis
Insulin resistance
Diabetes
Potential roles of lipid metabolism in Alzheimer’s disease

Abnormal lipid synthesis, degradation, trafficking and modification

Abeta production, aggregation and clearance

APOE isoform, Neuroinflammation, Tau phosphorylation

Synaptic function, learning and memory

AD pathogenesis
Concluding Remarks

- Alzheimer’s disease is a complex pathology with multiple contributing factors, among which lipids and lipid homeostasis play central roles.

- Prevailing data suggest that abnormal lipid metabolism influences Aβ metabolism and deposition in both brain parenchyma and vasculature as well as tau hyperphosphorylation and aggregation.

- Specific lipid signatures or changes in the lipid environment as disease-predisposing factors can possibly be revealed, providing new potential methods for improved diagnostics and ultimate prevention of AD.