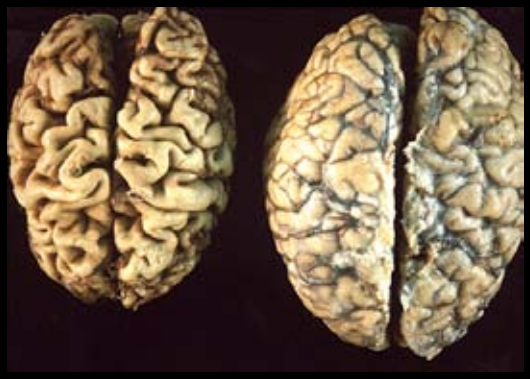
Alzheimer's Disease

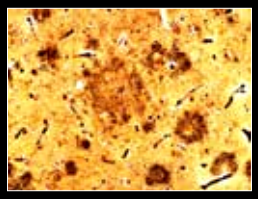
Joachim Herz

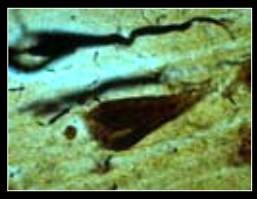
STARS
January 11, 2010



The Hallmarks of Alzheimer Disease

Amyloid Plaques | Neurofibrillary Tangles





From: Medical Library of Utah

- **1906** First description of Alzheimer's Disease
- **1984** George Glenner identifies the Aβ protein as the main component of amyloid plaques, giving birth to the amyloid hypothesis
- **1987** Cloning of the gene encoding the amyloid precursor protein (APP)
- **1991** Identification of mutations in the amyloid precursor protein in patients with familial (early onset) Alzheimer's Disease
- **1995** Identification of mutations in presenilins, the proteases (secretases) that release Aβ from APP
- **1999** Immunization of transgenic, amyloid producing mice removes Aβ deposits from their brains

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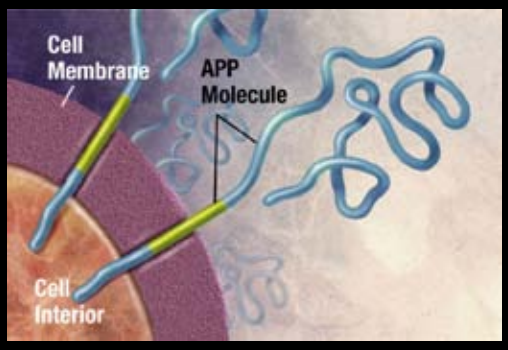
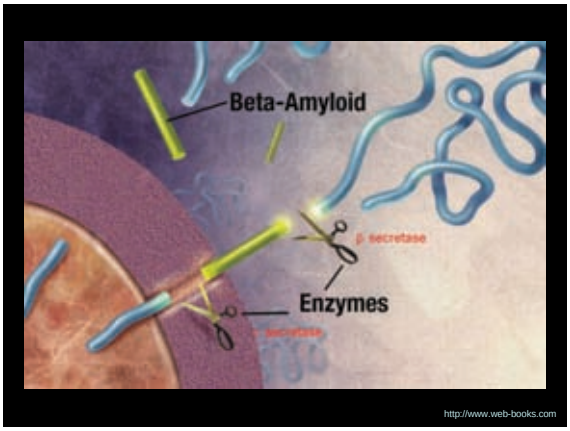
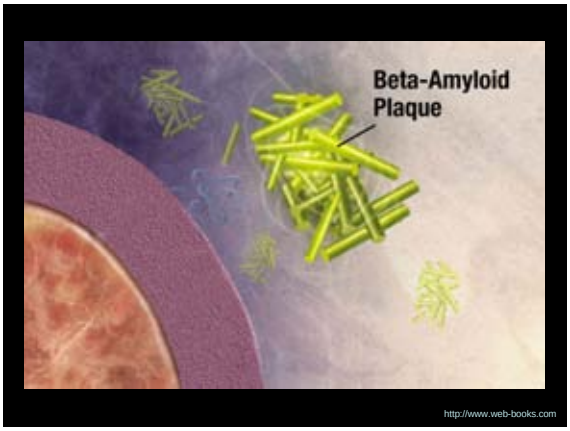
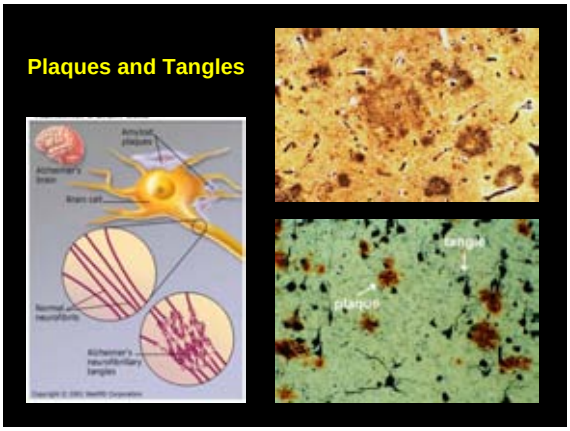
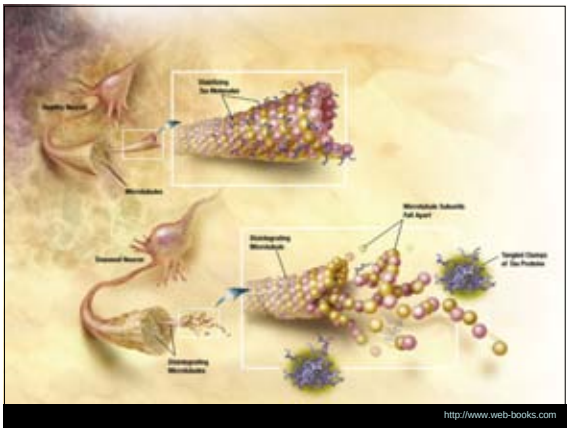


http://www.web-books.com


Beta-Amyloid
β secretase
Enzymes
γ secretase
http://www.web-books.com


Beta-Amyloid
Plaque
http://www.web-books.com


Plaques and Tangles
tangle
plaque

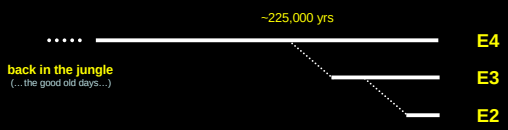


Apolipoprotein E

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

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

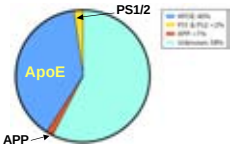
Evolution of ApoE Isoforms



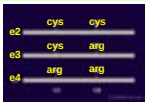
	112	158	GP	AD
E4	Arg	Arg	20	~50
E3	Cys	Arg	75	~50
E2	Cys	Cys	5	~ 1

Alzheimer's Disease - Genetic Risk Factors

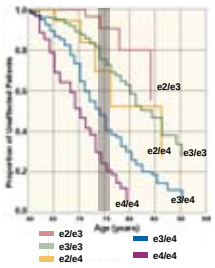
Genetic risk factors for AD



ApoE is the major apolipoprotein in the brain. Humans have three ApoE alleles: ε2, ε3, ε4.



ε4 allele of apoE predisposes its carrier to AD.



Percentage of Survivors

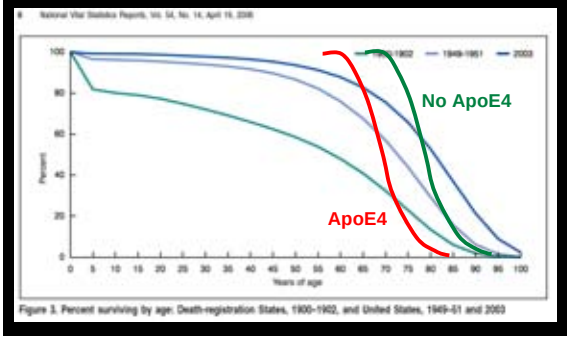
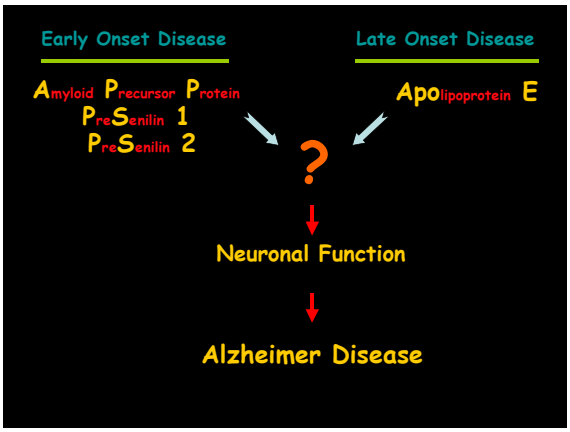
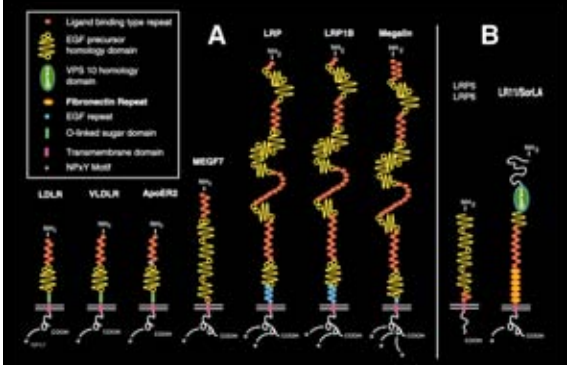


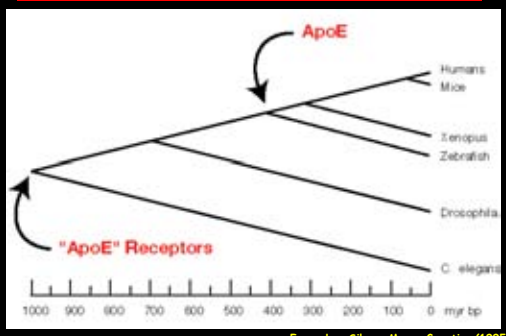
Figure 3. Percent surviving by age: Death-registration States, 1900–1902, and United States, 1949–51 and 2003



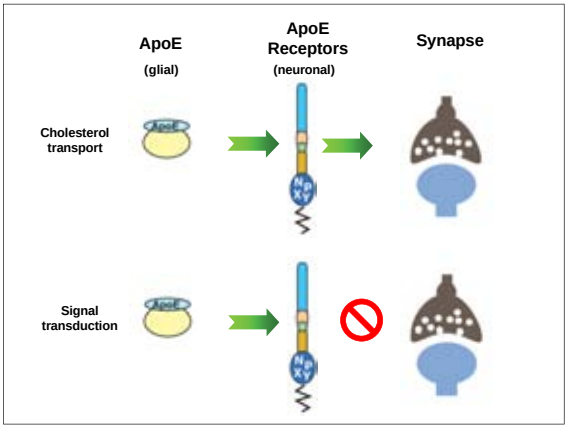
The LDL Receptor Gene Family

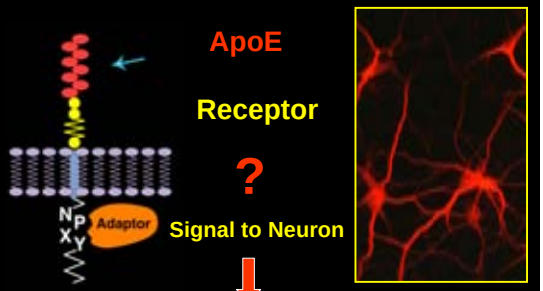


Evolution of ApoE and "ApoE" Receptors



From: Lee Silver, Mouse Genetics (1995)

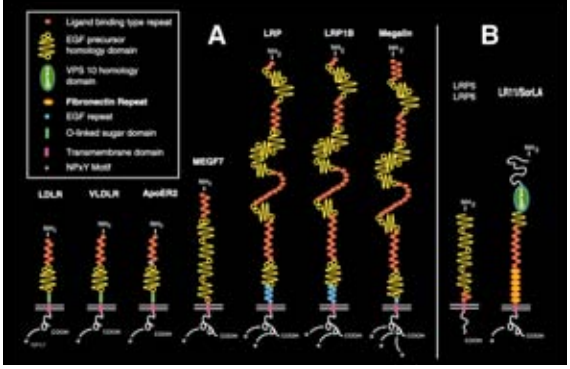




Mouse

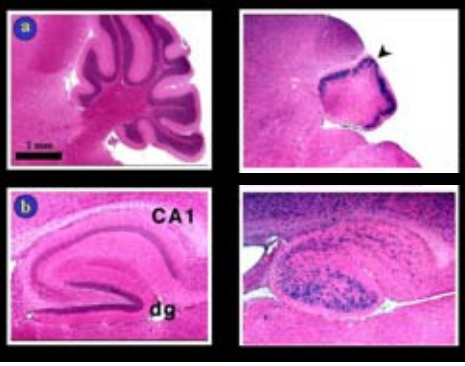
- Rapid, prospective experiments
- Large pedigrees, multigeneration analysis
- Genetics can be manipulated at will (Inbred, backcross, intercross)
- Invasive physiological experiments possible

The LDL Receptor Gene Family

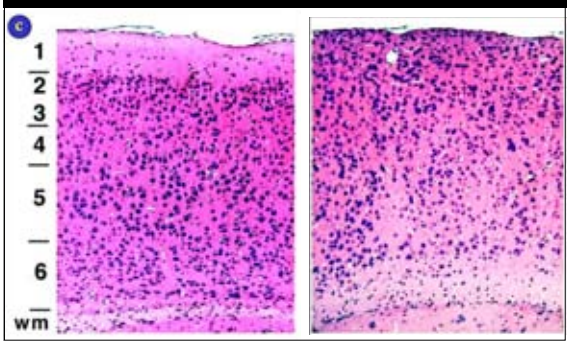


Ataxia in VLDLR/ApoER2 Double Knockout Mice

Normal Mutant



Normal **Mutant**

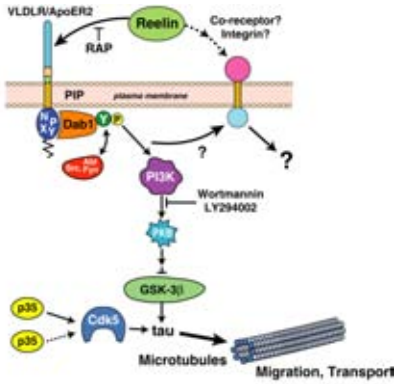


The identical phenotype has been observed in two independent strains of mice:

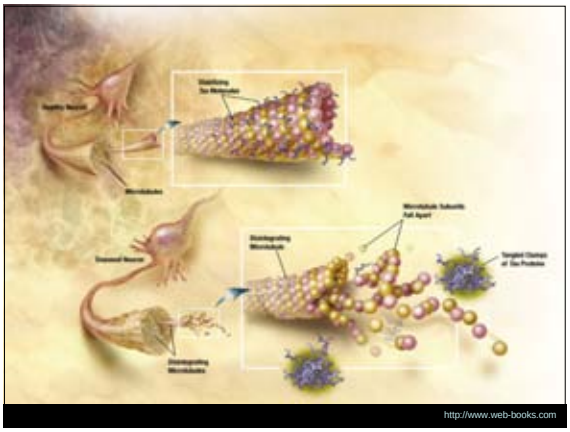
reeler: extracellular — **Loss of function mutation in a gene encoding a large secreted signaling molecule (Reelin)**

ApoE Receptors at the Plasma Membrane

scrambler: intracellular — **Loss of function mutation in a gene encoding a cytoplasmic adaptor protein (mammalian Disabled-1; Dab1)**

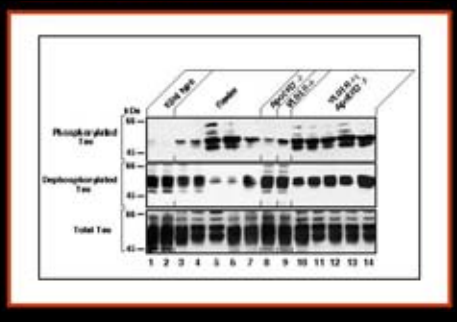


Hans Bock, Uwe Beffert



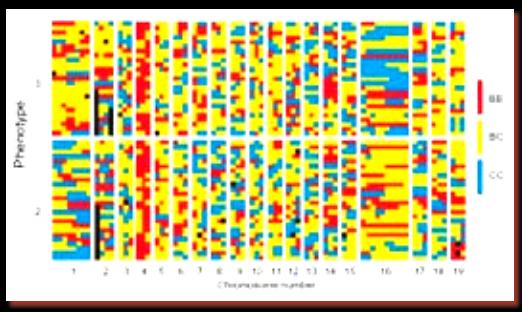
Argyrophilic Inclusions Resembling Tangles in ApoE Receptor Knockout Mice

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



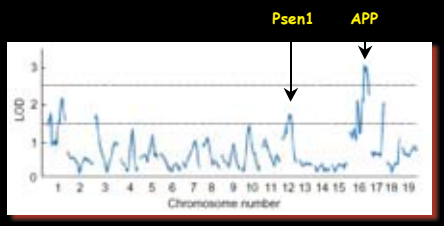
Genetic Diversity

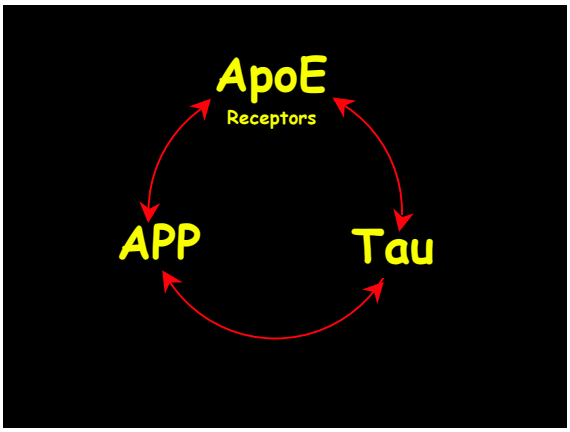
Allele and Phenotype Distribution in F_2-Intercrosses

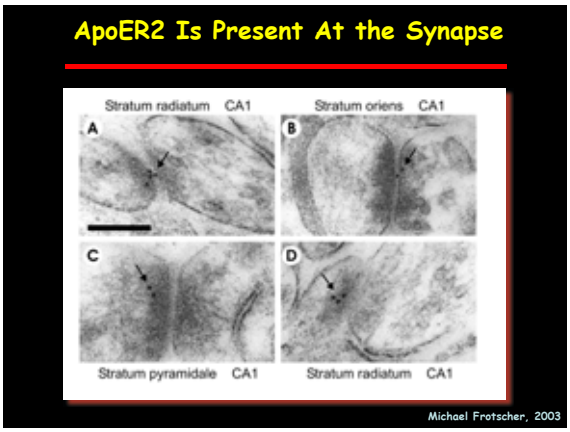


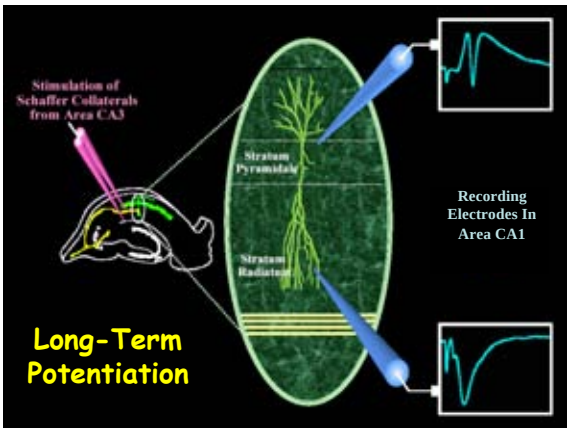
0=low P-τ; 2=high P-τ; B=Balb/c; C=C57BL/6

QTLs in the Mouse Genome that Modulate τ-Phosphorylation

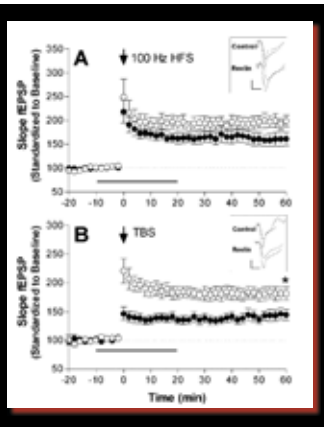



ApoE
Receptors
APP
Tau

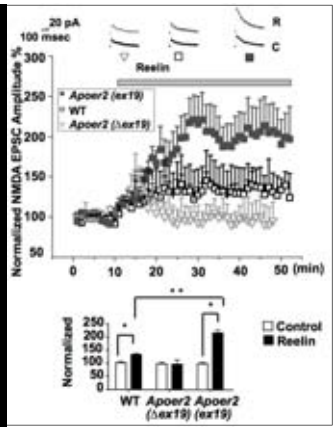

ApoER2 Is Present At the Synapse
Stratum radiatum CA1
Stratum oriens CA1
A
B
C
D
Stratum pyramidale CA1
Stratum radiatum CA1
Michael Frotscher, 2003


Stimulation of Schaffer Collaterals from Area CA3
Stratum Pyramidale
Stratum Radiatum
Recording Electrodes In Area CA1
Long-Term Potentiation

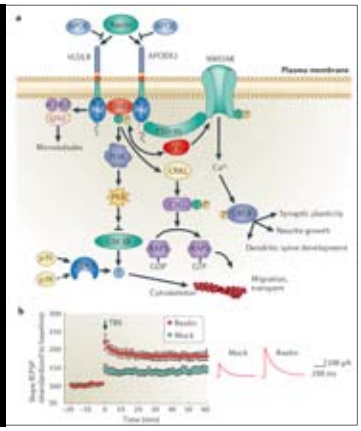
Reelin Stimulates LTP in Hippocampal Slices from Wild Type Mice



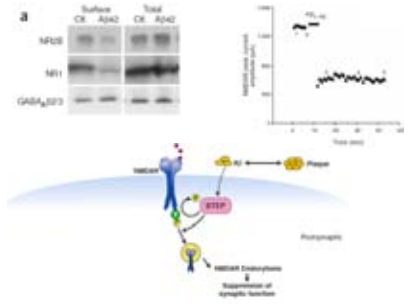
The Alternatively Spliced Cytoplasmic Exon 19 Is Required for the Reelin-Induced Increase in Excitatory Postsynaptic NMDAR-Dependent Currents



Targets Of The Reelin Signaling Pathway In Neurons



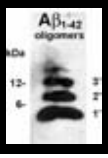
Aβ Decreases NMDA Receptor Surface Expression by Promoting its Endocytosis

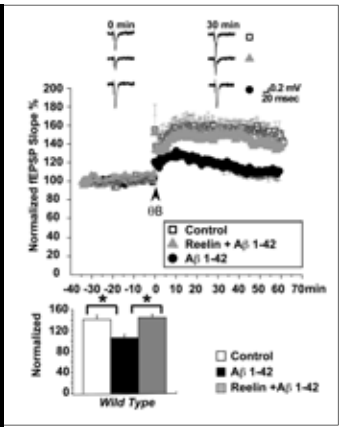


Snyder et al, *Nature Neuroscience*, 2005

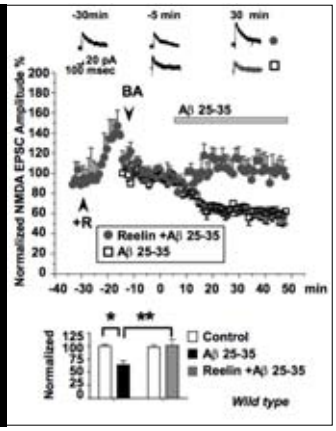
Signal Amplification by Reelin and Apoer2 Reverses β-Amyloid Induced Synaptic Depression

Reelin Reverses $A\beta_{1-42}$ - Induced Reduction of Hippocampal LTP

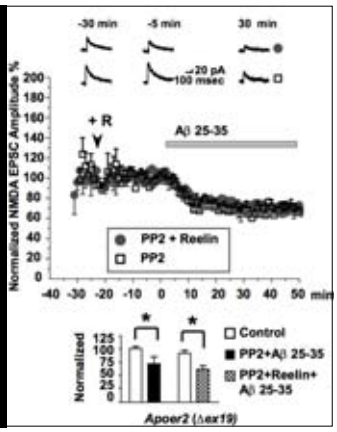




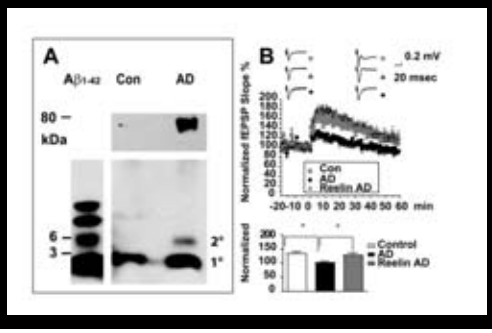
Reelin Prevents $A\beta_{25-35}$ Induced Reduction of Excitatory Postsynaptic NMDAR-Dependent Currents



Reversal of Aβ Induced Suppression of NMDAR-Dependent Excitatory Postsynaptic Currents Requires SFK Activity

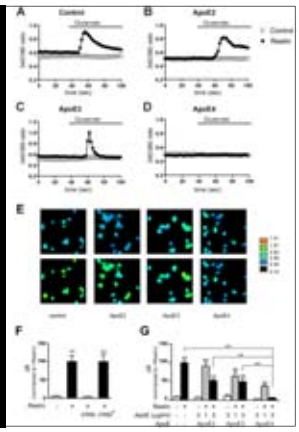


ApoE receptor Signaling Recovers Synaptic Depression Induced by Human Brain Amyloid

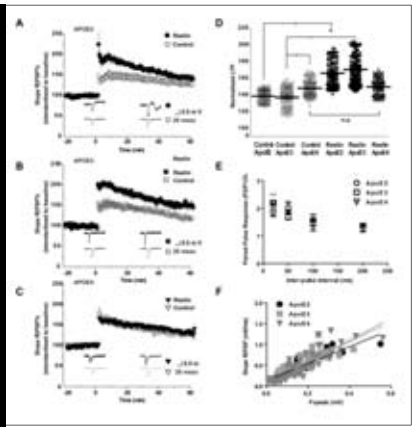


Signal Amplification by Reelin and Apoer2 Reverses β-Amyloid Induced Synaptic Depression

Selective Impairment of NMDA Receptor Dependent Ca2+ Influx by Different ApoE Isoforms

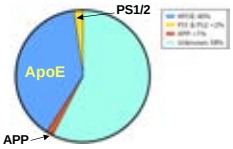


ApoE Isoforms Selectively Impair Synaptic Plasticity

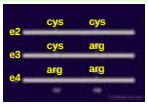


Alzheimer's Disease - Genetic Risk Factors

Genetic risk factors for AD



ApoE is the major apolipoprotein in the brain. Humans have three ApoE alleles: ε2,ε3,ε4.



ε4 allele of apoE predisposes its carrier to AD.