Cholesterol, APOE, and Aβ in cell and animal models of Alzheimer’s disease

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Connections between cholesterol and Alzheimer’s disease

- **APOE**
- **Epidemiology**
  - Increased risk of AD associated with high cholesterol in mid-life
  - Decreased risk of AD associated with use of statins
- **Cell culture**
  - High cholesterol - more Aβ
  - Low cholesterol - less Aβ
Connections between cholesterol and Alzheimer’s disease: animal models

- Niemann-Pick type C disease
  - Intracellular cholesterol transport
- Statin treatment of TgAPP mice
  - Cholesterol lowering drugs
- High cholesterol diets for TgAPP mice
Niemann Pick type C disease

Atorvastatin (Lipitor) reduces brain Aβ in PS-APP mice

Petanceska, 2003
High cholesterol diet increases brain Aβ in PS-APP mice

Aβ detection by IP/mass spectroscopy

Refolo, 2000
Brain Aβ levels are modulated by hypercholesterolemia and a cholesterol-lowering drug.

Refolo, 2001
Oversimplified cholesterol hypothesis

APOE

High brain cholesterol levels

diet

increased brain Aβ

AD

statins
Oversimplified cholesterol hypothesis

APOE

High brain cholesterol levels

increased brain Aβ → AD

diet →

⇒

statins
How to detect effects on brain cholesterol

• Most brain cholesterol is in myelin
  – Measure non-myelin lipids

• Alterations in brain cholesterol affect cholesterol homeostasis genes
  – Cleavage of SREBP to regulate gene transcription
  – Generation of oxysterols to regulate gene transcription
Proteolysis of SREBP by low cholesterol levels

LDL receptor
HMG CoA reductase

(reminiscent of APP proteolysis)
Induction of LXR by high cholesterol levels
Induction of genes in neuroblastoma cells by LXR activation: gene chip analysis of mRNA

<table>
<thead>
<tr>
<th>Gene</th>
<th>Fold Change</th>
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</thead>
<tbody>
<tr>
<td>ABC-G1</td>
<td>4.2</td>
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<tr>
<td>ABC-A1</td>
<td>2.6</td>
</tr>
<tr>
<td>SREBP-1</td>
<td>2.3</td>
</tr>
<tr>
<td>Fatty acid CoA ligase</td>
<td>1.7</td>
</tr>
<tr>
<td>Stearoyl CoA desaturase</td>
<td>1.7</td>
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</tbody>
</table>
ApoE levels are altered by LXR agonists and cholesterol

- apoE
- control
- cholesterol
- lovastatin

TO TO/RA control RA

BV-2 cells

primary glial cultures
Activation of LXR induces cholesterol efflux to apoE
APOE genotype alters levels of SREBP cleaved fragment

GFAP-APOE mice
(APOE replacement mice)
Diet and a cholesterol-lowering drug affect brain APOE mRNA

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Plasma Cholesterol (mg/dl)</th>
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<tbody>
<tr>
<td>High cholesterol</td>
<td>200</td>
</tr>
<tr>
<td>Vehicle</td>
<td>75</td>
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<tr>
<td>BM 15.766</td>
<td>28</td>
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</tbody>
</table>

Petanceska, 2004
Brain-permeable statins affect brain cholesterol

Synaptosomal Plasma Membrane Cholesterol (% control)

Lipophilicity: ++ ++ --

Vehicle Zocor Mevacor Lipitor
Oversimplified cholesterol hypothesis

APOE

High brain cholesterol levels

diet

increased brain Aβ

statins

AD
APOE-ε4 increases brain Aβ levels

GFAP-APOE mice
(APOE replacement mice)
Statins decrease brain Aβ
How could effects on brain cholesterol alter Aß levels?

• Effects on membrane (like SREBP)
  – APP is transmembrane
    \( \alpha-, \beta-, \gamma \)-secretases are transmembrane proteins
• Effects on gene expression (downstream)
  – Cholesterol equilibrium mechanisms
APOE affects $\gamma$-secretase activity in lipid rafts
Cholesterol could affect Aβ levels through induction of LXR system
Activation of LXR increases secreted Aβ42 levels

Aβ42 levels

24 hours 48 hours

**
• Therapeutic potential for statin treatment?
• Importance of blood brain barrier?
• Testing of other cholesterol-altering drugs?
• Potential for dietary reduction in cholesterol?
• APOE genotype-statin interactions?
24-Hydroxycholesterol induces ABCA1 expression in Neuro2A cells
APOE genotype alters cholesterol hydroxylation

Ben Wolozin
Niemann Pick type C

Cholesterol synthesis

3 Hydroxy-3-methylglutaryl-CoA ➔ Statins ➔ Mevalonate ➔ Farnesyl pyrophosphate ➔ Squalene ➔ Desmosterol ➔ BM15.766 ➔ Cholesterol