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 cannot 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 β fibrils accumulation of amyloid β-peptide (Aβ)
- Aβ interact with ApoE-containing lipoproteins before being endocytosed by neurons. Inside cells, free ApoE associates with Aβ and promotes its aggregation.
- ApoE seems to be implicated by two possible models
- Changes in neuronal cytoskeleton: hyperphosphorylation of Tau protein
- Cholesterol synthesis: low lanosterol and seladin-1 expression
- 24S-OH-C: deregulation in cholesterol elimination from CNS

**Huntington’s Disease**
- HTT mutated protein
- SREBP interacts with SCAP. SREBP activates cholesterogenic genes transcription. In presence of sterols in cell, sterols bind SCAP, preventing SCAP-SREBP complex. SCAP and INSIG 1 interact when cholesterol is present, inhibiting its biosynthesis. GP78 is required for ubiquitination and degradation of INSIG1 when cholesterol deficient. Valenza, M. et al. 2011.

**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, J.E. 2012 (modified)

**Smith-Lemli Opitz Syndrome**
- 7-dehydrocholesterol reductase (DHCR7) mutation
- 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
- Cholesterol regulation is affected in different pathways on each disease
- 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.