A group of six people, three men and three women, are standing outdoors at night. They are dressed in winter clothing, including jackets and coats. The background shows a building with windows and streetlights. The text is overlaid on the image.

# Cholesterol, APOE, and A $\beta$ in cell and animal models of Alzheimer's disease

G. William Rebeck

Georgetown University

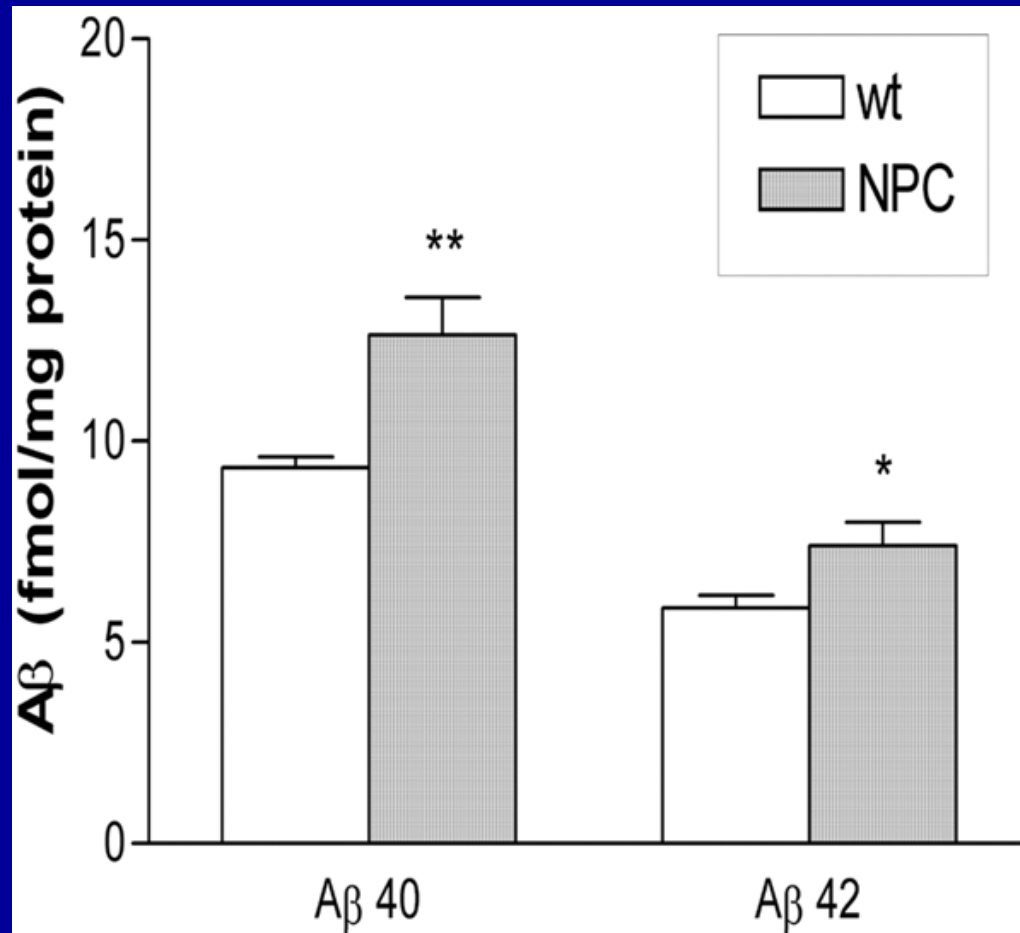
# Connections between cholesterol and Alzheimer's disease

- 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 A $\beta$
  - Low cholesterol - less A $\beta$

# Connections between cholesterol and Alzheimer's disease: animal models

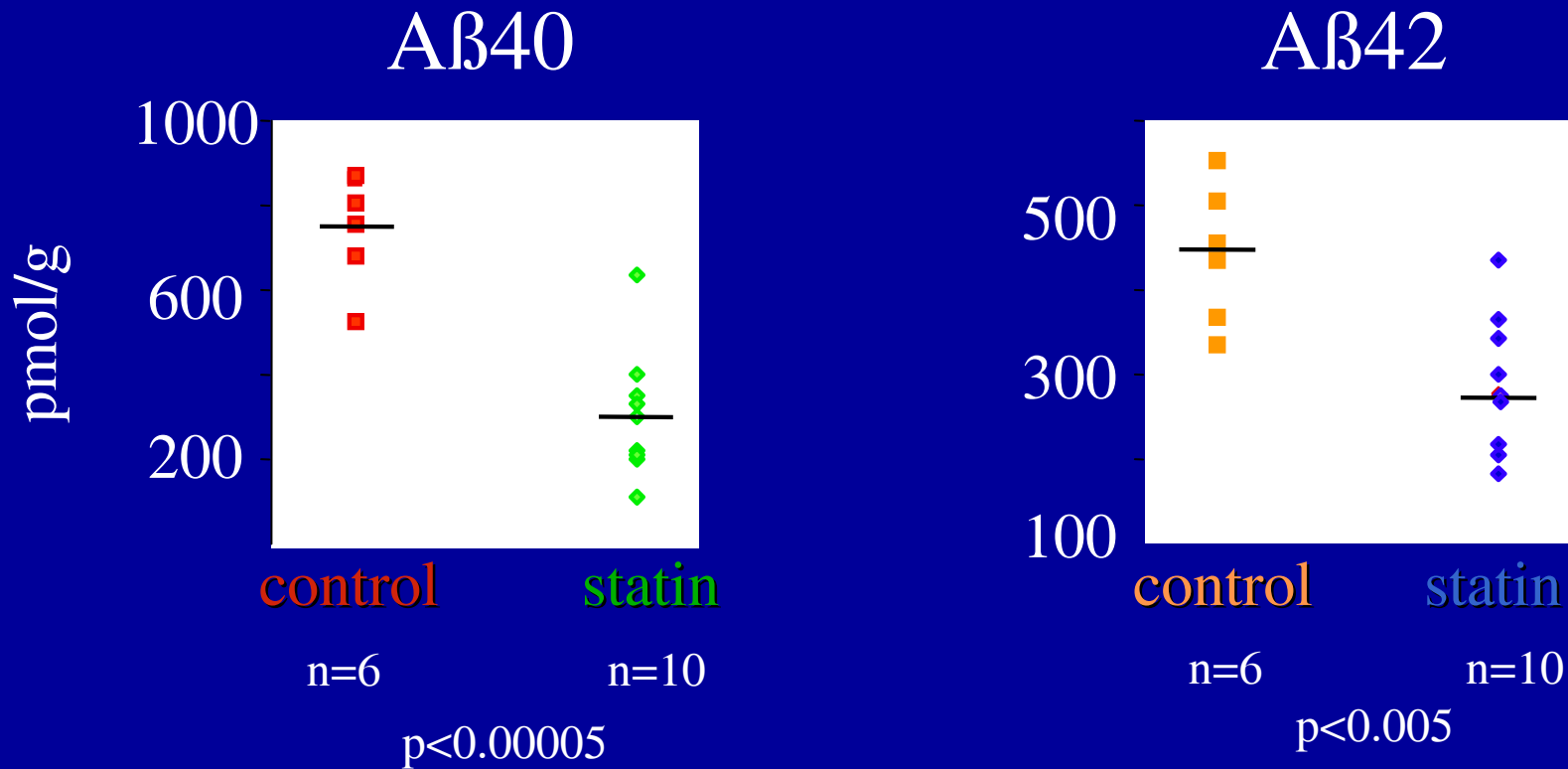
- Niemann-Pick type C disease
  - Intracellular cholesterol transport
- Statin treatment of TgAPP mice
  - Cholesterol lowering drugs
- High cholesterol diets for TgAPP mice

# Niemann Pick type C disease



Burns et al, J Neurosci (2003) 23:5645

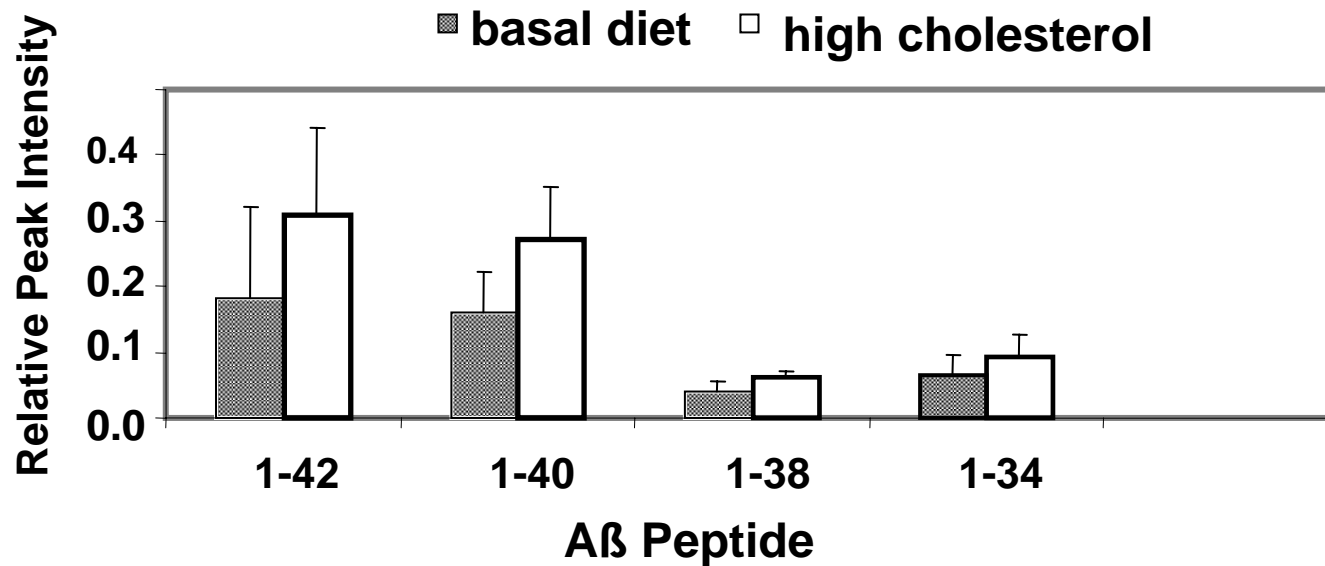
# Atorvastatin (Lipitor) reduces brain A $\beta$ in PS-APP mice



Petanceska, 2003

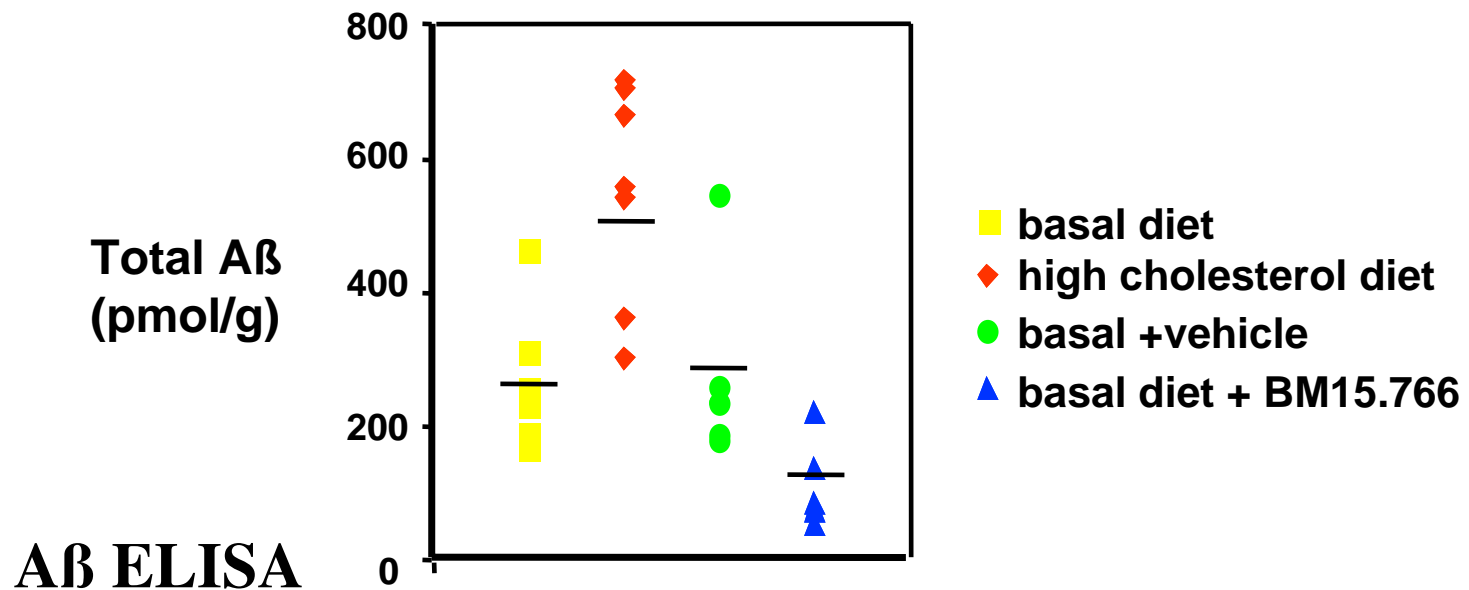
# High cholesterol diet increases brain A $\beta$ in PS-APP mice

A $\beta$  detection by IP/mass spectroscopy

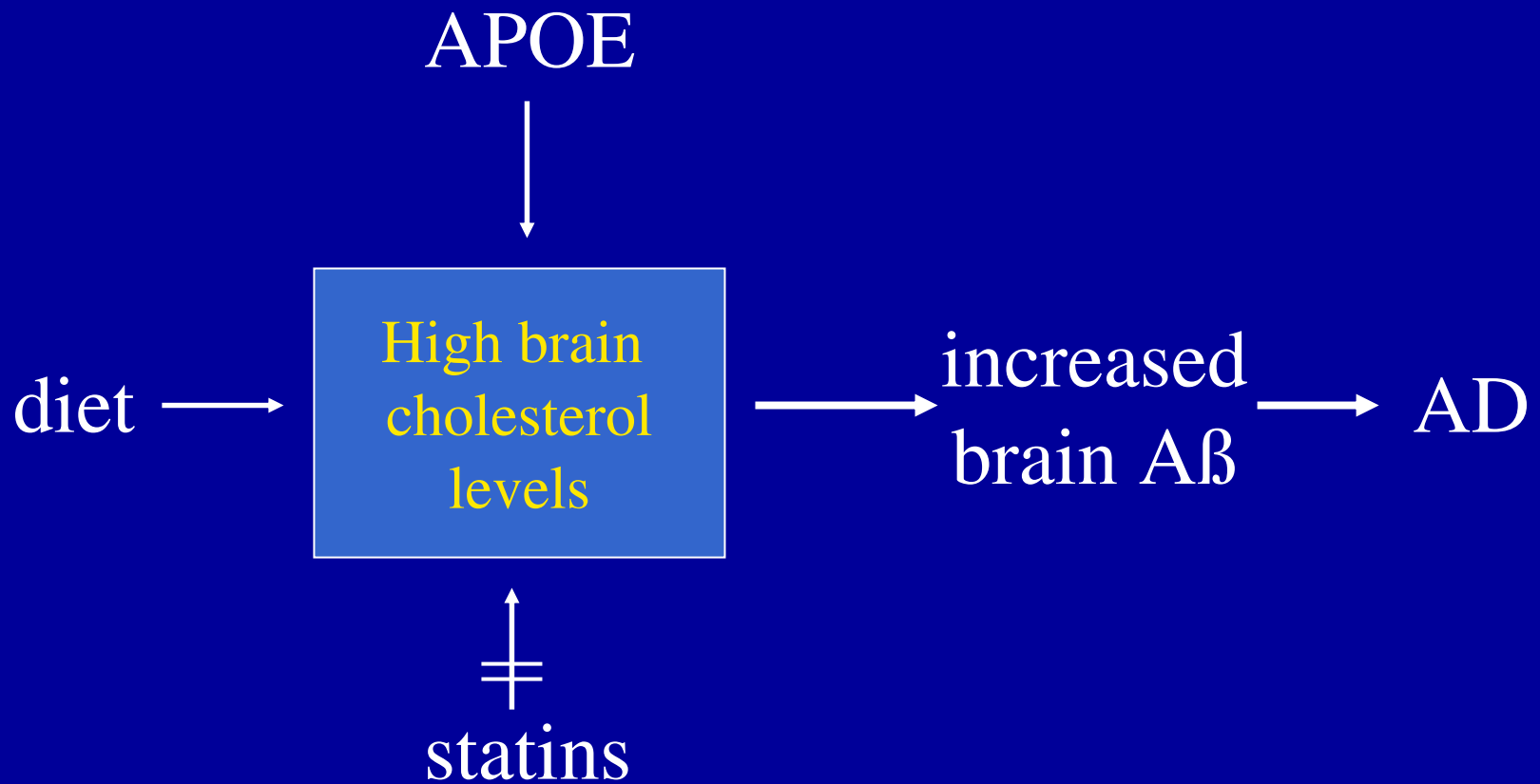


Refolo, 2000

# Brain A $\beta$ levels are modulated by hypercholesterolemia and a cholesterol-lowering drug



# Oversimplified cholesterol hypothesis





Georgetown University

Hyang-Sook Hoe

Mark Burns

Geetanjali Chakraborty

Chris Harris

Casandra Cartagena

Yasuji Matsuoka

Paul Aisen

NKI

Suzana Petanceska

Karen Duff

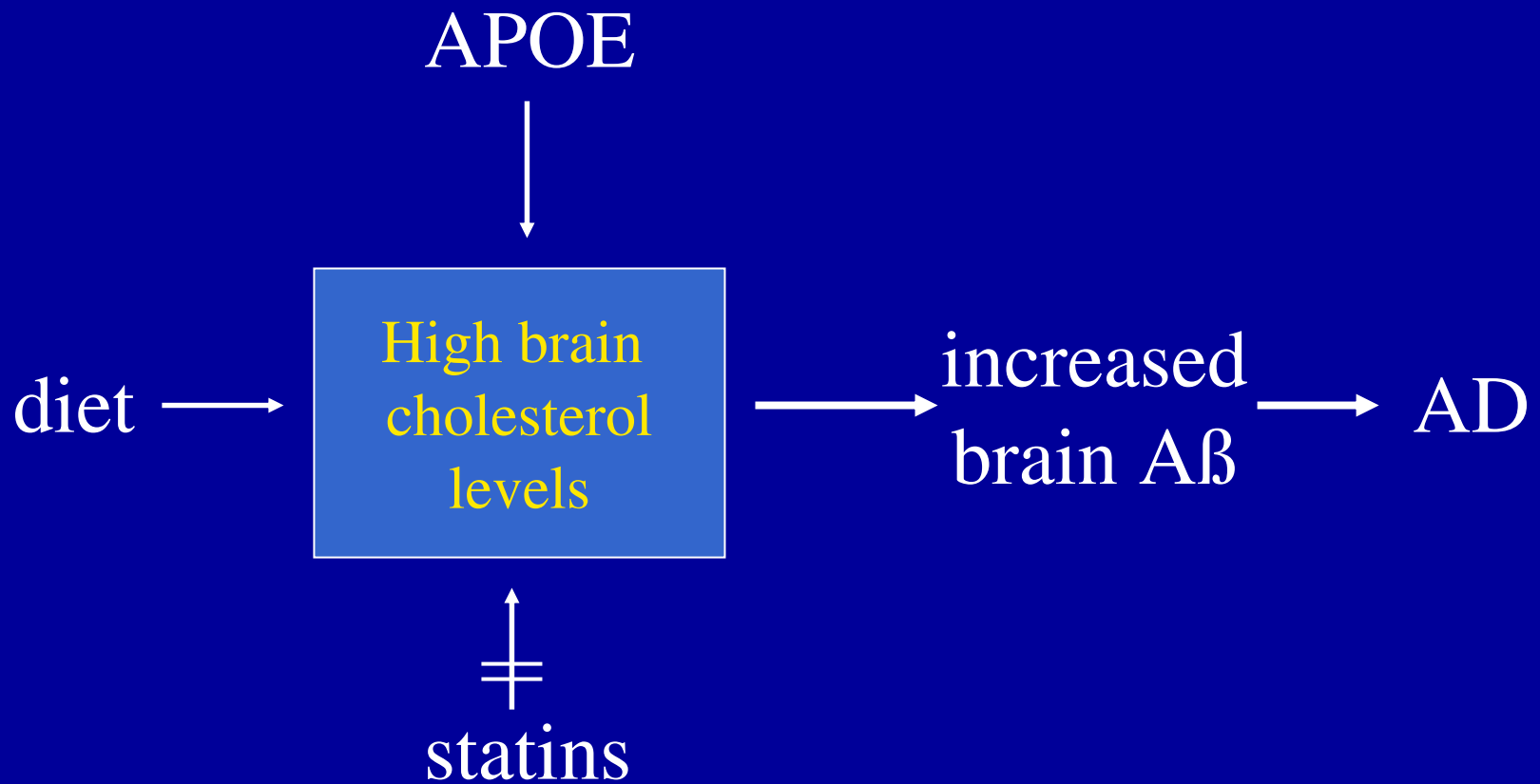
MGH

Brad Hyman

Mike Irizarry

Amy Deng

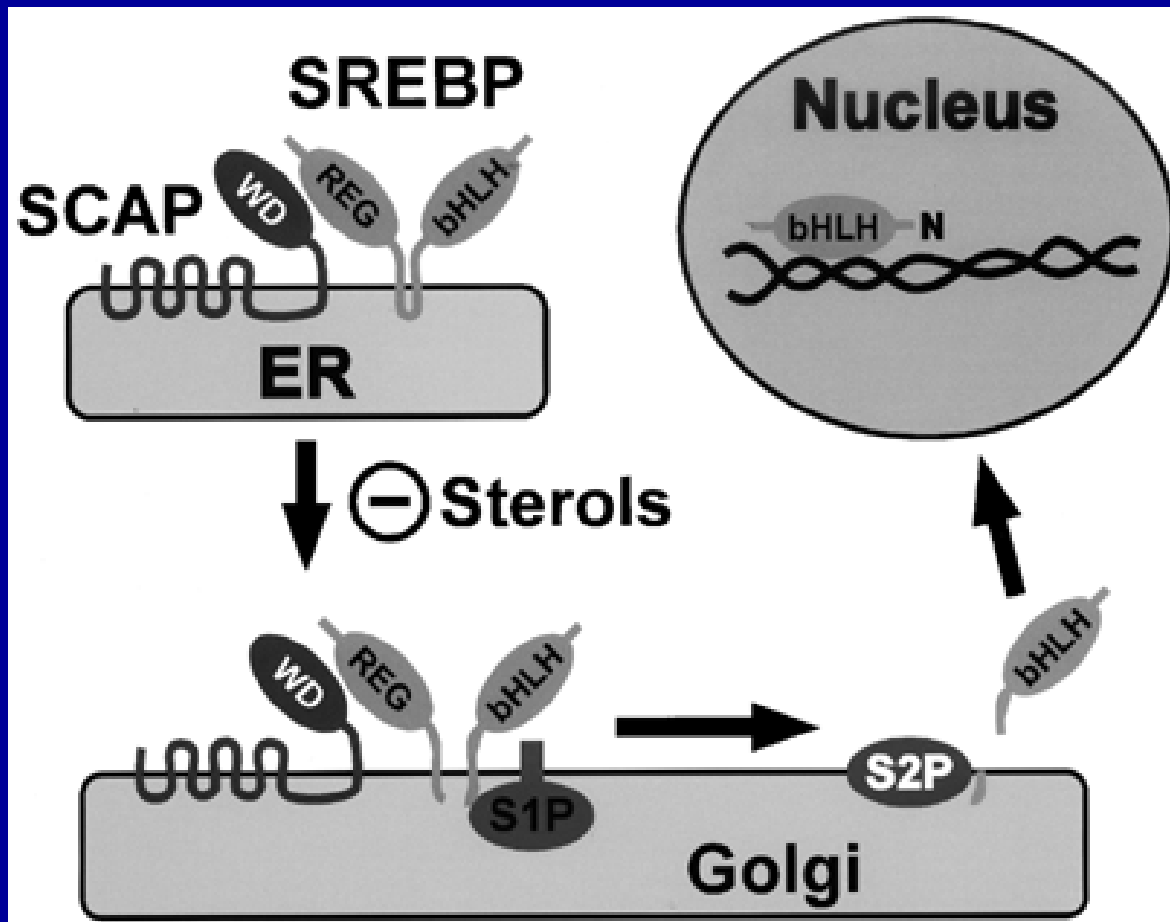
# Oversimplified cholesterol hypothesis



# 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

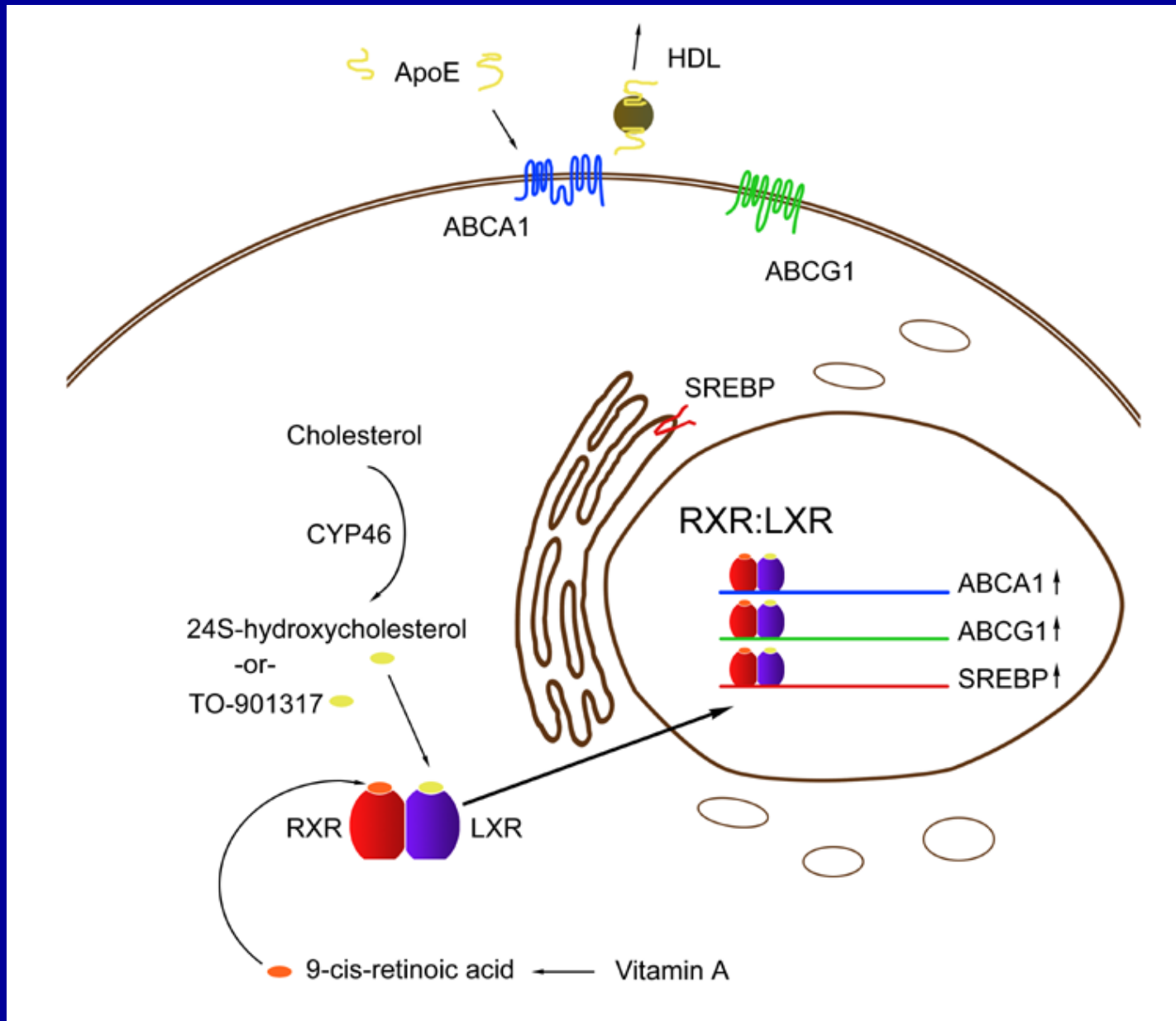
# Proteolysis of SREBP by low cholesterol levels



LDL receptor  
HMG CoA  
reductase

(reminiscent of  
APP proteolysis)

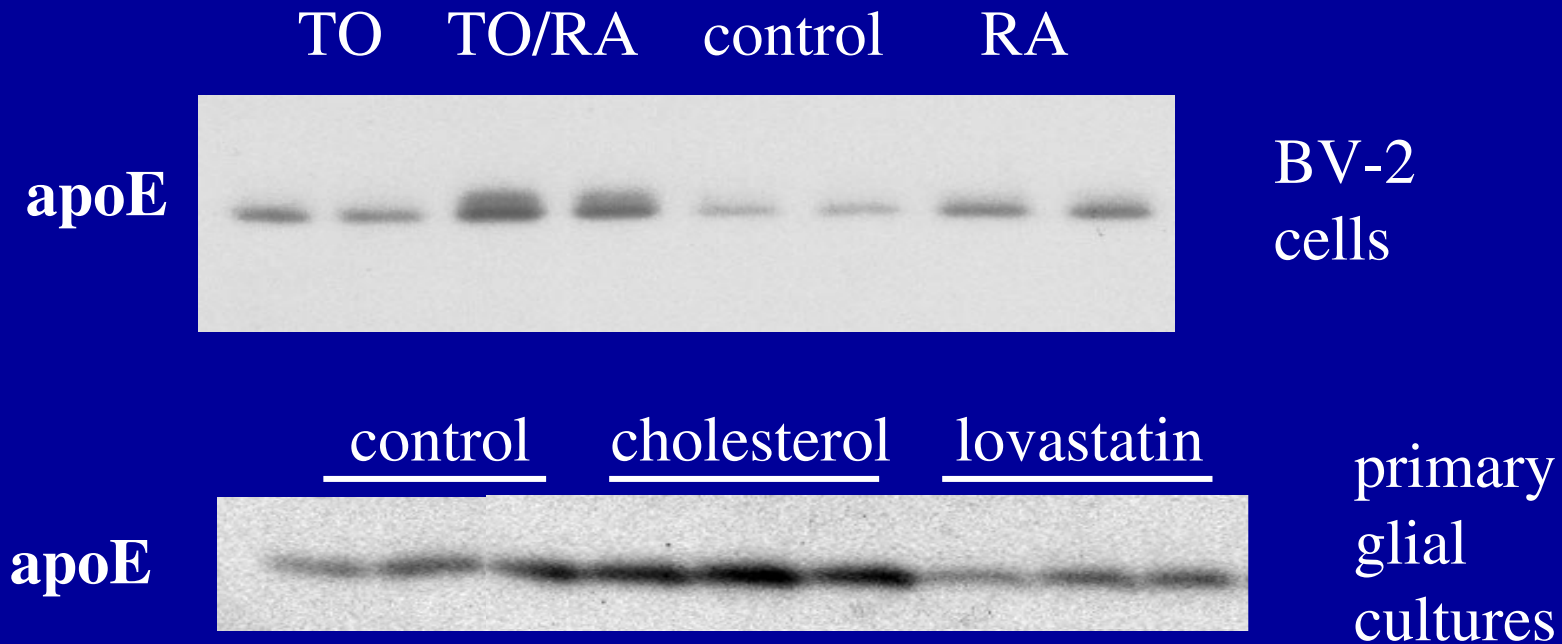
# Induction of LXR by high cholesterol levels



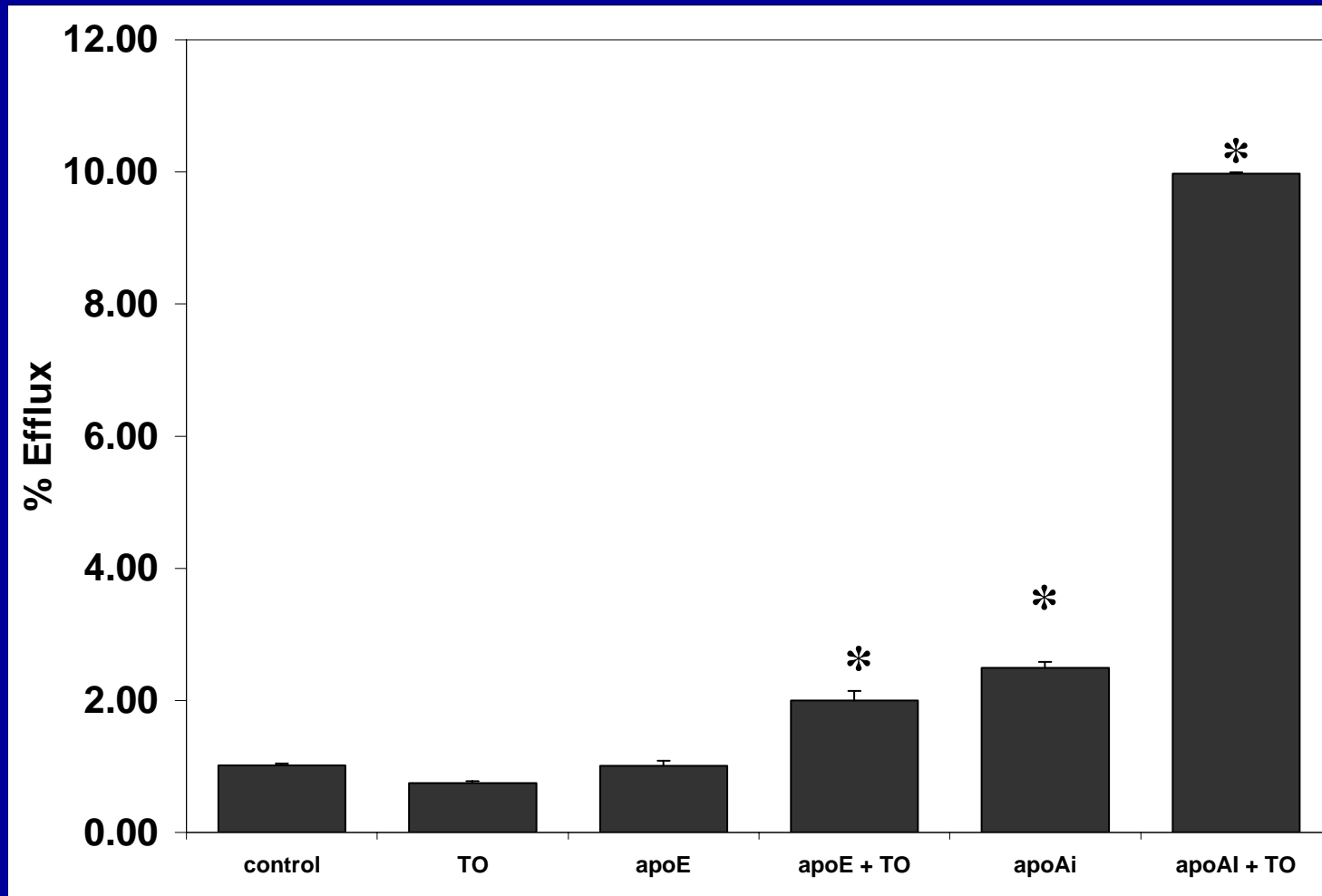
# Induction of genes in neuroblastoma cells by LXR activation: gene chip analysis of mRNA

	<u>fold change</u>
• ABC-G1	4.2
• ABC-A1	2.6
• SREBP-1	2.3
• Fatty acid CoA ligase	1.7
• Stearoyl CoA desaturase	1.7

# ApoE levels are altered by LXR agonists and cholesterol



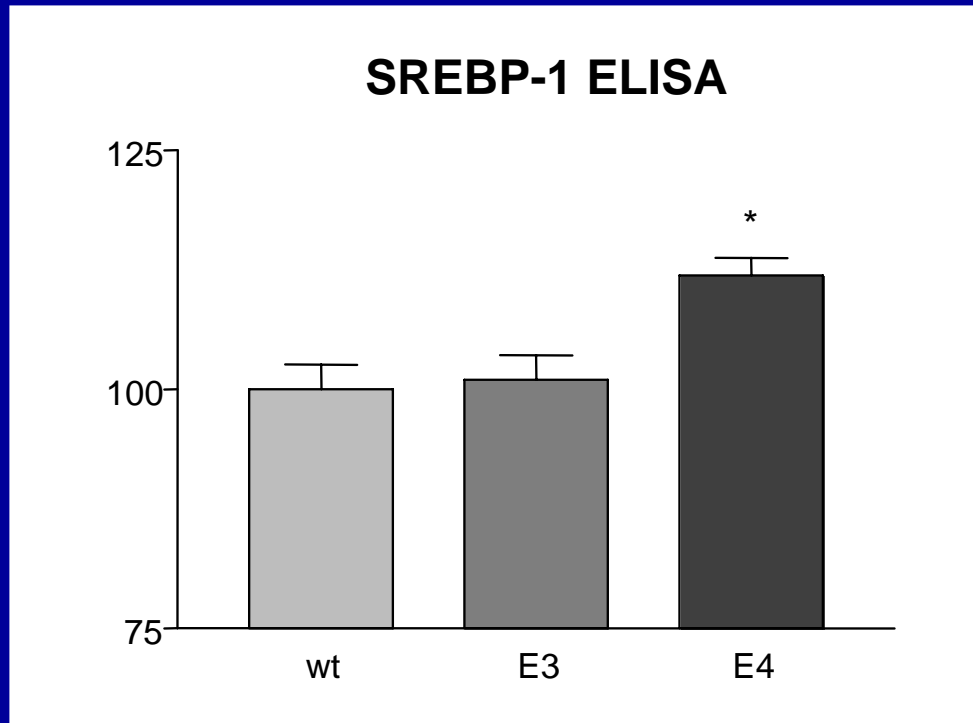
# Activation of LXR induces cholesterol efflux to apoE





# APOE genotype alters levels of SREBP cleaved fragment

% wt  
control

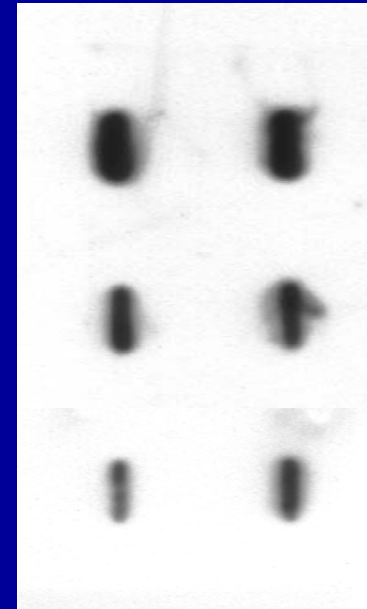


GFAP-APOE mice  
(APOE replacement mice)

# Diet and a cholesterol-lowering drug affect brain APOE mRNA

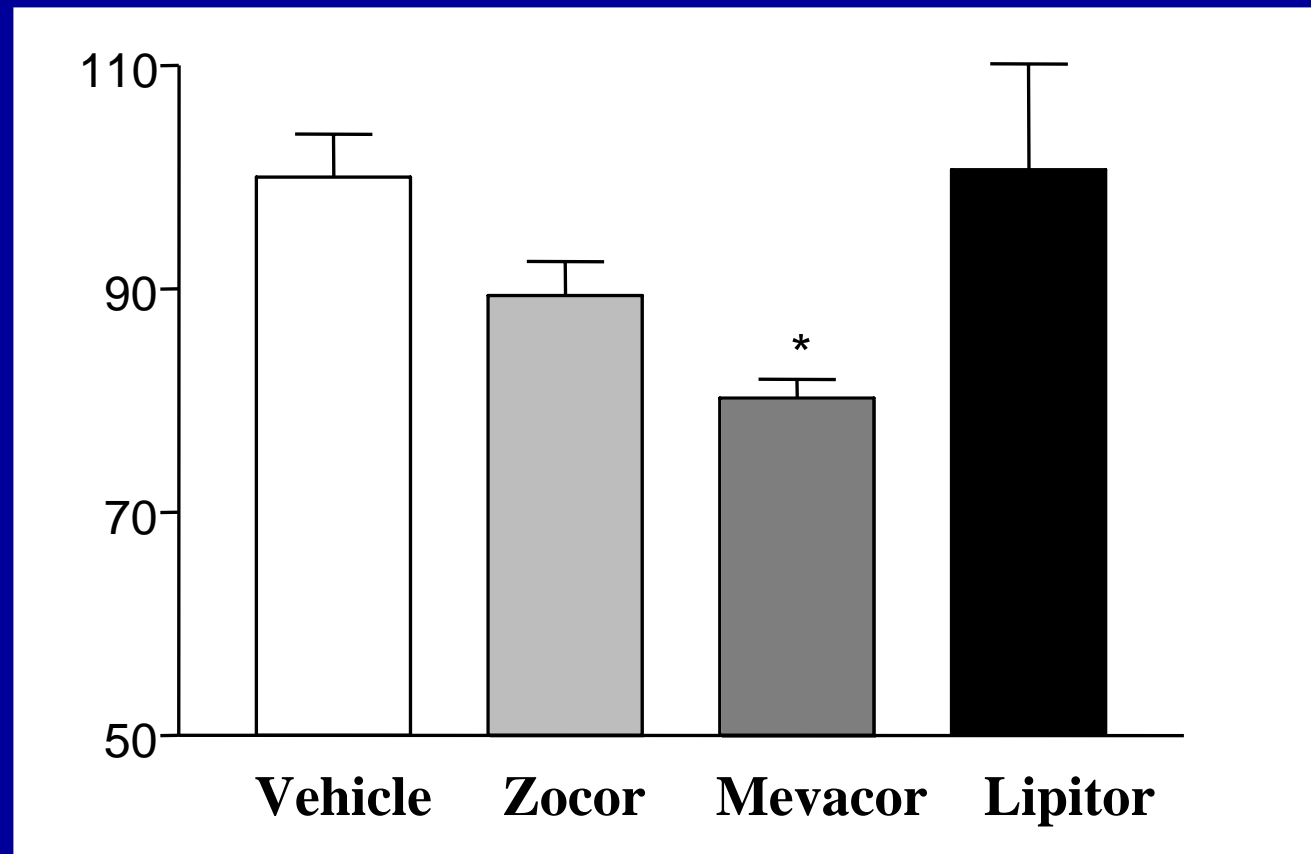
## Treatment      Plasma Cholesterol (mg/dl)

High cholesterol	200
Vehicle	75
BM 15.766	28



Petanceska, 2004

# Brain-permeable statins affect brain cholesterol



Synaptosomal  
Plasma  
Membrane  
Cholesterol  
(% control)

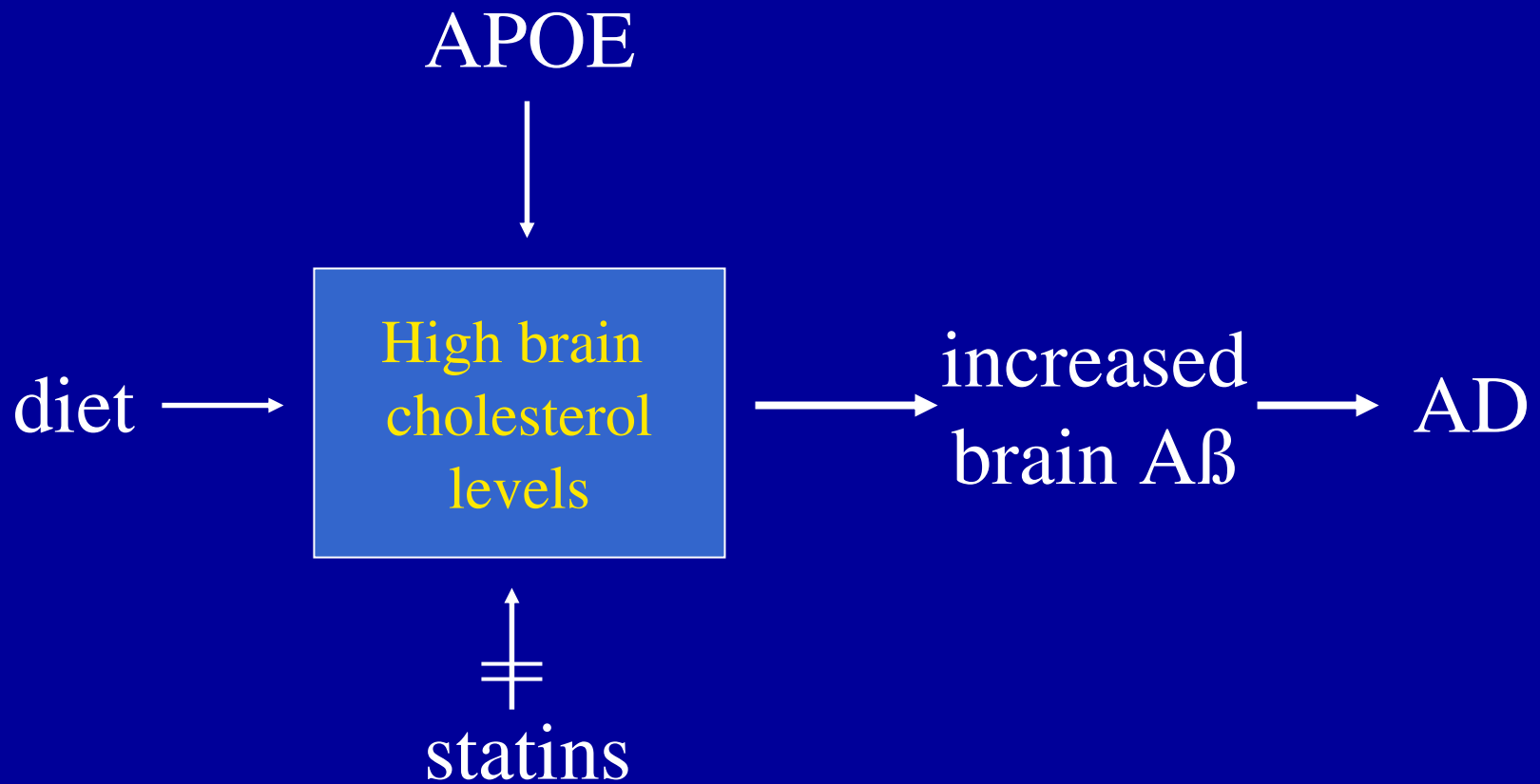
Lipophilicity:

++

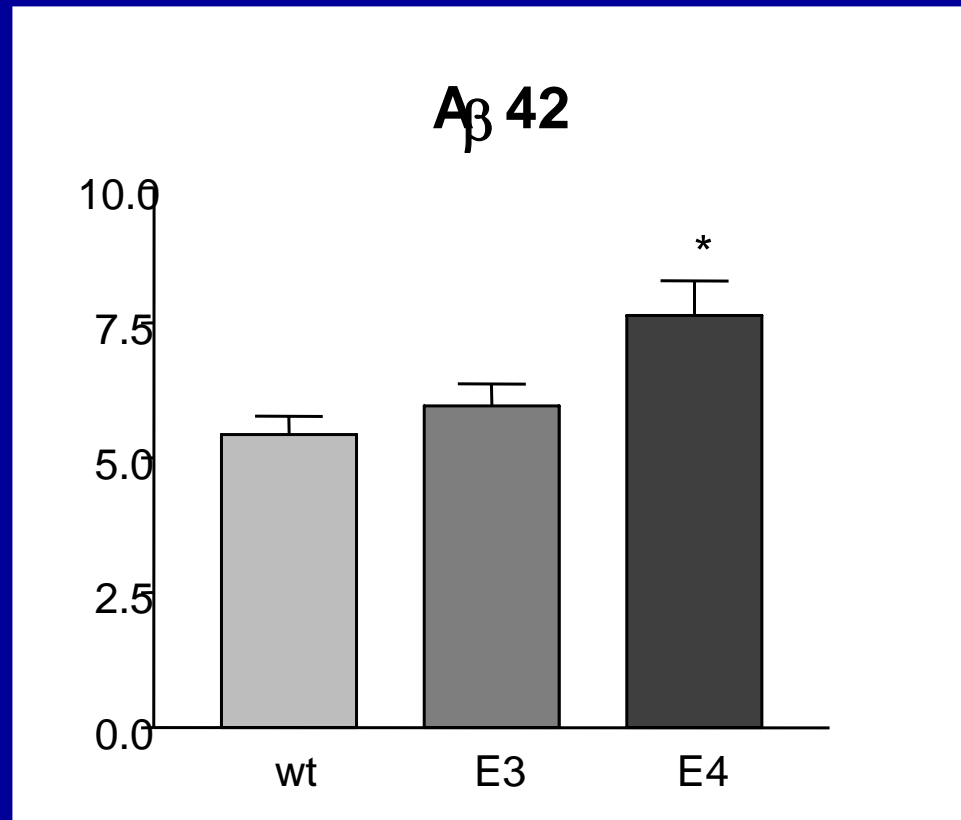
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# Oversimplified cholesterol hypothesis

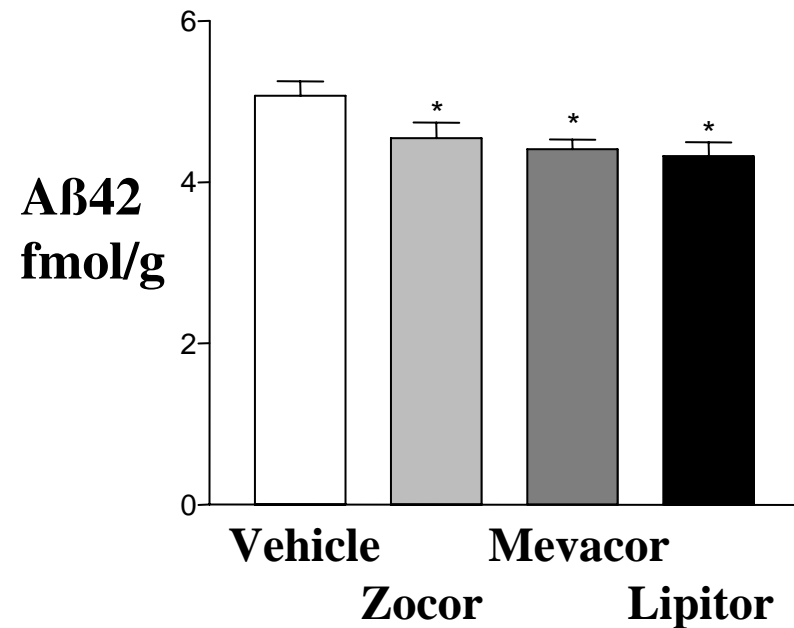
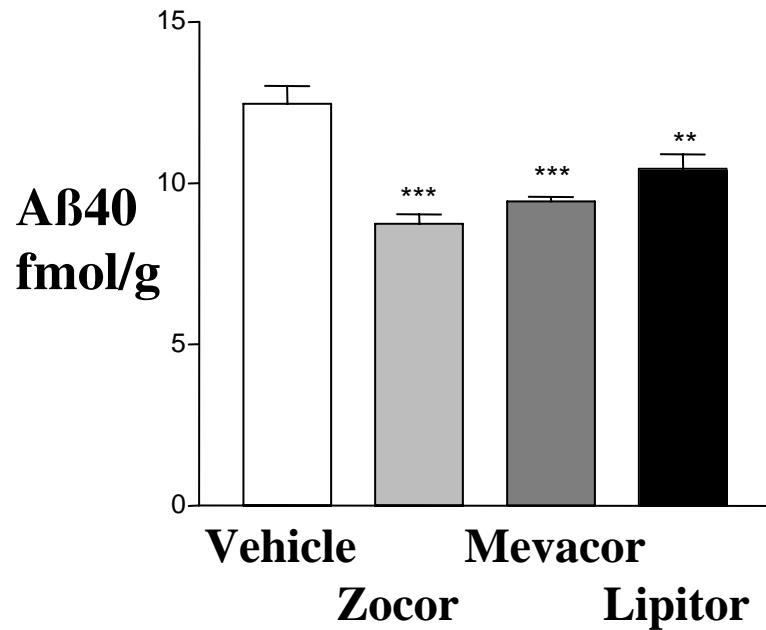


# APOE- $\epsilon$ 4 increases brain A $\beta$ levels



GFAP-APOE mice  
(APOE replacement mice)

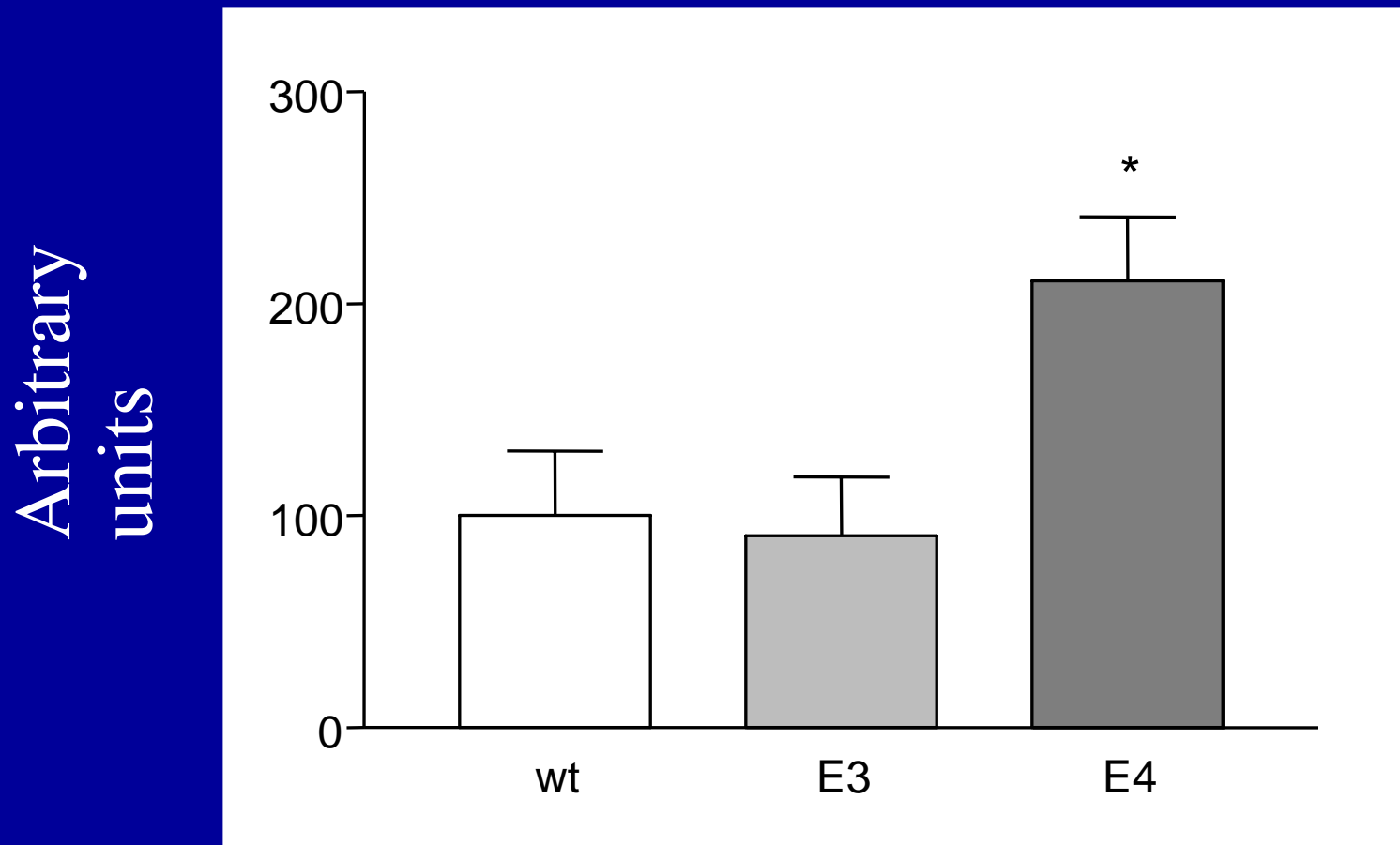
# Statins decrease brain A $\beta$



# How could effects on brain cholesterol alter A $\beta$ levels?

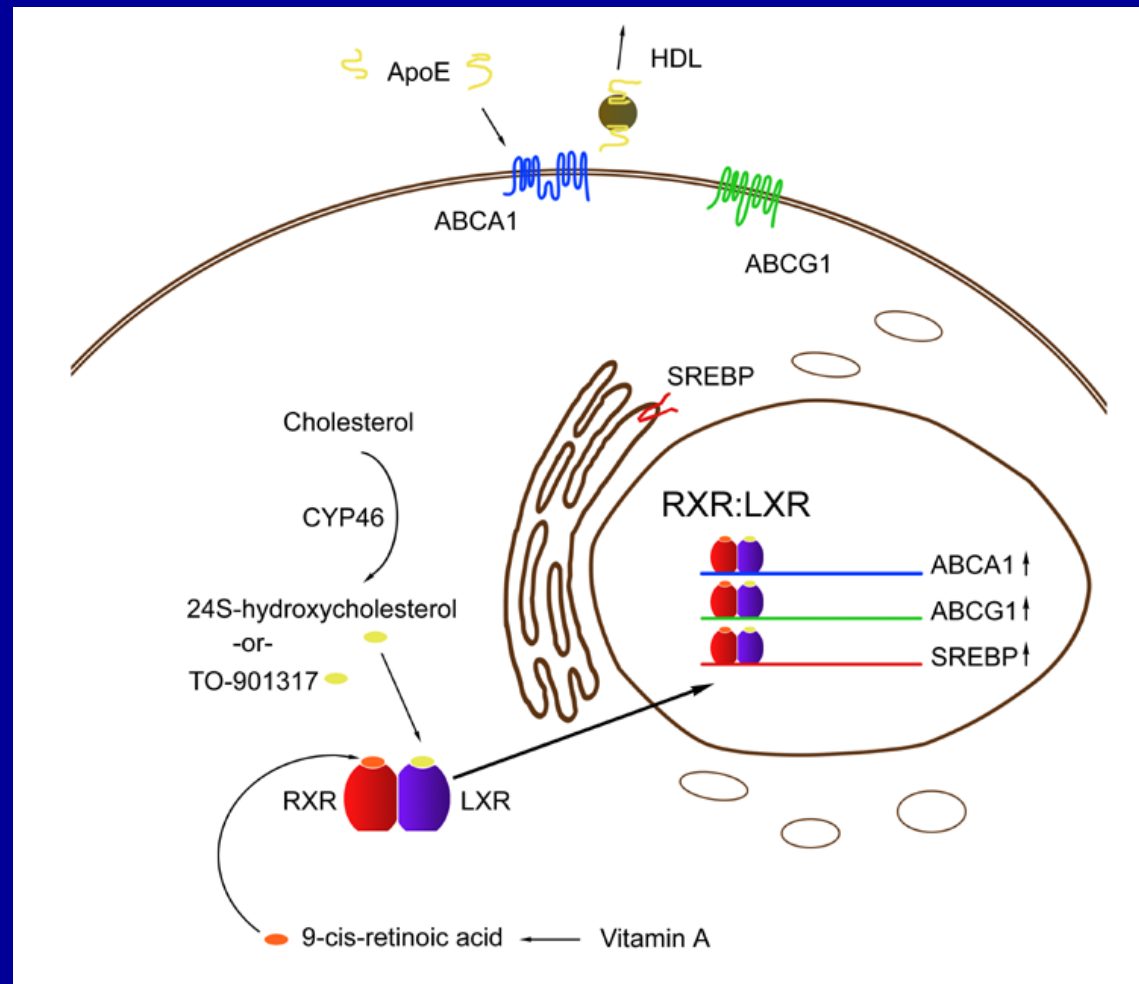
- Effects on membrane (like SREBP)
  - APP is transmembrane
    - $\alpha$ -,  $\beta$ -,  $\gamma$ -secretases are transmembrane proteins
- Effects on gene expression (downstream)
  - Cholesterol equilibrium mechanisms

# APOE affects $\gamma$ -secretase activity in lipid rafts



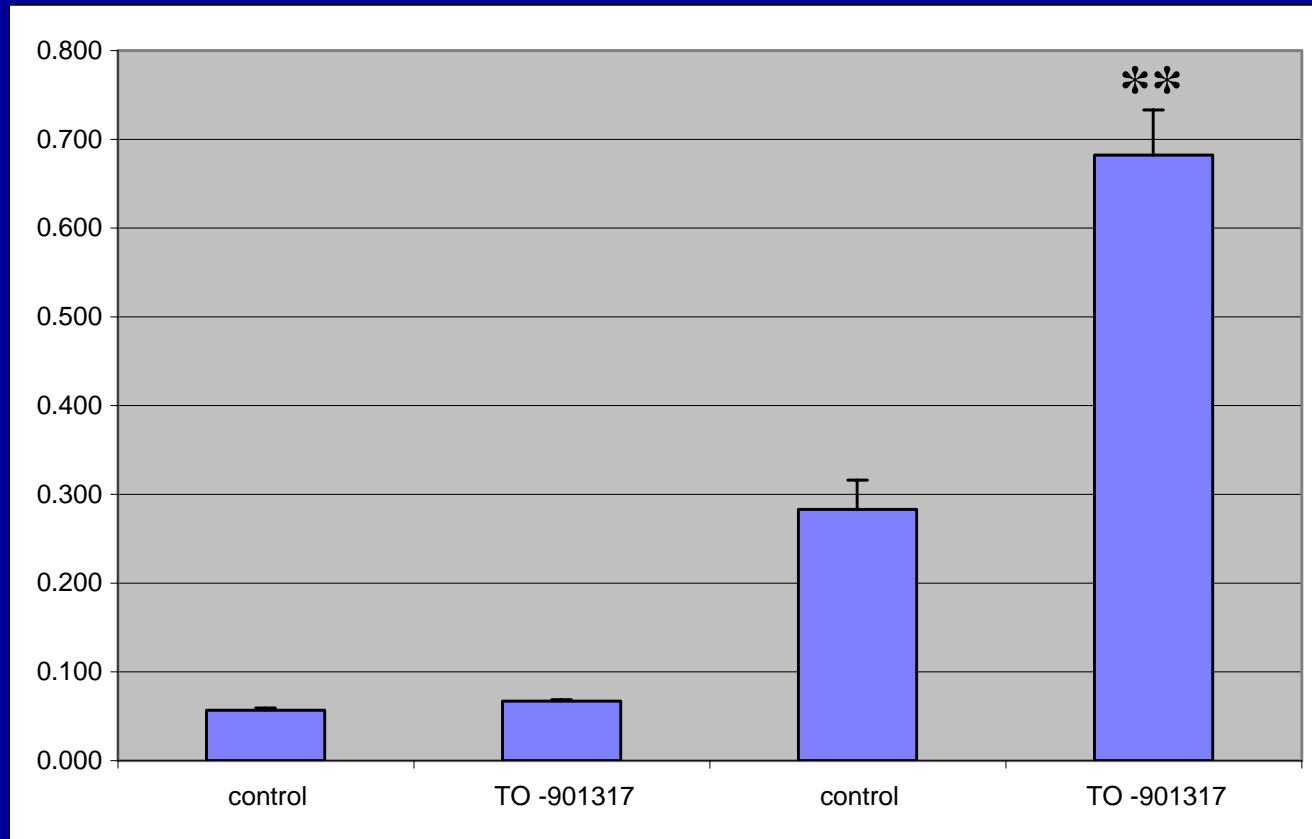


# Cholesterol could affect A $\beta$ levels through induction of LXR system



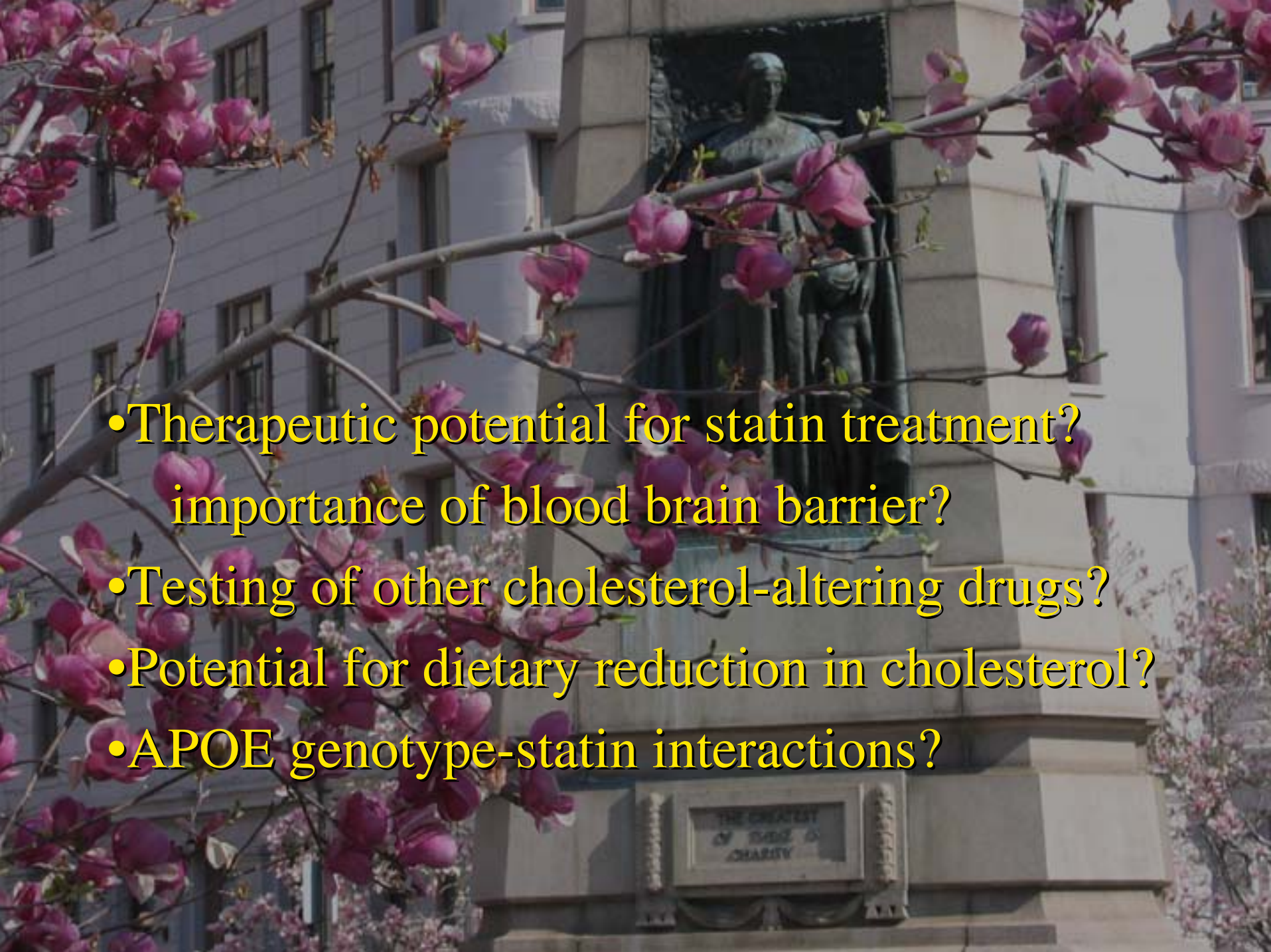
# Activation of LXR increases secreted A $\beta$ 42 levels

A $\beta$ 42  
levels



24 hours

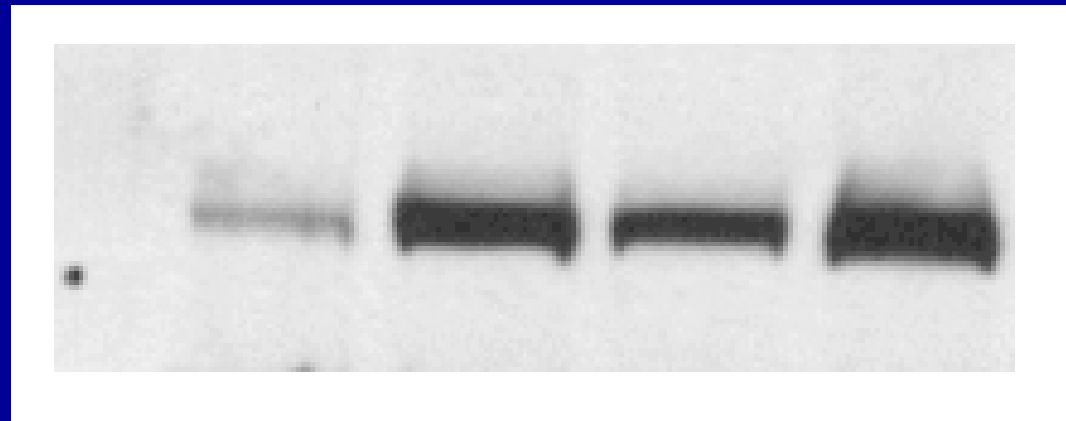
48 hours

- 
- A photograph of a building with a statue and pink flowers in the foreground. The statue is a dark, standing figure on a pedestal. The building is light-colored with many windows. The foreground is filled with pink flowers on thin branches. The text is overlaid on the image in a yellow, bold font.
- 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

con    22OH    24OH    24OH  
         RA        RA

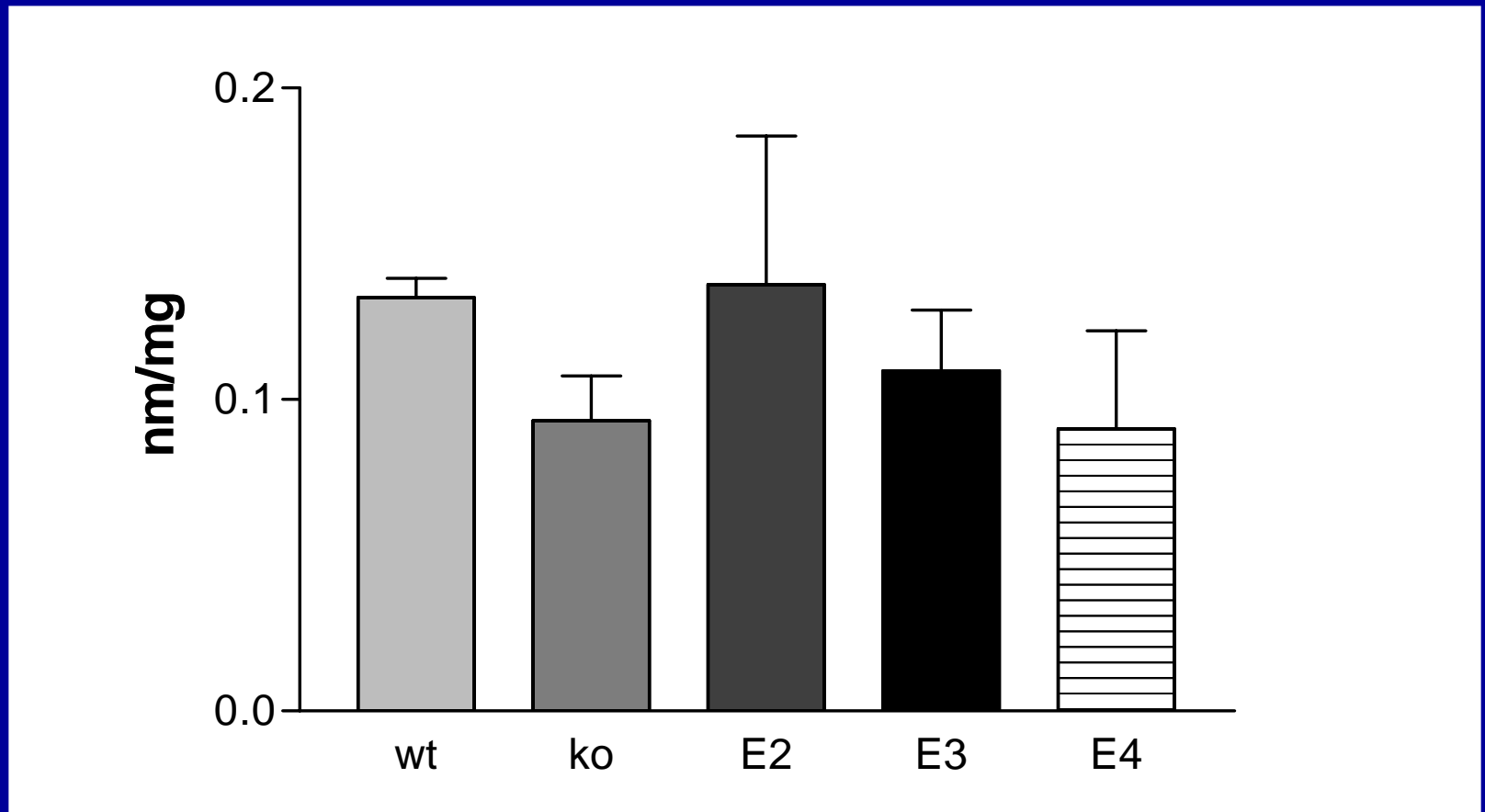
ABC-A1



QuickTime™ and a  
TIFF (Uncompressed) decompressor  
are needed to see this picture.

Burns et al, J Neurosci (2003) 23:5645

# APOE genotype alters cholesterol hydroxylation



QuickTime™ and a  
TIFF (Uncompressed) decompressor  
are needed to see this picture.

Tontonoz and Mangelsdorf, 2003

# Niemann Pick type C



Burns et al, J Neurosci (2003) 23:5645



# Cholesterol synthesis

3 Hydroxy-3-methylglutaryl-CoA



Mevalonate



Farnesyl pyrophosphate



Squalene



Desmosterol



**Cholesterol**