

How Lipoprotein Receptors  
Shape Your Brain

Lecture 3

September 29, 2005

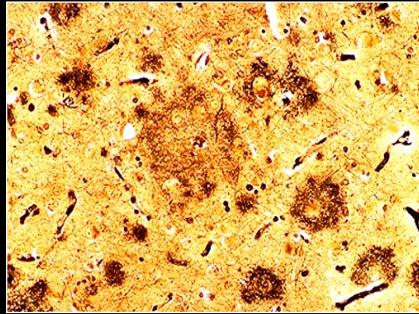
ERFINDER

- I. Roles of Lipoprotein Receptors in the Embryonic Development of the Brain
- II. Using Knockouts to Map Genetic Modifiers
- III. How the Findings in the Embryo Translate into the Function of the Adult Brain

# The Hallmarks of Alzheimer Disease

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**Amyloid Plaques**



**Neurofibrillary Tangles**



From: Medical Library of Utah

# Apolipoprotein E

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Is a component of lipoproteins and mediates their binding to LDL receptor family members

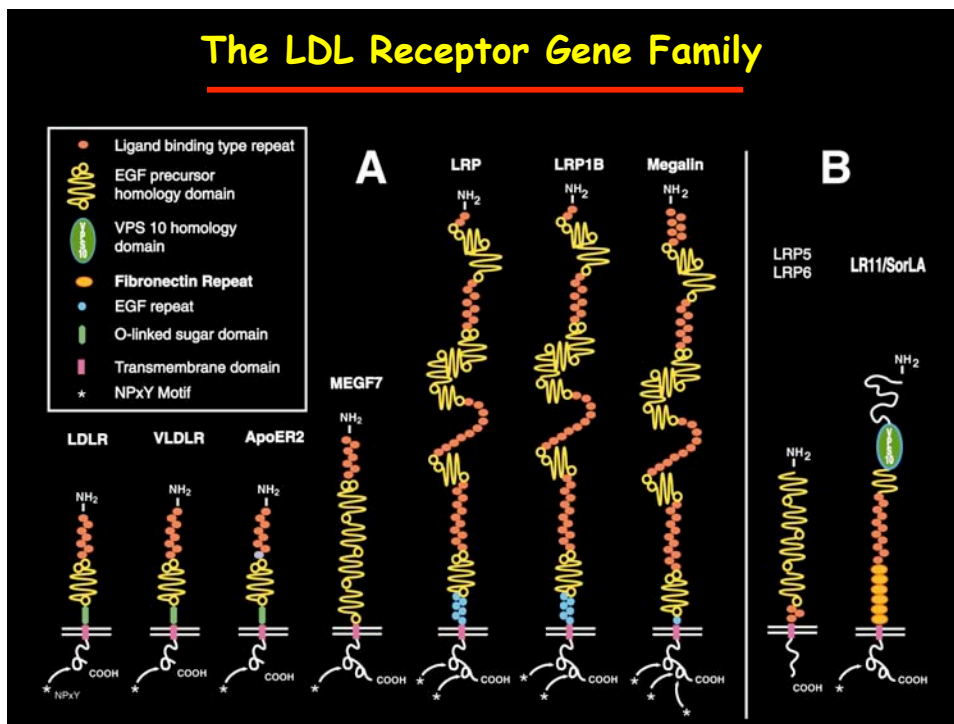
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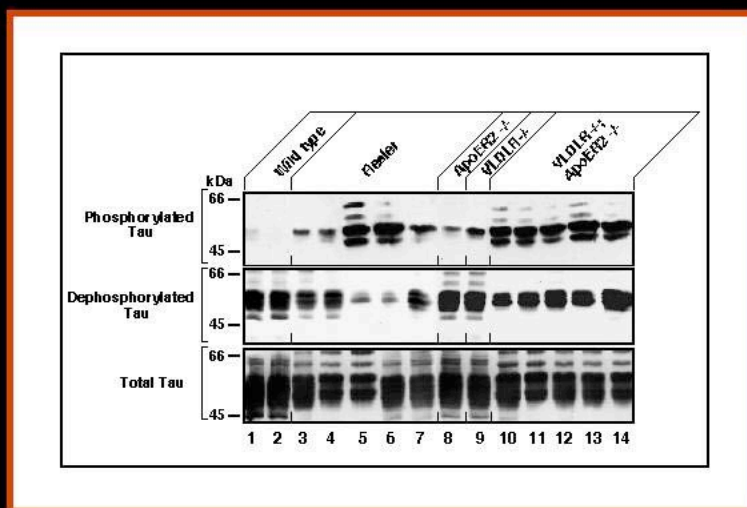
In 1993 Allan Roses and his group report that the ApoE4 isoform predisposes its carriers to late-onset Alzheimer Disease



## The LDL Receptor Gene Family



## Tau Hyperphosphorylation in *reeler*, *apoer2*, and *vldlr* Knockout Mice

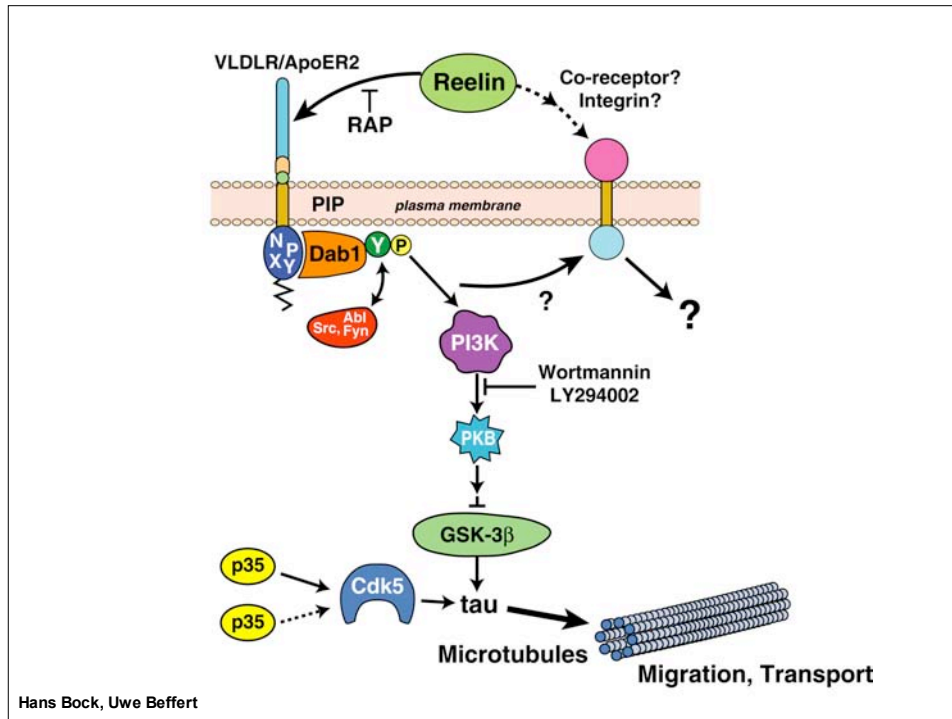


## Reelin Suppresses $\tau$ -Phosphorylation in Primary Embryonic Neurons



## Reelin Induced Phosphorylation of PKB and GSK-3 $\beta$ Involves PI3-Kinase

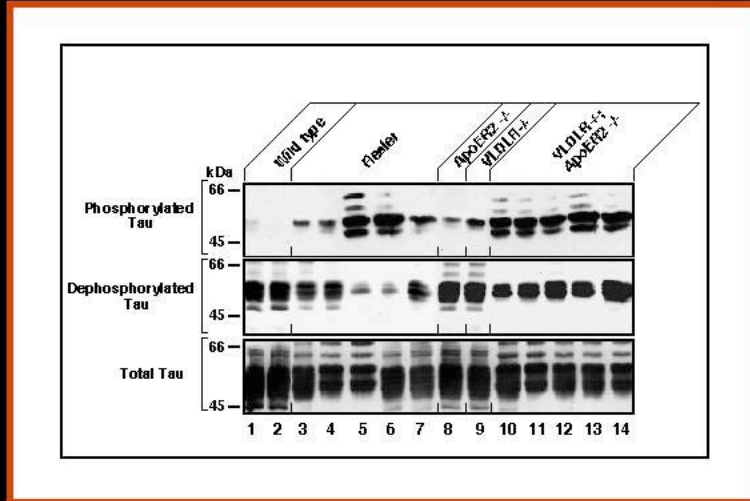




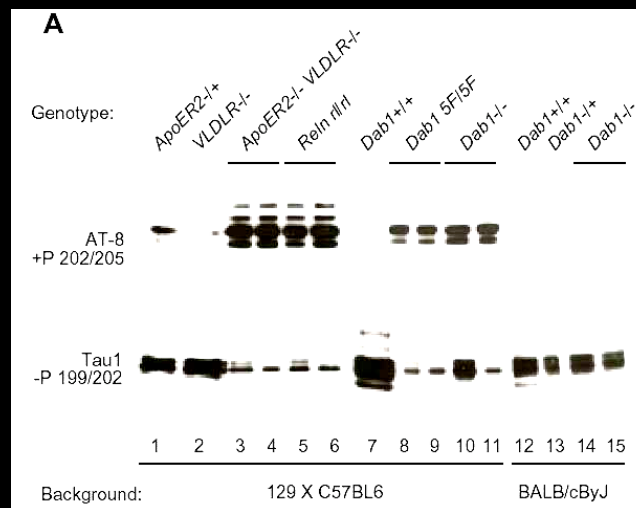
## Expanding Functions of ApoE Receptors

- ApoE Receptor Signaling Controls Neuronal Positioning During Brain Development
- ApoE Receptor Signaling Regulates  $\tau$ -Phosphorylation
- Mapping of Genes that Modify  $\tau$ -Phosphorylation
- ApoE Receptors Modulate Neurotransmission
- Tyrosine-Phosphorylation of ApoE Receptors and Control of Vascular Wall Integrity

## Tau Hyperphosphorylation in *reeler*, *apoer2*, and *vldlr* Knockout Mice



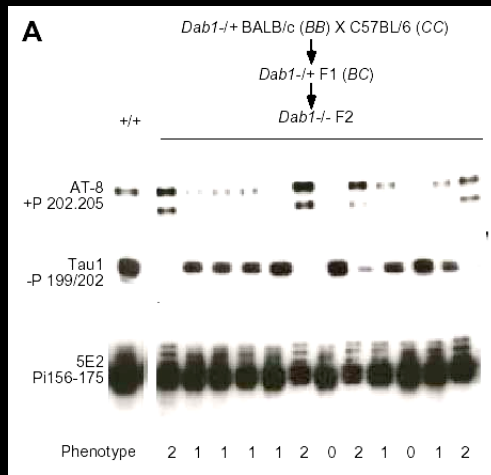
## Role of Dab1 and Strain Background on $\tau$ -Phosphorylation in Mice



Jochen  
Brich, 2001

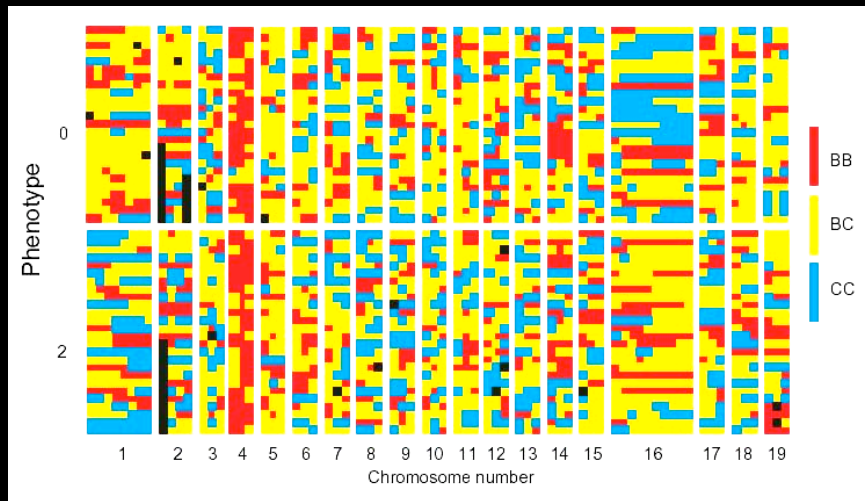
Jon  
Cooper, 2001

## $\tau$ -Phosphorylation in *dab1*-Deficient F2 Mice



Jochen  
Brich, 2001

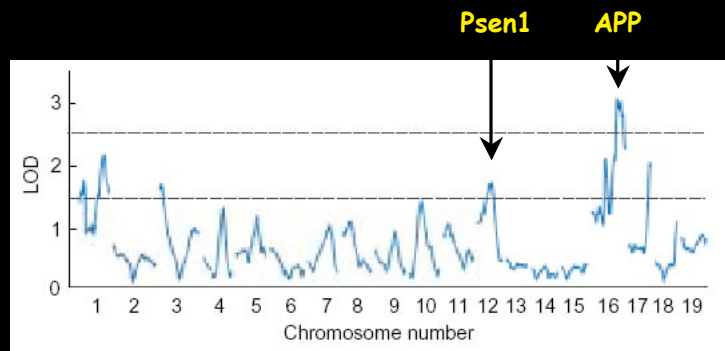
## Allele and Phenotype Distribution in F<sub>2</sub>-Intercrosses



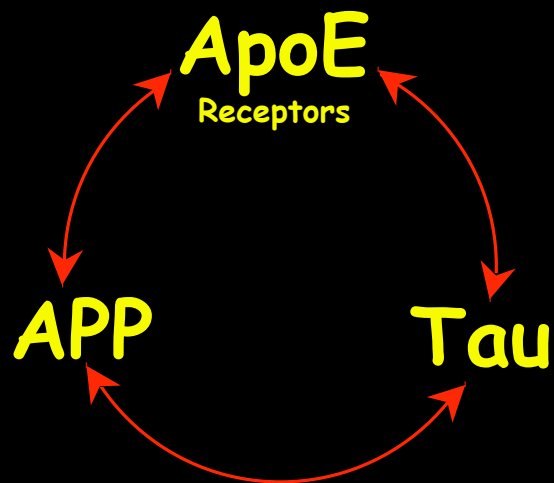
0=low P- $\tau$ ; 2=high P- $\tau$ ; B=Balb/c; C=C57BL/6

Jochen Brich, 2001

## QTLs in the Mouse Genome that Modulate $\tau$ -Phosphorylation



Gary Churchill, 2002



- **ApoE Receptors Control Neuronal Migration During Brain Development**
- **ApoE Receptor Signaling Modulates  $\tau$ -phosphorylation in the postnatal mouse brain**

- **ApoE Receptors Control Neuronal Migration During Brain Development**
- **ApoE Receptor Signaling Modulates  $\tau$ -phosphorylation in the postnatal mouse brain**
- **ApoER2, VLDLR and Dab1 Continue to Be Expressed by Neurons in the Adult Brain**
- **Reelin Is Now Expressed by A Subset of GABAergic Interneurons**

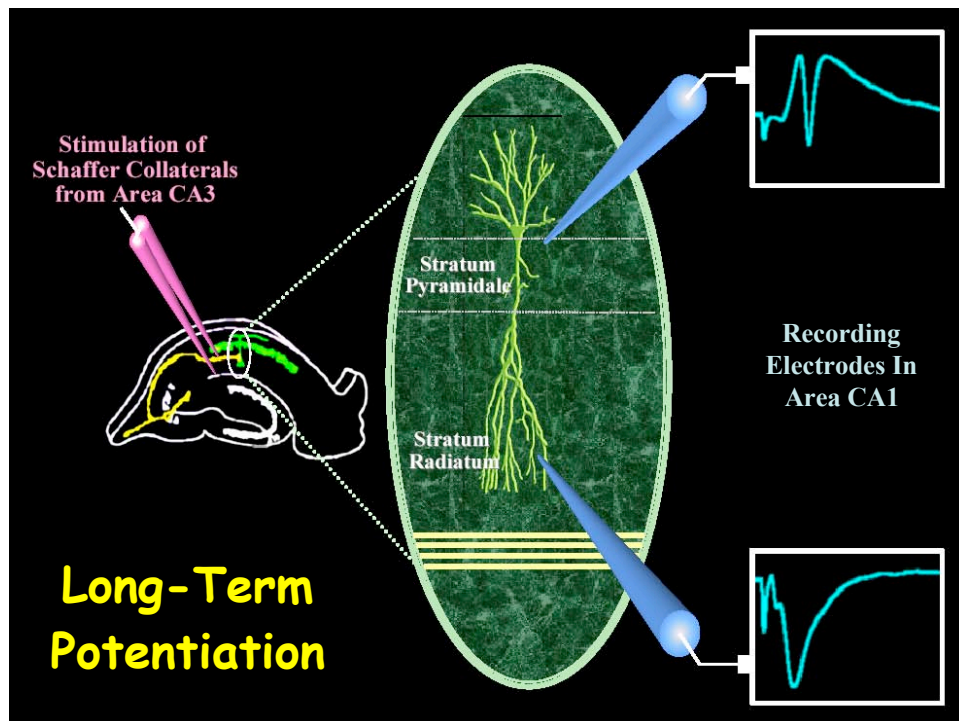
## Loss of Synapses

- Not Plaques or Tangles -

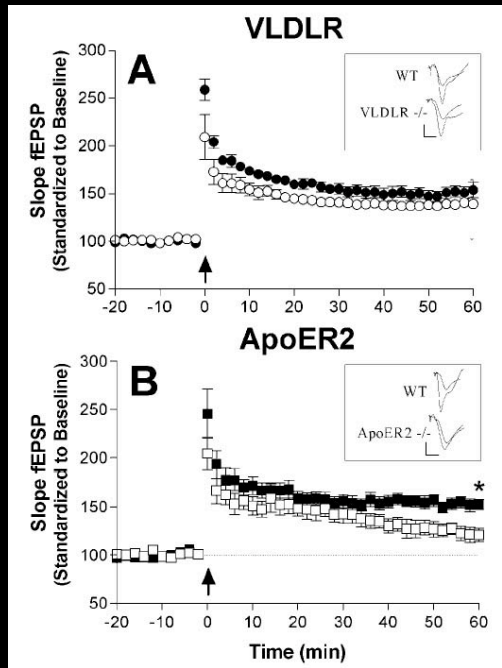
Correlates Most Closely With  
Alzheimer's Dementia

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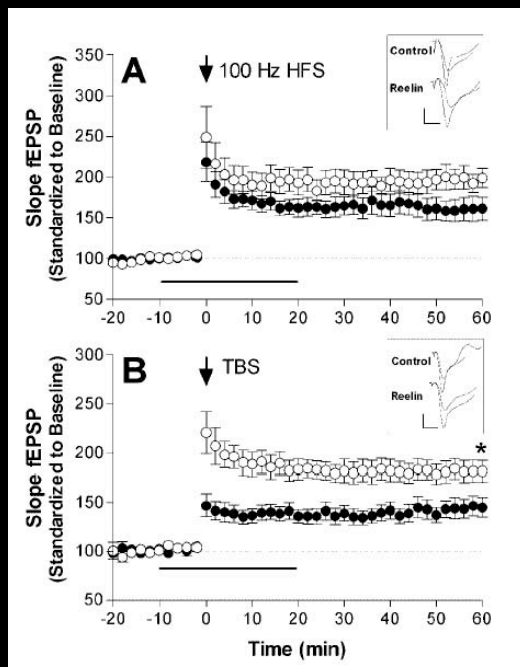
Do ApoE Receptors Function  
at the Level of the Synapse?



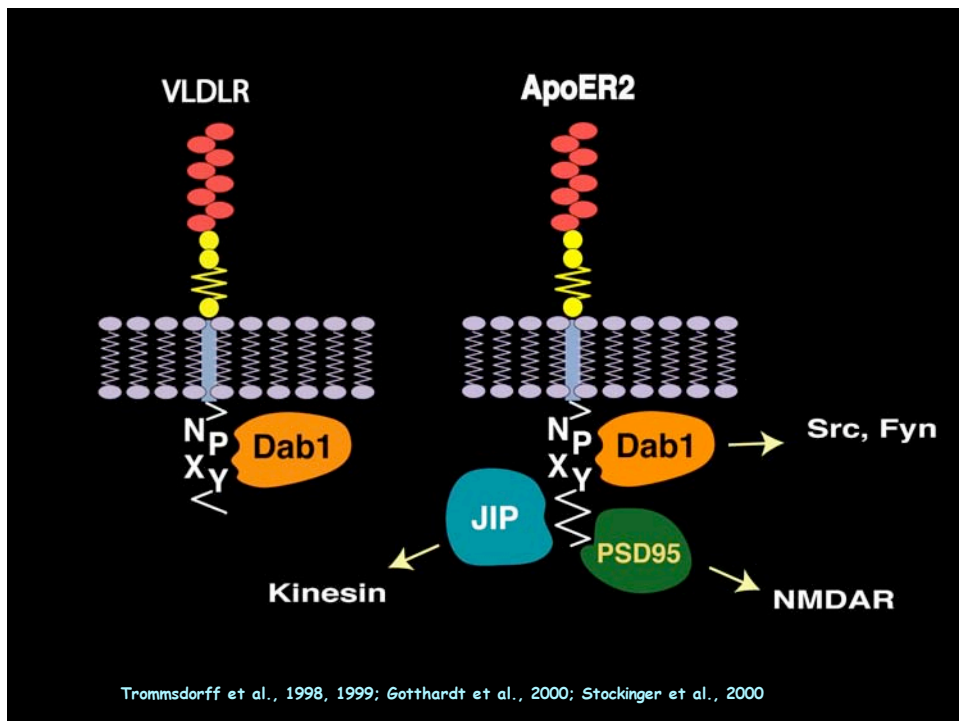
**LTP  
Defect  
in  
ApoER2  
Knockout  
Mice**



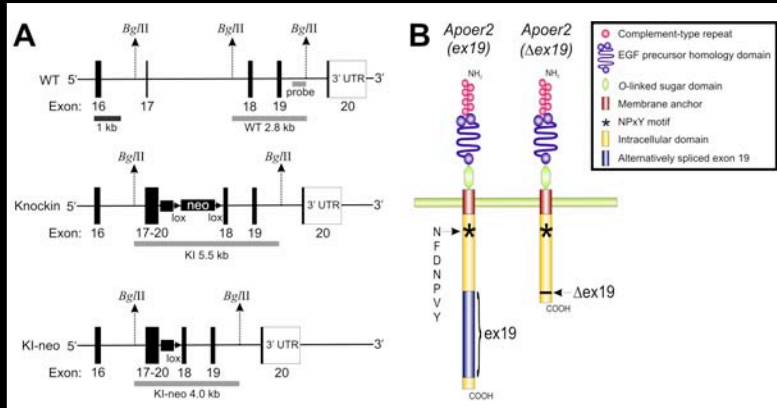
**Reelin  
Stimulates  
LTP in  
Hippocampal  
Slices  
from Wild  
Type Mice**



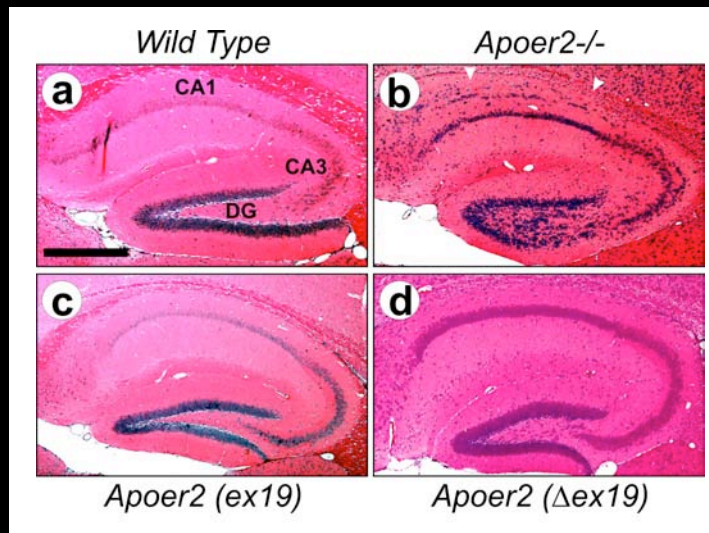
# How Does It Work?



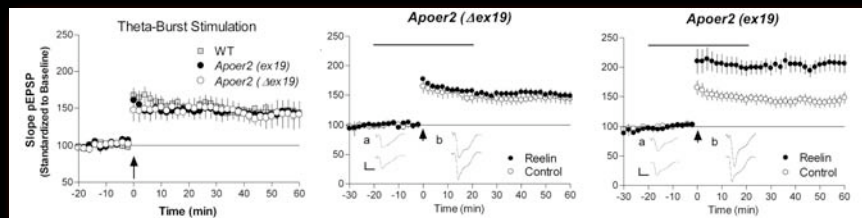
## Generation of ApoER2 Knockin Splice Variants



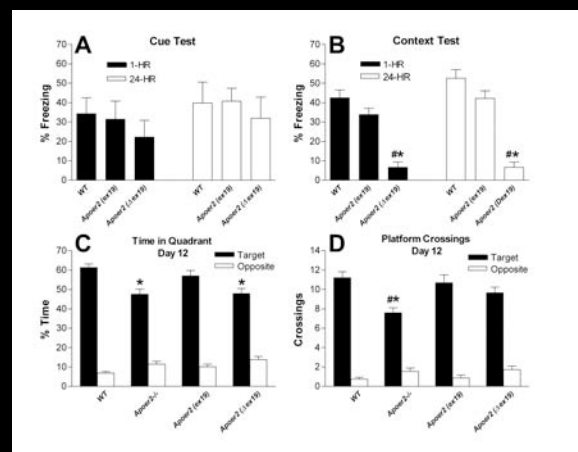
## Normal Hippocampal Anatomy in Apoer2 Knockin Mutants



## LTP Enhancement by Reelin Requires the Alternatively Spliced Exon 19

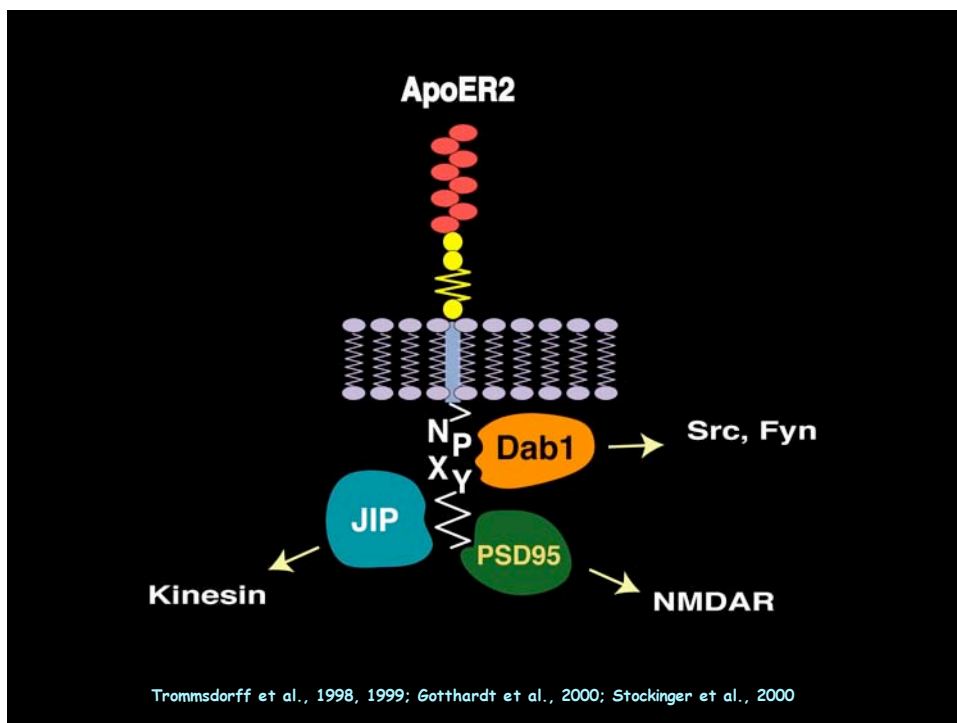


## Memory and Learning Defects in ApoER2 Mutant Mice

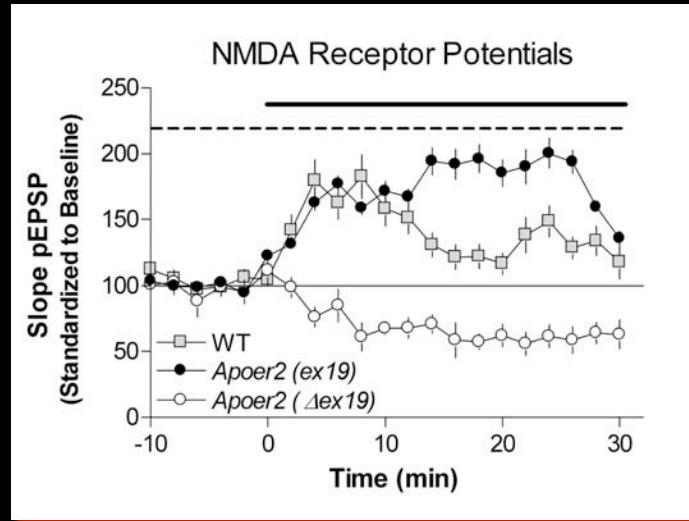


**A Single Alternatively Spliced Exon in the  
Cytoplasmic Domain of ApoER2 Is Required  
for the Effect of the Reelin Signal on LTP,  
Learning and Behavior**

**What is the Mechanism?**

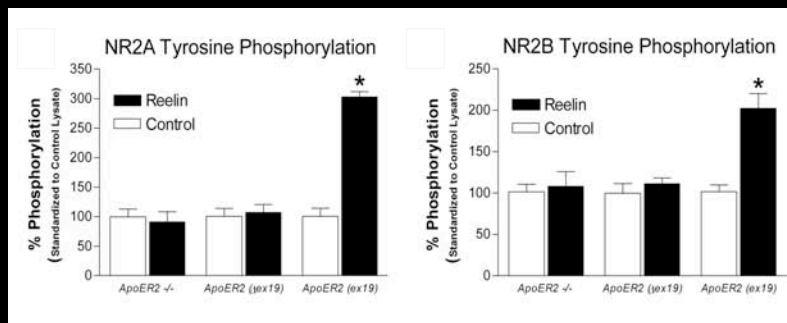


## Exon 19 Is Required for Activating NMDA Receptors

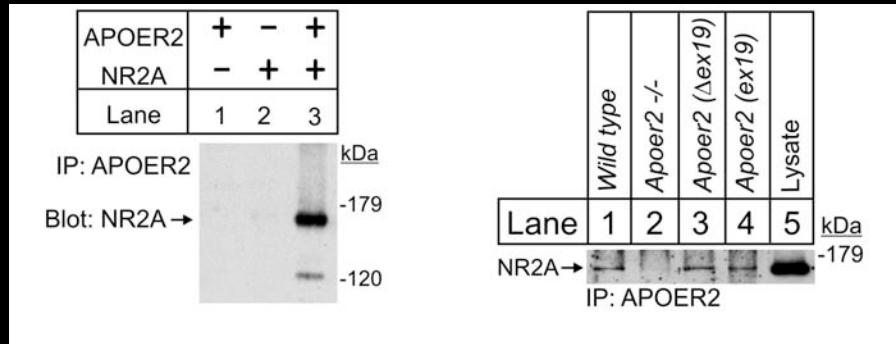


(determined in presence of CNQX)

## Reelin Mediates Tyrosine-Phosphorylation of the NMDA Receptor Through ApoER2



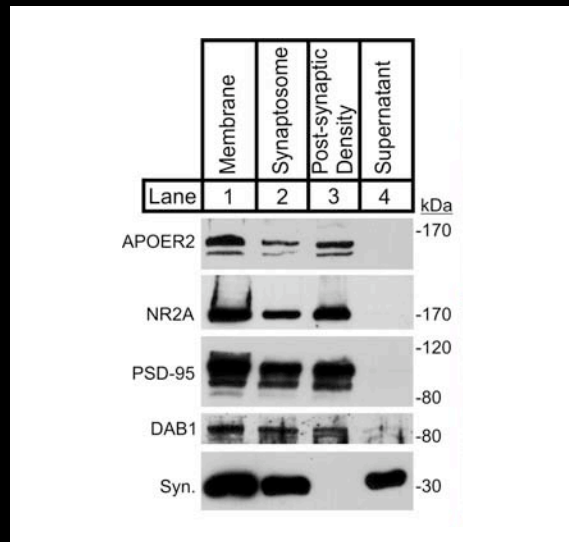
## ApoER2 Directly Interacts With NMDA Receptors



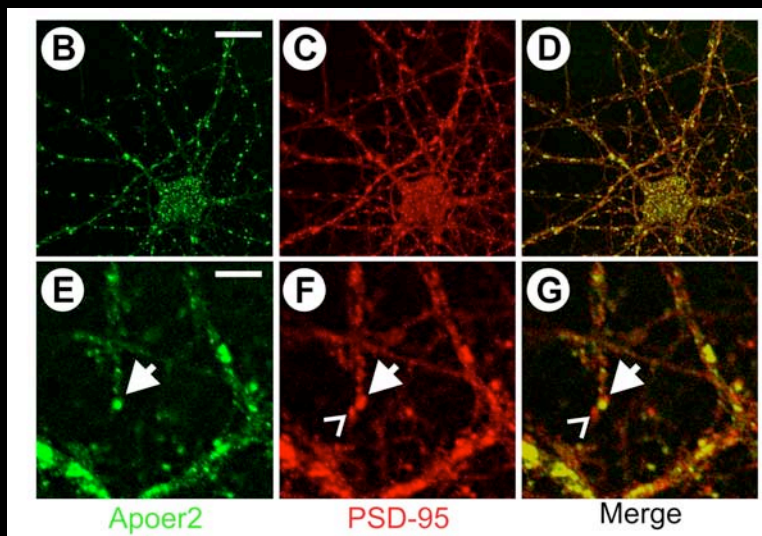
**ApoER2 Interacts With the NMDA Receptor  
And Appears to Modulate Its Function....**

**...But Is It Actually in the Synapse?**

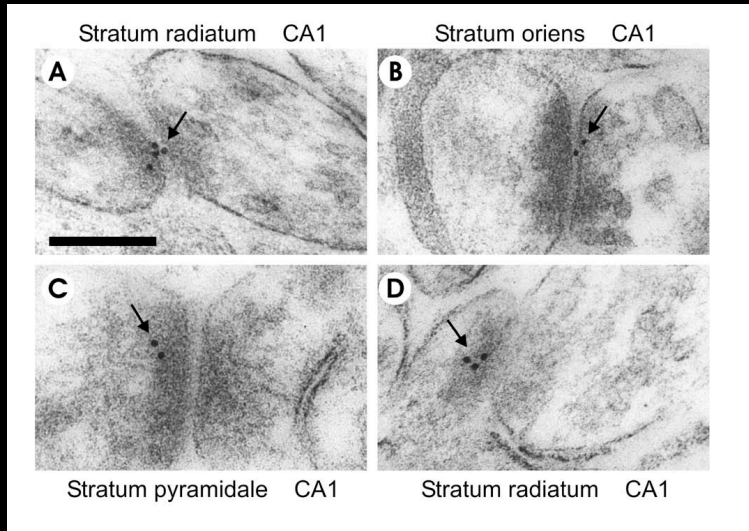
## ApoER2 and Dab1 Are Present in the Postsynaptic Density



## ApoER2 Colocalizes with PSD95 To A Subset of Synapses

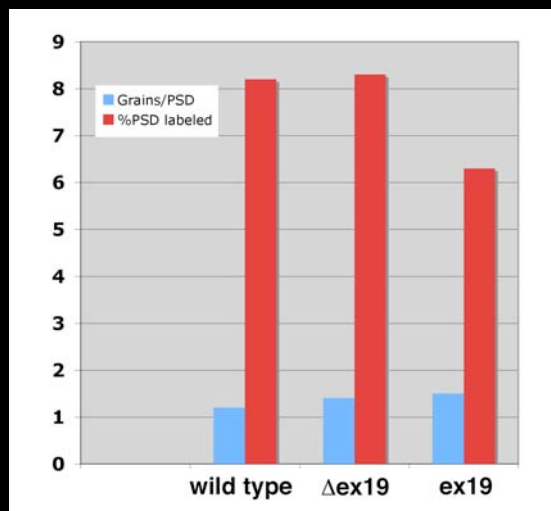


## ApoER2 Is Present At the Synapse

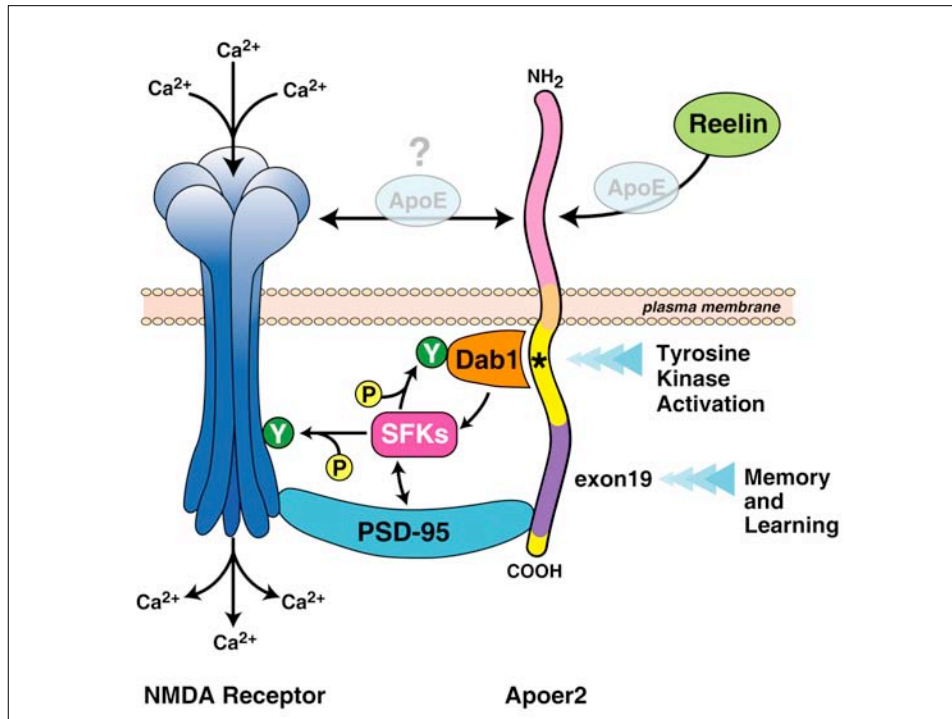


Michael Frotscher, 2003

## Distribution of ApoER2 in CA1 Synapses



Giselind Adelman, 2004



## Conclusions

The LDL receptor gene family controls a wide variety of cellular signaling pathways. This includes the direct activation as well as indirect modulation of tyrosine kinases and ion channel conductance.

**ApoE receptors** (ApoER2 and VLDLR) regulate both brain development and synaptic transmission through similar basic mechanisms that involve signaling through Reelin and the adaptor protein Dab1.

Do ApoE isoforms differentially affect the coupling of ApoE receptors to the NMDA receptor. Could this play a role in the pathogenesis of Alzheimer's disease?

