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Review Article

Neuroprotective Effects of High Density Lipoproteins (APOE) and Neurodegenerative Disorders Related to ApoE-HDL

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ABSTRACT

There are a number of potential mechanisms through which HDL could act to protect neural function. Apolipoproteins E is the most abundant apolipoproteins in the brain. ApoE-HDL and cholesterol are synthesized mainly by de novo synthesis in astrocytes. Three major functions of astrocyte-derived ApoE-containing lipoproteins includes transfer of phospholipids and cholesterol via ATP-binding cassette (ABC) transporters such as ABCA1 and ABCG1,interaction with the LDLR super family of proteins located on the surface of neurons to facilitate axonal growth and neuronal survival and interaction with the LRP1-dependent cellular uptake pathway in the deposition of amyloid plaques. Cholesterol is a very important membrane lipid to keep function and survival of neurons in the brain. The brain contains about 20% of whole body cholesterol. Brain cholesterol is involved in axonal elongation, dendrite differentiation, synapse development and synapse formation, long-term potentiation, Learning and memory

Neuroprotective effects of ApoE-HDL in the brain includes suppression of Aβ production by decreasing cellular cholesterol, can directly bind excess Aβ and thereby inhibit cholesterol oligomerisation, remove Aβ that accumulates in the vessel wall during the course of VD, decrease oxidative stress and thereby indirectly decrease Aβ production, can act on astrocytes to attenuate a local inflammatory reaction, accelerates maturation of synapses and maintain of synaptic plasticity.

Disturbances in cholesterol homeostasis have been associated to the onset and the development of several neurological disorders such as AD, NPC and HD disease.

Keywords:- ApoE-HDL, Neuroprotection, Brain cholesterol, synapse development, synaptic plasticity, Neurodegenerative disorders

1. INTRODUCTION

Lipoprotein metabolism in the brain is dynamic. Neurons in the brain require a rapid lipid turnover and reverse cholesterol transport and even though the central nervous system (CNS) accounts for only 2.1% of body weight, it contains 23% of total body cholesterol. The fact that the rate of cholesterol synthesis in the adult brain is larger than the accumulation rate indicates that there must be a mechanism by which cholesterol turn over take place (Dietschy JM et al 2004).There are a number of potential mechanisms through which lipoproteins could act to protect neural function. Cholesterols are synthesized mainly by de novo synthesis in astrocytes.

1.1 Lipoproteins in the brain

Apolipoproteins E and ApoJ are the most abundant apolipoproteins in the brain, are mostly synthesized by astrocytes, and are found on HDL (Hong Wang et al 2014). Unlike plasma, the most abundant apolipoprotein in CSF lipoproteins is ApoE,

which is usually localized to the largest particles. ApoA-I and ApoA-II are present on smaller particles, and ApoJ is distributed across the particle size-range. Astrocytes produce and release ApoE, whereas neurons metabolize cholesterol to 24(S)-hydroxycholesterol (Hong Wang et al 2014). Similar to plasma HDL, CSF lipoproteins can be remodeled by lecithin-cholesterol acyltransferase and phospholipid transfer protein; by contrast, cholesteryl ester transfer protein (CETP) is absent from CSF (Demeester N et al 2000).Cholesterol efflux from astrocytes is facilitated by apolipoproteins alone or lipoprotein particles, whereas cholesterol removal from neurons is triggered only by lipoprotein particles. ABCA1- and ABCG1- regulated cholesterol efflux occurs only in astrocytes whereas ABCG4-mediated cholesterol efflux takes place only in neurons (Chen, J. et al 2013).

1.2 The major functions of ApoE in the brain

In brief, three major functions have been suggested for astrocyte-derived ApoE-containing lipoproteins: (i) the transfer of phospholipids and cholesterol via ATP-binding cassette (ABC) transporters such as ABCA1 and ABCG1; (ii) interaction with the LDLR superfamily of proteins located on the surface of neurons to facilitate axonal growth and neuronal survival (Hayashi, H. et al 2007); and (iii) interaction with the LRP1-dependent cellular uptake pathway in the deposition of amyloid plaques (Martiskainen, H. et al 2013). Although there is minimal direct interaction between ApoE and soluble Ab in CSF, ApoEisoforms in ApoE-containing lipoprotein complexes can regulate the metabolism of soluble Ab by competing for the binding of LRP1 with Ab in astrocytes (Verghese, P.B. et al 2013). ApoE is produced within the CNS and interacts with Aβ. CSF lipoproteins carry amyloid-β (Aβ), a 39- to 43-aa peptide produced in neuronal cells, which is the major component of senile amyloid plaques. The availability of cholesterol and of apoE are thought to affect amyloidogenesis and apoE (in particular the isoform apoE4) promoting the formation of amyloid fibrils from soluble Aβ in the CNS (Verghese, P.B. et al 2013).ApoE knockout mice placed on a diet enriched in homocysteine to induce oxidative stress, show impaired learning and memory. There are three major isoforms of ApoE – ApoE2, ApoE3, and ApoE4.ApoE4 confers the major risk for Alzheimer's disease (AD). The expression of the ApoE4 allele usually results in increased expression of ApoC1 (Evola, M. et al. (2010). Mice overexpressing human ApoC1 also display impaired learning and memory. Interestingly Apoc1_/_ mice also show impaired hippocampal-dependent memory with no gross changes in brain morphology or brain cholesterol levels, but increased expression of the proinflammatory marker tumor necrosis factor-a (Berbee, J.F. et al 2011).

1.3 Lipoprotein receptors in the central nervous system (CNS)

The LDLR superfamily of proteins are a class of single membrane-spanning domain receptors that bind ApoB100 or ApoE and also endocytose a variety of distinct extracellular proteins. For example, HDL binds to a different set of cell surface receptors, some for cholesterol efflux (i.e., ABCA1 and ABCG1) and others for uptake and degradation (i.e., SR-B1)(Hong Wang et al 2014). Some of these receptors are SR-B1, LDLR, VLDLR and LRP1. SR-B1 mediates the selective uptake of HDL-associated CE independently from HDL internalization. LDLR knockout (Ldlr_/_) mice show no major deficits in sensory or motor function, but exhibit increased locomotor activity (Moreira, E.L. et al 2012, Elder, G.A. et al 2008). Ldlr_/_ mice also show a decrease in learning and memory regardless of diet (de, O.J. et al 2011Berbee, J.F. et al 2011). VLDLR binds TG-rich lipoproteins but not LDL, and, in the periphery, also serves as a remnant lipoprotein receptor. The VLDLR in various tissues usually functions in concert with LPL. In the brain, various mutations in

VLDLR have been associated with disequilibrium syndrome (DES) (Ali, B.R. et al 2012, Moheb, L.A. et al 2008.LRP1 is an endocytic receptor that mediates the cellular uptake of various ligands including chylomicron remnants. In brain, LRP1 is expressed at high levels in both glial and neuronal cells to mediate endocytosis of ligands, regulate calcium influx into neurons after stimulation with NMDA, interact with amyloid precursor protein (APP) to regulate Ab clearing, and interact with PSD-95 to regulate synaptic transmission (Fernandez-Castaneda, A. et al2013,. Matsuo, M. et al 2011, Liu, Q. et al 2007, Liu, Q. et al 2010).

2. Neuroprotective effects of APOE HDL in the brain

2.1. Effects of HDL on Aβ metabolism

The complexity of the mechanistic relationship between ApoE-HDL and brain function is immediately apparent when we look at Aβ metabolism, ApoE HDL causes improved metabolism of Aβ, the major pathway involved in the pathogenesis of AD. Brain ApoE-HDL can exert several neuroprotective effects .First, as neuronal production of Aβ frequently parallels membrane content of cholesterol, ApoE-HDL can suppress Aβ production by decreasing cellular cholesterol through the activation of reverse cholesterol transport mediated by ABC transporters(Lesne S et al 2006).Second, ApoE-HDL can directly bind excess Aβ and thereby inhibit its oligomerisation the latter representing a major step in the transformation of the monomeric nontoxic peptide to the aggregated neurotoxic form that can account for memory impairment. As ApoE-HDL transports Aβ in both CSF and plasma, elimination of the excess peptide from the brain may follow. In addition, ApoE-HDL might also remove Aβ that accumulates in the vessel wall during the course of VD by analogy with reverse cholesterol transport, such a process can be termed "reverse amyloid transport." (Hardy J et al 2006). (Wahrle SE et al 2008, Lesne S et al 2006, Kontush A et al 2003).

2.2. Amyloid beta-protein and lipid metabolism

The main characteristics of AD are massive cerebral accumulation of amyloid composed of fibrillary aggregates of the amyloid beta peptide (Aβ) and intracellular accumulation of abnormally phosphorylated Tau protein leading to widespread neurodegeneration. The clinical picture is characterized by progressive and irreversible dementia, which is eventually fatal (Eva G. Zinser et al 2007).

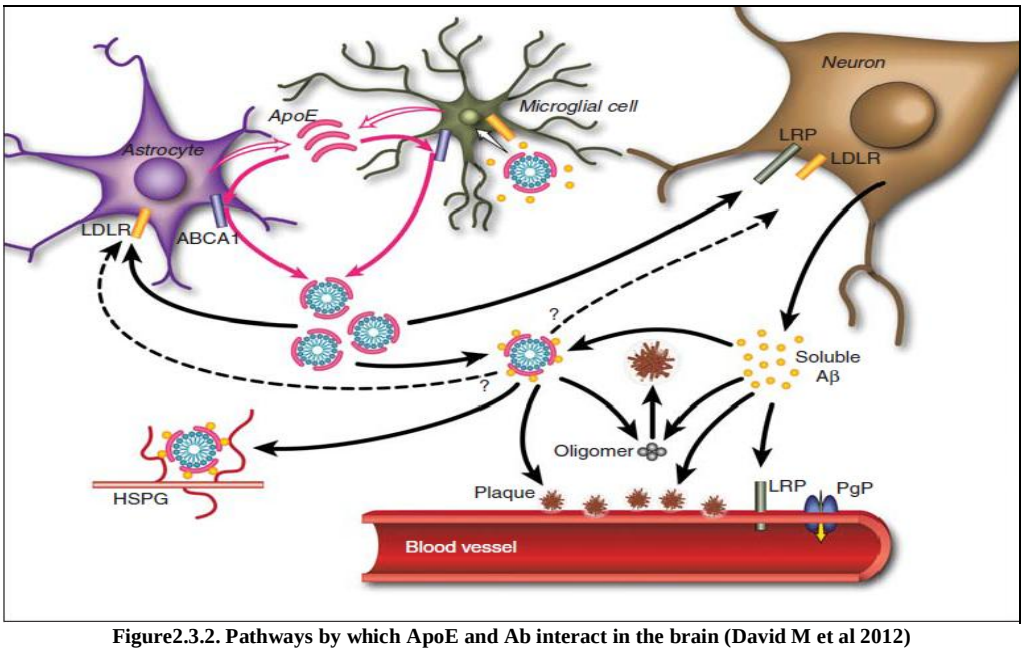

Figure2.3.2. Pathways by which ApoE and Ab interact in the brain (David M et al 2012)

ApoE is primarily produced by both astrocytes and microglia and is subsequently lipidated by ABCA1 to form lipoprotein particles. In the extracellular space, lipidatedapoE binds to soluble Aβin an isoform-dependent pattern (E2,E3, E4) and influences the formation of parenchymal amyloid plaques and transport of Aβ within the CNS. ApoE is endocytosed into various cell types within the brain by different members of the LDL receptor family, including LDLR and LRP1. ApoE may also facilitate the cellular uptake ofAβthrough the endocytosis of a complex of apoE-containing lipoprotein particles bound to Aβ in a manner that likely depends on the isoforms and its level of lipidation (David M et al 2012). Furthermore, apoE has been shown to directly enhance both the degradation of Aβ within microglial cells and the ability of astrocytes to clear diffuse Aβ deposits. Aβ associated with apoE containing lipoprotein particles may also be retained within the CNS through their binding to heparin sulfate proteoglycan (HSPG) moieties present in the extracellular space. At the blood–brain barrier (BBB), soluble Aβ is predominantly transported from the interstitial fluid into the bloodstream via LRP1 and P-glycoprotein. ApoE has been shown to slow the transport of Aβ across the BBB in an isoform-dependent manner (E4, E3, E2). In addition, apoE can influence the pathogenesis of CAA in an amyloid protein precursor (APP)- transgenic mouse model, with apoE4 increasing the amount of vascular plaques in comparison to apoE3 (David M et al 2012).

The APOE ε3 allele, the most common form, is found in 70 percent to 80 percent of the population and appears to play a neutral role in the disease. The APOE ε4 allele, found in 10 percent to 15 percent of the population, increases risk for Alzheimer's disease by three- to eight-fold, depending on whether a person has one or two copies of the allele. The APOE ε4 allele is also associated with an earlier age of disease onset. APOE ε4 is called a risk-factor gene because it increases a person's risk of developing the disease but is not the direct cause. Inheriting an APOE ε4 allele does not mean that a person will definitely develop Alzheimer's. Some people with an APOE ε4 allele never get the disease, and many who develop Alzheimer's do not have any APOE ε4 alleles.

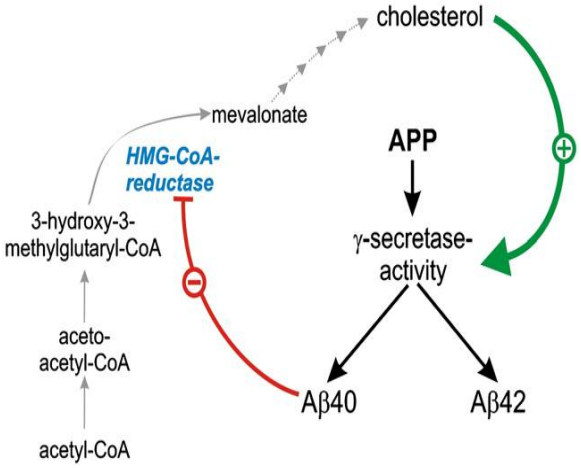

Fig. 2.3.3.Model of the feedback regulation between cholesterol homeostasis and APP processing.

Cholesterol increases γ-secretase activity, which leads to an increased Aβ production. In return Aβ downregulates cholesterol de novo synthesis leading to a regulatory cycle (Eva G. Zinser et al 2007).

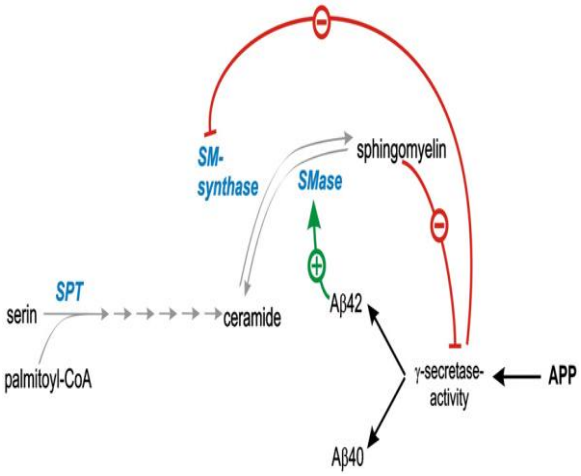

Fig.2.3.4. Model of the feed forward regulatory cycle between sphingolipids and APP processing. Sphingomyelin decreases γ-secretase activity and in return reduced γ-secretase activity leads to decreased nSMase activity and therefore an increased SM level. SMase and SM-synthase are regulated inversely (Eva G. Zinser et al 2007).

2.3. Antioxidant effects of HDL

Oxidative stress induces enhanced production of Aβ as a potentially protective response (monomeric Aβ is a particularly

strong chelator of prooxidant transition metal ions in their free form) in turn.,ApoE-HDL can decrease oxidative stress and thereby indirectly decrease Aβ production. It exhibits both antioxidant and anti-inflammatory properties that could affect the inflammatory response in the brain. ApoE-HDL-mediated reverse cholesterol transport could also reduce atherosclerotic burden in brain vessels such as the Circle of Willis, thus limiting the developing of vascular dementia (Cecilia Vitali et al 2014). Oxidative stress, including lipid peroxidation, has been shown to be the mediator of the pathologic effects of numerous risk factors of Alzheimer's disease(Cecilia Vitali et al 2014).

2.4. Anti-inflammatory effects of HDL

Fourth, HDL can act on astrocytes to attenuate a local inflammatory reaction (Wahrle SE et al 2008, Lesne S et al 2006).HDL also has potent beneficial effects on endothelial function and as the brain contains >25% of the body's total vascular network, ApoE-HDL may also affect cerebrovascular function that will in turn influence neuronal activity(Cecilia Vitali et al 2014). It promotes the generation of M2 polarized macrophages that exhibit a reduced proinflammatory phenotype. Moreover, ApoE-HDL inhibits cytokine-induced expression of adhesion molecules in endothelial cells. All these properties may contribute to the suppression of the immune system (Cecilia Vitali et al 2014).

2.5. Effects of ApoE-HDL in accelerating maturation of synapses

Cholesterol is also particularly abundant in synaptosomal membranes, influencing synapse formation, stability and neurotransmitter release. At pre-synaptic level, this molecule localizes prevalently in the inner leaflet of the lipidic bilayer, with a predominant structural role. In post-synaptic terminals, it functions as a constituent of lipid rafts, that anchors and regulates the activity of several neurotransmitter receptors (e.g. GABAa receptors and AMPA-type glutamate receptors) and other post-synaptic elements on the membrane(G. F. Lewis et al 2005, J. G).

Microtubular transport of synaptic vesicles within the cytosol, subsequent fusion and release via SNARE protein interaction also depend on high cholesterol levels. Specifically, high cholesterol concentration is required for the correct membrane curvature and for the assembly of vesicle-specific proteins and lipids (G. F. Lewis et al 2005).

Since ApoE-HDL is the lipoprotein responsible for the efflux of cholesterol within cells of the brain, it may be that deficient levels or dysfunction of HDL-cholesterol may contribute to certain tauopathies or dysgenesis of synaptic processes, such that individuals with dyslipidemia may be more susceptible to neurodegenerative disease. The maintenance of spine and synapse number during development is critical for neuronal circuit formation and function. Cell adhesion proteins regulate spine and synapse morphogenesis during development. Low plasma concentrations of HDL-C have been repeatedly reported in association with dementia (Singh-Manoux A 2008).

2.6. Effects of ApoE-HDL in maintenance of synaptic plasticity

Here it has been addressed the question of the role of cholesterol in synaptic changes during long-term potentiation (LTP). It has been found that *N*-methyl-d-aspartate–type glutamate receptor (NMDAR) activation during LTP induction leads to a rapid and sustained loss or redistribution of intracellular cholesterol in the neuron. A reduction in cholesterol, in turn, leads to the activation of Cdc42 and the mobilization of GluA1-containing □ -amino-3-hydroxy-5- methyl-4-isoxazolepropionic acid–type glutamate receptors (AMPARs) from Rab11-recycling endosomes into the synaptic membrane, leading to synaptic potentiation. This process is accompanied by an increase of NMDAR function and an enhancement of LTP. These results imply that cholesterol acts as a sensor of NMDAR activation and

as a trigger of downstream signaling to engage small GTPase (guanosine triphosphatase) activation and AMPAR synaptic delivery during LTP(Segatto M, et al 2013,Anna Brachet 2015,Edwin J et al 2014).

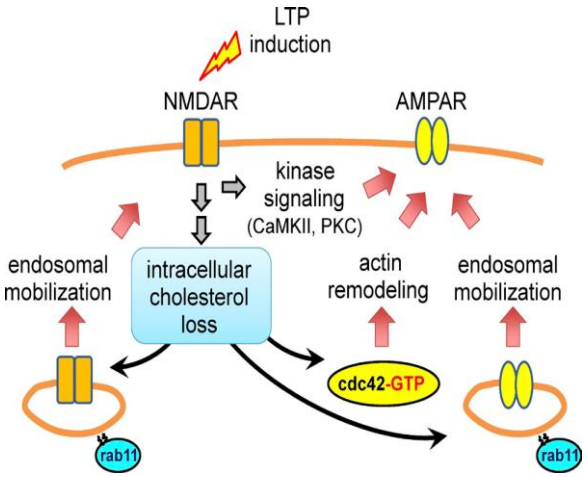

Fig. 2.7.1.Schematic representation of cholesterol regulation during LTP and participation in synaptic plasticity mechanisms (Anna Brachet 2015 et al).

3. Imbalance of cholesterol metabolism and CNS disorders (neurodegenerative events)

In view of the importance of this lipid in the CNS, it is not surprising that disturbances in cholesterol homeostasis have been associated to the onset and the development of several neurological and neuropsychiatric disorders such as AD, HD, and NPC disease. Lipoproteins such as HDL may influence neurodegeneration as a carrier of cholesterol. The extracellular deposition of amyloid beta (Aβ) in senile plaques constitutes one of the defining hallmarks of AD.

3.1. Alzheimer's disease

Alzheimer's disease (AD) is a neurological degenerative disorder characterized by a poor prognosis. (Hashimoto M et al 2003). Aβ is a toxic peptide, produced by the proteolytic cleavage of the amyloid precursor protein (APP). This enzymatic processing is operated by the activity of β-secretase (beta-site APP cleaving enzyme 1, BACE1) and the γ-secretase complex (Sebastiao, A.M. et al 2013, McIntire LB et al 2011).

During the last decade, several findings have highlighted an involvement of cholesterol in Aβ production. In particular, β- and γ-secretase complexes reside in cholesterol-rich lipid rafts, and the enzymatic activity of both the protein complexes are conditioned by the cellular cholesterol content. The dependence of amyloidogenesis on cholesterol metabolism is also strengthened by the relation between Aβ production and the rise in cholesteryl-ester levels, which are derived from cholesterol esterification operated by acyl-coenzyme A: cholesterolacyl transferase (ACAT). It is suggested that apoE4 is able to promote Aβ aggregation and/or reduce the clearance of amyloid plaques. Moreover, it was observed that human apoE4 knock-in mice show a decrease in long-term potentiation, excitatory synaptic transmission and dendritic arborization, which determine impaired synaptic and cognitive functions (Jain, S. et al 2013, McIntire LB et al 2011).

Cholesterol

Low levels of ApoE-HDL and apoA-I have been correlated with short-term memory loss and Alzheimer's disease (AD) (Andrew J et al 2009). The dependence of Aβ production on cholesterol levels indicates that a pharmacological approach focused on the modulation of cholesterol metabolism could reduce the risk of AD. For instance, ACAT inhibition leads to a decrease in the amount of cholesterol esters, thus reducing Aβ secretion. This observation corroborates with the reduction in Aβ load and cognitive decline after genetic ablation of ACAT in a mouse model of AD (Cecilia Vitali et al 2014).

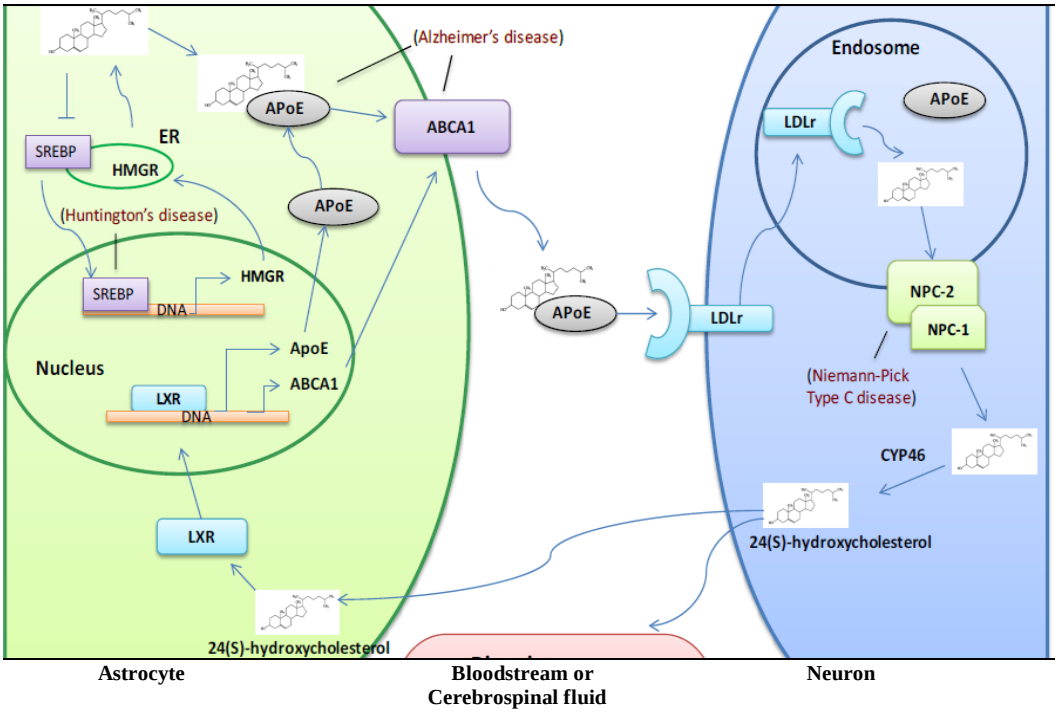

Figure 3.1.1: Schematic illustration of intercellular cholesterol transport from astrocytes to neurons.

3.2. Niemann-Pick type C disease

Niemann-Pick type C disease (NPC, MIM 257220) is a rare genetic autosomal-recessive neurovisceral disorder caused by a progressive and abnormal intracellular storage of unesterified cholesterol and glycosphingolipids in the endosomal/ lysosomal compartments. The pattern of lipid storage is peculiar in the brain with respect to other organs and tissues. The onset of NPC disease is caused by mutations in the NPC1 or NPC2 genes, whose products are involved in the regulation of cholesterol efflux (Lecis C et al 2014).As far as is known, after LDL cholesteryl ester hydrolysis into lysosomes, NPC2 binds cholesterol. Subsequently, NPC2 transfers the sterol to NPC1, thus determining the exit of free cholesterol from lysosomes (Lecis C et al 2014).

3.3. Huntington's disease

Huntington's disease (HD) is an autosomal-dominant genetic disorder characterized by a progressive neurodegeneration. Recently, the prospective role of cholesterol imbalance in determining the pathological aspects of HD has attracted increasing interest. Experimental data highlight that mutated HTT is responsible for the transcriptional suppression of genes involved in cholesterol and fatty acid synthesis in striatal cell lines with inducible expression of mutant HTT. The possibility must be considered that in the case of HD, the mutated HTT is less able to upregulate LXR and LXR-targeted genes, including SREBP. Such a mechanism is a possible link between the HTT mutation and the disturbances in cholesterol metabolism. Further work is needed, however, to establish this (ValenzaM et al 2011, Lecis C et al 2014).

4. CONCLUSIONS

Apolipoproteins E is the most abundant apolipoproteins in the brain. There are a number of potential mechanisms through which APOE-HDL could act to protect neural function. Neuroprotective effects of ApoE-HDL in the brain includes suppression of Aβ production by decreasing cellular cholesterol, can directly bind excess Aβ and thereby inhibit cholesterol oligomerisation, remove Aβ that accumulates in the vessel wall during the course of VD, decrease oxidative stress and thereby indirectly decrease Aβ production, can act on astrocytes to attenuate a local

inflammatory reaction, accelerates maturation of synapses and maintain of synaptic plasticity. Disturbances in cholesterol homeostasis have been associated to the onset and the development of several neurological disorders such as AD, NPC and HD disease.

5. FUTURE ISSUES

- The question why almost all (at least 99%) cholesterol in the nervous system remain unesterified is not clear
- The presence or absence of CETP activity in CSF is controversial.
- The transport processes which bring cholesterol to the enzyme in the ER membrane is not known.
- How subcellular localization of cholesterol 24-hydroxylase affects cholesterol turnover remain unclear.
- Do binding proteins target the enzyme to defined subcellular localizations at which cholesterol turnover takes place?
- Is enzyme activity regulated by synaptic activity?
- Are there naturally occurring mutations in the human cholesterol 24-hydroxylase gene, and if so, what are their clinical consequences?
- Questions like whether all neurons rely on cholesterol supplied by astrocytes and the regulation of their cholesterol transport still remain unclear.

Lists of abbreviation

CNS-Centeral nervous system
CSF-Cerebrospinal fluid
CETP-Cholesteryl transfer protein
ABCA1/ABCG1-ATP-binding cassete transporter protein A1 and G1
LDLR-Low density lipoprotein receptor
SR-B1-Scavenger receptor-B1
VLDLR-Very low density lipoprotein receptor
LRP1-Low density related protein
DES-Disequilibrium syndrome
NDMAR-N-methyl-D-aspartic acid receptor
AMPAR-α-amino-hydroxyl--methyl-isoxazolepropionate receptor
APP-Amyloid precursor protein
AD-Alzheimer's disease
VD-Vascular dementia
GABA-Gaba amino butyric acid
LTP-Long term potentiation
HD-Huntington's disease
NPC –Neimann-pick type C disease
BACE-Beta site APP cleaving enzyme
HTT-Huntingtin protein
SREBP-Steroid regulatory element binding protein
LXR-Nuclear Liver x receptor

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