

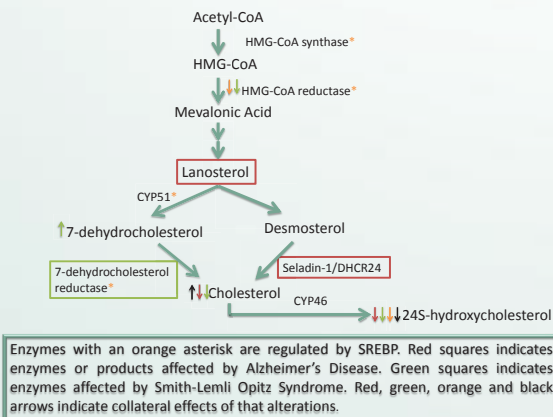
# Cholesterol homeostasis role in neurodegenerative diseases

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Brain's cholesterol homeostasis deregulations are common in several neurodegenerative diseases. This study aims to find any relationship between brain's cholesterol regulation and neurodegenerative disorders comparing some of them: Alzheimer's Disease, Huntington's Disease, Niemann-Pick type C Disease and Smith-Lemli Opitz syndrome. This comparison would allow us to guide a pharmacology research destined to solve this problem.

## Cholesterol in Central Nervous System

### Cholesterol Biosynthesis Pathway

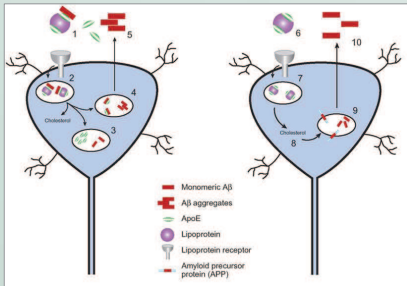


### Cholesterol Regulation

- Due to plasma lipoproteins can not go through the Blood Brain Barrier (BBB) almost all brain cholesterol is synthesized *in situ*
- LXR is a transcription factor that regulates several cholesterol homeostasis implicated genes
- Cholesterol efflux from glial cells is mediated by ABC transporters
- Cholesterol exchange between brain cells is mediated by lipoproteins derived from glia. Outside cells, cholesterol and phospholipids associates with apolipoprotein E (ApoE)
- ApoE-containing lipoproteins are recognized by LDL family receptors in neurons
- Cholesterol excess is removed from brain
- CYP46 catalyzes 24S-hydroxycholesterol (24S-OH-C) formation → It can go through the BBB

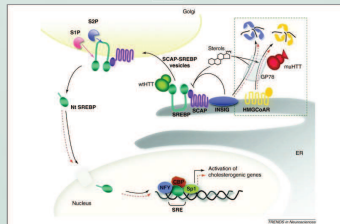
### Alzheimer's Disease

- Extracellular deposits of amyloid  $\beta$  fibrils ← accumulation of amyloid  $\beta$ -peptide ( $A\beta$ )
- ApoE seems to be implicated by two possible models
  - $A\beta$  interact with ApoE-containing lipoproteins before being endocytosed by neurons. Inside cells, free ApoE associates with  $A\beta$  and promotes its aggregation.
  - ApoE modify cholesterol levels in cells. High cholesterol levels within cell up-regulates  $A\beta$  formation.
- Changes in neuronal cytoskeleton ← hyperphosphorylation of Tau protein
- ↓ Cholesterol synthesis ← low lanosterol levels and seladin-1 expression
- ↓ [24S-OH-C] ← Deregulation in cholesterol elimination from CNS



### Huntington's Disease

- HTT mutated protein
  - ↑ LXR transcription
  - ↓ SREBP expression
  - GP78 function alteration
  - ↓ HMG-CoA activity
  - No degradation of INSIG 1
  - ↓ Cholesterol precursors
  - ↓ Cholesterogenic genes transcription
  - ↓ Cholesterol synthesis
- ↓ [24S-OH-C]



### Niemann-Pick type C Disease

- Mutation in *npc1/2* genes
- NPC1 or NPC2 proteins deficiency in cells
- Cholesterol accumulation in lysosomes/late endosomes
- Intracellular cholesterol transport alteration
- NPC1 and NPC2 are required for cholesterol release from lysosomes/late endosomes. Vance JE. 2012 (modified)
- ↓ [24S-OH-C]

### Smith-Lemli Opitz Syndrome

- 7-dehydrocholesterol reductase (DHCR7) mutation
- ↓ Cholesterol Synthesis
- ↑ 7-dehydrocholesterol
- Hmgcr inhibition
- ↓ [24S-OH-C]

## Conclusions

- It has been shown a relationship between a deregulation in cholesterol homeostasis and neurodegenerative diseases
  - Although having some common points, there is no reason to say that these neurodegenerative diseases are related
  - These disorders do not affect the same brain zones
  - In all four diseases should be increased the synthesis of 24S-OH-C to prevent brain cholesterol accumulation, probably with a common treatment
  - Due to cholesterol homeostasis complexity it is difficult to find a proper treatment.
- No common therapy
- Cholesterol regulation is affected in different pathways on each disease

## References

- Block, R.C., Dorsey, E.R., Beck, C.A., Brenna, J.T., Shoulson, I. 2010. Altered Cholesterol and Fatty Acid Metabolism in Huntington Disease. J Clin Lipidol 4, 17-23.
- Martin M, Dotti CG, Ledesma MD. 2010. Brain cholesterol in normal and pathological aging. Biochimica et Biophysica Acta 1801, 934-944.
- Pugliese, L., Tanzi, R.E., Kovacs, D.M. 2003. Alzheimer's disease: the cholesterol connection. Nature neuroscience 6, 345-351.
- Valenza, M., Cattaneo, E. 2011. Emerging roles for cholesterol in Huntington's disease. Trends in Neurosciences, Vol. 34, 474-486.
- Vance JE. 2012. Dysregulation of cholesterol balance in the brain: contribution to neurodegenerative diseases. Disease Models & Mechanisms 5, 746-755.
- Image behind title: Lipids LTD <http://www.lipids.co.uk/page1/index.html>