

Cholesterol Metabolism in Huntington's Disease

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1. Introduction

Cholesterol is present in all vertebrate cells where has several important functions. Being a structural element in plasma membranes it supports the structure and function of lipid bilayers and is regarded to be the most important "fluidity buffer" of the membrane. It is also a precursor of bile acids, steroid hormones and vitamin D. While cholesterol is involved in many cellular processes, a strong indicator of its importance is that it is the only major lipid in mammals not used in energy generation.

De novo synthesis and uptake from circulating lipoproteins cover the cholesterol needs of the cells. Almost all the mammalian cells are able to synthesize cholesterol and express the sophisticated and energy demanding enzymatic machinery required for the de novo synthesis.

In general, the cells in the body are able to release and take up cholesterol to maintain their cholesterol homeostasis: some are able to produce an excess to provide other cells, some others need exogenous cholesterol because of limited synthetic capacity.

Excess cholesterol may be toxic for the cells and a number of strategies have evolved either to export it or to store it in an esterified form. The exogenous cell supply is covered via the Low Density Lipoproteins (LDL) cycle and most of the excess is exported by the High Density Lipoprotein (HDL) mechanism (reverse cholesterol transport), mediated by members of the ATP-Binding Cassette (ABC)-transporter family.

Under normal conditions, about the 60% of the body's cholesterol is synthesized (about 700 mg/day) and the remaining is provided by the diet. The liver accounts for approximately 10% of total synthesis in humans, as does the small intestines.

The biosynthesis of cholesterol may be divided into five stages: 1) synthesis of mevalonate from acetyl-coenzymeA (CoA); 2) synthesis of isoprenoid units from mevalonate by loss of CO₂; 3) condensation of six isoprenoids units to form squalene; 4) cyclization of squalene to give the parental steroid, lanosterol; 5) formation of cholesterol by rearranging the lanosterol molecule (Fig. 1).

The most important rate limiting step is the conversion of the 3 α -hydroxy-3-methylglutarylcoenzyme A (HMG-CoA) into mevalonate, catalysed by the microsomal HMG-CoA reductase (Rodwell et al., 1976). The activity of the enzyme is regulated by a negative feedback mechanism both at the protein level and at the transcriptional level. To some extent the latter effects may be mediated by oxysterols and bile acids.

Lanosterol is the first sterol formed during cholesterol biosynthesis by conversion of squalene, while lathosterol is a further precursor synthesised in later steps (Kandutsch-Russel pathway). In humans, lanosterol and lathosterol are regarded to be suitable plasma surrogate marker for whole body cholesterol synthesis (Kempen et al., 1988; Bloch et al., 1957; Matthan et al., 2000).

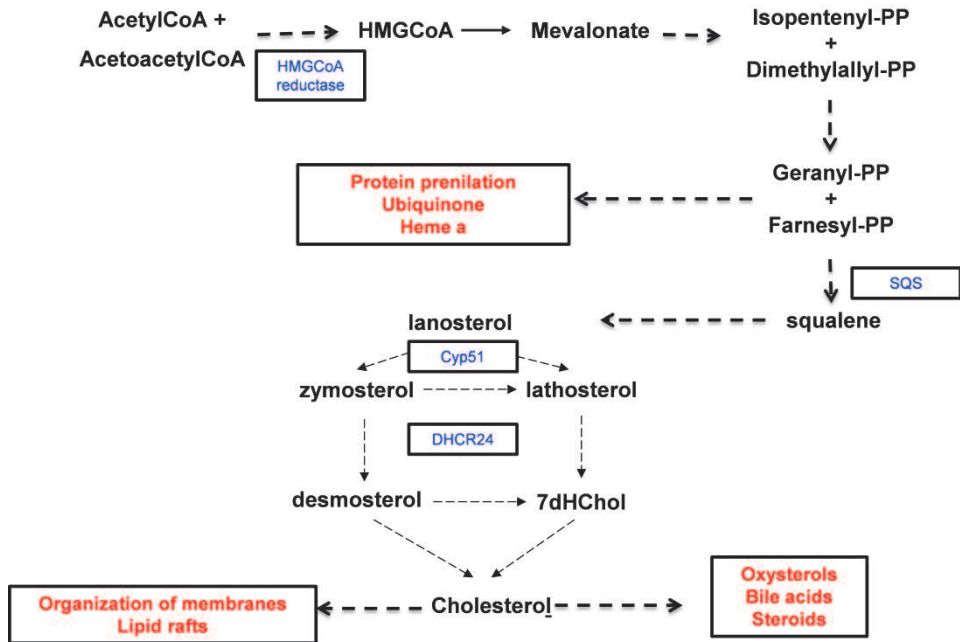


Fig. 1. Simplified diagram of cholesterol metabolism in the cells. Filled arrows mean direct enzymatic reaction, dot arrows mean metabolic reactions not presented in the figure.

Cholesterol synthesis begins with the transport of acetyl-CoA from the mitochondrion to the cytosol. Rate limiting step occurs at the 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase followed by mevalonate formation. Phosphorylation is required to solubilize the isoprenoid intermediates in the pathway (the PP abbreviation stands for pyrophosphate). Intermediates in the pathway are used for the synthesis of prenylated proteins, dolichol, coenzyme Q and the side chain of heme a. Pyrophosphated isoprenoids are condensed and cyclised by squalene synthetase (SQS) then the first sterol, lanosterol is formed. Two alternative pathways (Block and Kandush-Russel) lead to cholesterol formation. Precursor sterols can be converted by 3 β -hydroxycholesterol Δ^{24} reductase (DHCR24). Cholesterol is involved in structure, organisation and function of cellular membranes and is precursor of oxysterols, bile acids and steroids.

Cholesterol is insoluble in water and is transported in the circulation associated with lipoproteins. Cholesterol is absorbed from the intestinal lumen and transported to the liver via chylomicrons. The cholesterol in these particles can be esterified, converted into bile acids or secreted into bile or collected in Very Low Density Lipoproteins (VLDL) to be transported to the extrahepatic tissues. VLDL can be remodelled by the action of lipoprotein lipase that removes triacyl-glycerol, transferring Apolipoprotein A (ApoA) and Apolipoprotein C (ApoC) from VLDL to HDL. The product of these remodelling is LDL which supplies peripheral tissues with cholesterol. The intake of cellular LDL is strictly regulated via the LDL receptors (LDLR) and Apolipoprotein B (ApoB). The influx of cholesterol inhibits HMG-CoA reductase and cholesterol synthesis and stimulates the cholesterol esterification by acylCoA:cholesterol acyltransferase (ACAT).

The reverse cholesterol transport, whereby cells from different organs eliminate excess cholesterol through the liver, is mediated by HDL. The HDL particles contain ApoA1 and acquire cholesterol directly from the plasma membrane. This transfer is mediated by members of the ABC-transporter family.

About 1 g of cholesterol is eliminated from the body every day. Approximately half of this is excreted into the faeces after conversion into bile acids; the remainder is excreted as non-metabolized cholesterol or the bacterial metabolite coprostanol. The bile acids formed have an important role in the solubilisation and absorption of fats, cholesterol, vitamins and drugs. Approximately 95% of the bile acids are reabsorbed from the intestine and reach the liver via the portal vein (entero-hepatic cycling).

There are two different major pathways in bile acid synthesis. The neutral pathway is initiated by the rate-limiting enzyme cholesterol 7 α -hydroxylase which is mainly expressed in hepatocytes. Under normal conditions the neutral pathway dominates in healthy adult humans (Russel, 2003). In contrast to the acid pathway the neutral pathway is under strict metabolic control.

In many cells and organs cholesterol is eliminated by side chain oxidation as an alternative to the classical HDL-mediated reversed cholesterol transport. Thus, almost all cells in the body contain the enzyme sterol 27-hydroxylase (CYP27A1) located in the inner membrane of the mitochondria. This enzyme is particularly expressed by macrophages. At high levels of CYP27A1, 27OHC may be further oxidized by CYP27A1 into 3 β -hydroxy-5-cholestenoic acid. The latter acid may be further converted into 7 α -hydroxy-3-oxo-cholesten-4-cholestenoic acid and then proceed in the acidic pathway for bile acid synthesis in the liver. The latter pathway is responsible for formation of about 10 % of the daily production of bile acids in humans (Duane & Javitt, 1999; Brown & Jessup, 2009).

2. Brain cholesterol metabolism

The content of cholesterol in the brain is about 10-fold higher than in any other organ and about the 25% of the total body cholesterol is located there (Dietschy & Turley, 2004). Synthesis and storage of such a large amount of cholesterol indicates a close link between the evolution of the nervous system and a specific role for cholesterol. Within the brain about 70% of cholesterol is present in myelin. It is likely that the requirement for efficient signalling despite a small transverse diameter of axons was a key selective pressure driving the accretion of cholesterol in the mammalian brain (Dietschy & Turley, 2004; Snipe & Suter, 1997; Björkhem & Meaney, 2004). The importance of such structural role is also suggested by

the long half-life of brain cholesterol: overall brain cholesterol turns over some 250-300 times slower than that in the circulation (Björkhem & Meaney, 2004).

Myelin sheath is formed by sections of plasma membrane repeatedly wrapped around an axon, with the extrusion of virtually all of the cytoplasm. Myelin is formed by two very specialized cells: the oligodendrocyte in CNS and the Schwann cell in the peripheral nervous system. As an individual axon may be ensheathed by myelin from several oligodendrocytes, periodic gaps are present in the sheath. These are called the “nodes of Ranvier” and are the site of propagation of the action potential. Myelin can thus be regarded as a discontinuous insulation that enables the saltatory conduction of the action potential (Dietschy & Turley, 2004; Snipe & Suter, 1997). In addition to a large lipid component myelin also contains many specific proteins such as proteo-lipid protein and myelin basic protein.

Recently evidence has been presented that cholesterol can regulate the correct targeting of one of the major membrane proteins of the periphery nervous system and thereby myelin compaction. These data extend the role of cholesterol in myelin from an essential structural component to a regulator of overall myelin structure (Saher et al., 2009).

Oligodendrocytes differentiate postnatally and the process of myelination both in rodents and humans occurs during the first weeks (or months) postnatally with a coordinated accumulation of cholesterol and myelin basic protein (Dietschy and Turley, 2004). During brain maturation there is a progressive accumulation of cholesterol which ends in the adulthood when the myelin formation is completed. Interestingly the rate of cholesterol synthesis is higher in the early stage of myelination and in the regions with myelin (and white matter, such as mid brain and spinal cord compared to cortex). Together with cholesterol, myelin basic protein is one of the major proteins of CNS myelin and it represents about the 30% of the brain total protein. Severe alterations to the myelin were described in case of the shiverer mutant mouse with deletion of the myelin basic protein gene (Baumann & Pham-Dinh, 2001). The remaining 30% of brain cholesterol is divided between glial cells (20%) and neurons (10%), mainly located in cellular membranes (Maxfield & Tabas, 2005). Cholesterol is organized in microdomains called lipid rafts which are involved in the maintenance of the properties of membrane proteins such as receptors and ion channels (Allen et al., 2007). In addition to its structural role, cholesterol is involved in synaptogenesis, turnover, maintenance, stabilisation and restore of synapses (Koudinov & Koudinova, 2001). In addition it is a limiting factor for outgrowth of neurites and involved in vesicle transport and exocytosis at synaptic levels (for review see also Pfrieger, 2003 a and b; Pfrieger, 2011).

According to various *in vitro* studies with cultured cells, astrocytes synthesize at least 5-10 fold more cholesterol than neurons, while oligodendrocytes have an even higher capacity for cholesterol synthesis, at least during periods of active myelination (Pitas et al., 1987; Björkhem & Meaney, 2004). According to the “outsourcing” hypothesis it was suggested that neurons down-regulate their cholesterol synthesis and rely at least in part on delivery of cholesterol from astrocytes which differentiate postnatally and release cholesterol rich lipoproteins (Pfrieger, 2011) (Fig. 2). This strategy may allow neurons to focus on generation of electrical activity rather than disperse energy on costly cholesterol synthesis. This may be of particular importance in presynaptic terminals and dendritic spines, which are distant from the soma (Dietschy & Turley, 2004; Pfrieger, 2003a; Pfrieger, 2003b; Pfrieger, 2011). ApoE is the main lipid carrier protein in the Central Nervous System (CNS) and is released by astrocytes in order to supply neurons and synaptogenesis with lipids and cholesterol (Bu, 2009; Posse de Chaves & Narayanaswam, 2008; Björkhem et al., 2010).

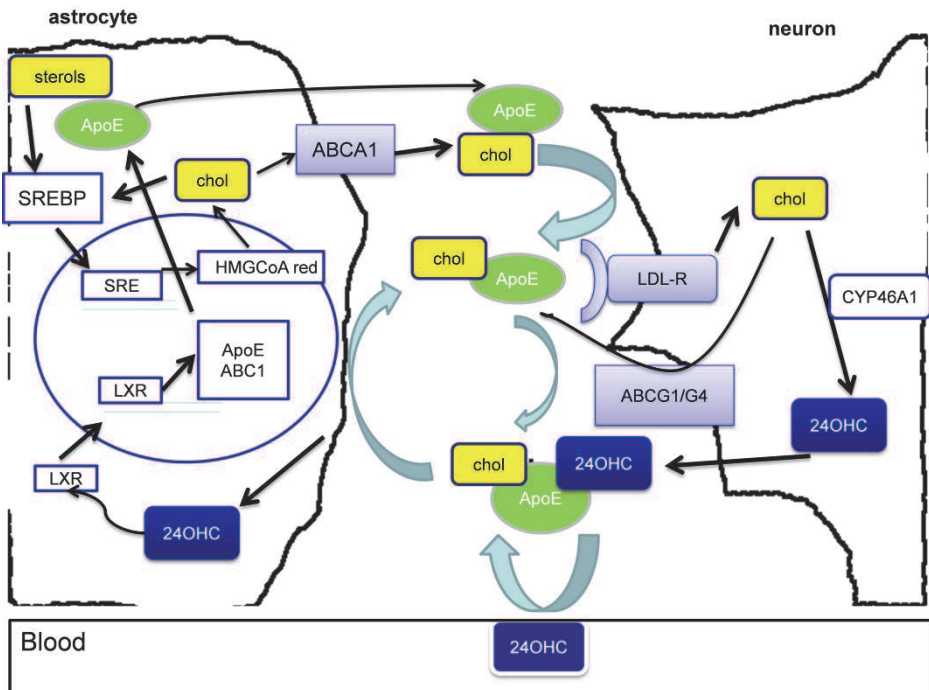


Fig. 2. Proposed model for cholesterol turnover in neurons and astrocytes. In mature brain neurons down regulate their cholesterol synthesis and rely on astrocytes delivery of cholesterol via ApoE lipoproteins. Cholesterol metabolism is a complex multisteps pathway involving endoplasmic reticulum or peroxisomes. Expression of hydroxy-methyl-glutaryl-Coenzyme A reductase (HMGCR), the rate limiting enzyme of the pathway, is regulated by feedback inhibition via the sterol-regulated element binding protein (SREBP) that binds to the sterol-regulated element (SRE-1) in the HMGCR gene. Cholesterol is loaded by astrocytes on ApoE involving also in the transport the ATP binding cassette (ABC) transporter A1 (ABCA1). The apoE-cholesterol complex is internalized via low-density lipoprotein receptors (LDLR). Excess of cholesterol is converted by neurons into the more polar 24S-hydroxycholesterol (24OHC) via the cholesterol 24-hydroxylase, CYP46. 24OHC and other oxysterols are important ligands of the liver X-activated receptor (LXR), which translocate to the nucleus (as circle in the figure) and induces expression of both the APOE and the ABCA1 genes in astrocytes. Cholesterol and 24OHC are excreted from neurons via ABC G1/G4 to ApoE particles or to CSF. 24OHC through the blood-brain barrier can be delivered into plasma for further elimination. The above proposed model is supported by a number of *in vitro* experiments with isolated neurons and astrocytes (Pfrieger, 2003a; Pfrieger, 2011; Abildayeva et al., 2006). The relation between 24OHC and ApoE is consistent with the finding of a correlation between these two factors in CSF from patients with neurodegeneration (Shafaati et al., 2007; Leoni et al., 2010). Such a relation was not found in CSF from healthy volunteers, however. The proposed model predicts a relation between levels of 24OHC and expression of LXR-target genes such as ApoE, ABCA1 and ABCG1. Such a relation was not found, however, in the brain of mice with elevated levels of 24OHC due to overexpression of CYP46A1 (Shafaati et al., 2011).

Neurons appear to produce a sufficient amounts of cholesterol to survive, to differentiate axons and dendrites and to form few and inefficient synapses. The massive formation of synapses, however, requires additional cholesterol delivered by astrocytes via ApoE-containing lipoproteins (Pfrieger 2003a; Pfrieger 2003 b; Pfrieger 2011).

Due to the efficient blood-brain barrier there is no passage of lipoprotein-bound cholesterol from the circulation into the brain (Dietschy & Turley, 2004; Snipe & Suter, 1997; Björkhem & Meaney, 2004). The blood-brain barrier thus prevents diffusion of large molecules at the level of tight junctional attachments between adjacent capillary endothelial cells. In addition to this, there is also no transvesicular movement of solution across the capillaries. It is possible that one or more members of the ATP binding cassette transporter superfamily may be involved in the exclusion of circulating cholesterol from the brain. All the cholesterol present in the brain (and in the peripheral nervous system) is thus formed by de novo synthesis. Except for active phases of specific pathological conditions, almost all (at least 99%) of the cholesterol in the nervous system is unesterified.

Cholesterol synthesis appears to be regulated by similar mechanisms both outside and inside the brain with hydroxy-methyl-glutaryl CoenzymeA reductase (HMGCR) being the most important regulatory enzyme (Snipe & Suter, 1997). However, in the brain, cholesterol synthesis via the 7-dehydrodesmosterol pathway seems to be preferred over the 7-dehydrocholesterol pathway and disruption of the gene coding for the delta 24-reductase (DHCR24) results in the accumulation of desmosterol without any accumulation of 7-dehydrodesmosterol (Wechsler et al., 2003).

In the adult brain most of the synthesis of cholesterol is balanced by formation of a hydroxylated metabolite, 24S-hydroxycholesterol (24OHC), which is able to pass across the blood-brain barrier and enter the circulation (Lütjohann et al., 1996; Björkhem & Meaney, 2004). About 6-8 mg/24h of cholesterol are released as 24OHC by the brain into the circulation (Lütjohann et al., 1996). In addition to this there is a small efflux of cholesterol from the brain in the form of ApoE containing lipoproteins via the cerebrospinal fluid (Xie et al., 2003).

Under normal conditions cholesterol 24-hydroxylase (CYP46A1), the enzyme system responsible for formation of 24S-OHC is only present in neuronal cells, mainly in cerebral cortex, hippocampus, dentate gyrus, amygdala, putamen and thalamus, i.e. associated with grey matter (Lund et al., 1999). The uptake of cholesterol by these cells may thus be balanced by the secretion of 24S-OHC. The 24S-OHC secreted from the neuronal cells may be of importance for regulation of cholesterol synthesis and secretion of this cholesterol in APOE-bound form from astroglia.

In the liver, the conversion of cholesterol into bile acids is regulated by highly sophisticated mechanisms (Russel, 2003). In the brain the expression of CYP46A1 appears to be resistant to regulatory axes known to regulate cholesterol homeostasis and bile acid synthesis. The promoter region of cholesterol 24-hydroxylase presents a high GC content, a feature often found in genes considered to have a largely housekeeping function (Ohyama et al., 2006). Oxidative stress was the only factor found to significantly affect its transcriptional activity. Cholesterol 24S-hydroxylase is localized in the neuronal cells and since these cells may depend on a flux of cholesterol from glial cells, it seems likely that substrate availability is an important regulatory factor for the enzyme under *in vivo* conditions (Björkhem, 2006).

24OHC is an endogenous regulator of the nuclear receptor Liver X Receptor (LXR). Under *in vitro* conditions 24OHC is able to regulate the expression, synthesis and secretion of ApoE (Abildayeva et al., 2006). Furthermore LXR-activation would be expected to increase expression of the sterol transporters ATP-binding cassette A1 (ABC-A1), G1 (ABC-G1) and G4 (ABC-G4) on astrocyte membranes, involved in the transport of cholesterol from glia to ApoE particles. Recently the importance of this mechanism *in vivo* was challenged by results obtained in a study on mice overexpressing CYP46A1 (Shafaati et al., 2011). Despite increased levels of 24OHC in the brain and in the circulation there was little or no increase in the expression of the different LXR target genes. In mice with combined *Abcg1* and *Abcg4* knockout results were obtained consistent with a role of these transporters in the efflux of cholesterol from neurons and glia in the CNS (Wang et al., 2008).

Cyp46a1 knock-out mice showed a modest reduction of hydroxy-methyl-glutaryl-CoA-reductase activity and cholesterol synthesis rate while the total brain cholesterol levels were unaffected (Xie et al., 2003). *Cyp46a1* (-/-) mice presented severe deficiencies in spatial, associative and motor learning associated with a delay of long lasting potential (Kotti et al., 2006). Also alterations in synaptic maturation were described. Treatment of hippocampal slices of wild type animals with an inhibitor of cholesterol synthesis essentially recapitulated the effects observed in the *Cyp46a1* (-/-) mice (Russell et al., 2009).

Finally under *in vitro* conditions 24OHC is an efficient inhibitor of the formation of A β counteracting the positive effect of cholesterol on Amyloid Precursor Protein cleavage by β -secretase (BACE1) resulting in formation of the amyloidogenic A β 1-42 fragment (Prasanthi et al., 2009; Bu, 2009).

In view of the fact that almost all 24OHC present in human circulation is of cerebral origin, (Björkhem et al., 2008) its plasma level is likely to be affected by the cholesterol homeostasis in the brain. It has been shown that the plasma levels are dependent both on the rate of secretion from the brain and the rate of hepatic metabolism (Bretillon et al., 2000a). Newborns have a size of the brain that is about three-fold that of the liver, whereas the size of the two organs is more or less similar in adults. As a consequence plasma levels of 24OHC are increased in children, infants and teenagers (Bretillon et al., 2000a) but are rather constant between the third to the seventh decades of life. According to one report the plasma concentrations of 24OHC are higher in males than in females (Vega et al., 2003). A similar observation was not reported by other more extensive studies. (Bretillon et al., 2000b; Leoni et al., 2008; Leoni et al., 2011; Leoni et al., 2002; Solomon et al., 2009b; van den Kommer et al., 2009; Burckhard et al., 2007).

In line with the fact that the number of metabolically active neuronal cells are decreased in the brain of patients with neurodegenerative diseases, the plasma levels of 24OHC have been reported to be decreased in Alzheimer's Disease (AD), Multiple Sclerosis (MS) and Huntington's Disease (HD) (Papassotiropoulos et al., 2000; Kolsch et al., 2004; Solomon et al., 2009b; Koschack et al., 2009; Bretillon et al., 2000a; Bretillon et al., 2000b; Leoni et al., 2002; Teunissen et al., 2003; Danylaité Karrenbauer et al., 2006; Leoni et al., 2008; Leoni et al., 2011). Plasma levels of 24OHC may thus be regarded as a surrogate marker for the number of metabolically active neurons located in the grey matter of the brain (Björkhem, 2006).

In addition to 24OHC also 27OHC is able to pass the blood-brain barrier (Leoni et al., 2003). A continuous flux of 27OHC from the circulation into the mammalian brain has thus been

demonstrated and this flux is of similar magnitude as the flux of 24OHC in the opposite direction (Heverin et al., 2005). In spite of the high influx of 27OHC into the brain the levels of this oxysterol is low, because of the rapid metabolism. It has been shown that most of the 27OHC present in CSF is derived from extracerebral 27OHC and that the levels are dependent upon the integrity of the blood-brain barrier. A damage of this barrier thus results in a higher flux of 27OHC from the circulation into the brain (Leoni et al., 2003; Heverin et al., 2005; Leoni et al., 2004). In view of the neurotoxic effect of 27OHC demonstrated in different *in vitro* experiments, the possibility has been discussed that the flux of 27OHC from the circulation into the brain could be a pathogenetic factor in the development of neurodegenerative diseases (Björkhem et al., 2009).

3. Cholesterol and neurodegenerative diseases other than Huntington's Disease

The importance of cholesterol synthesis in the function, development and maturation of the central nervous system is very well illustrated by the consequence of genetic disorders affecting cholesterol synthesis or metabolism with prominent neurologic manifestations such as malformations, mental retardation, cognitive impairment and ataxia (Benarroch, 2008; Porter & Herman, 2011).

The most important neurodegenerative diseases in which a disturbance in cholesterol synthesis or metabolism is the primary pathogenetic factor is Smith-Lemli-Opitz syndrome and Niemann Pick Disease Type C. For details concerning these two diseases the reader should refer to the excellent review by Porter and Herman 2011.

Smith-Lemli-Opitz syndrome (SLOs) is an autosomal recessive malformation syndrome due to a mutation in the DHCR7 gene encoding 7-dehydroxycholesterol (7-DHC) reductase (Porter, 2008). Both the accumulation of 7-DHC and the reduced cholesterol synthesis participate to the SLOs phenotype, which is extremely broad, including CNS malformations such as holoprosencephaly and agenesis of the corpus callosum, mental retardation and motorial defects (Benarroch, 2008; Porter, 2008).

Niemann Pick Disease Type C (NPC) is a rare autosomal recessive neurovisceral lipid storage disease (Vanier & Millat, 2003). Mutations in the Niemann-Pick Disease, type C1 (NPC1) and Niemann-Pick Disease, type C2 (NPC2) genes have been identified as the genetic cause of the disease. NPC1 is a large membrane anchored protein with homology to HMGCR, SREBP cleavage activating protein (SCAP) and patched (PTCH1), a gene involved in Hedgehog signalling (Davies & Ioannou, 2000). In contrast, NPC2 is a small soluble glycoprotein (Storch & Xu, 2009). NPC has extreme clinical heterogeneity (Patterson, 2003; Benarroch, 2008) ranging from a rapidly fatal disorder in neonates to a neurodegenerative disorder in adults. The most common manifestations of adult NPC were cerebellar ataxia, vertical supranuclear ophthalmoplegia, dysarthria, and cognitive disturbances, followed by movement disorders (Patterson, 2003; Benarroch, 2008).

Important neurodegenerative diseases in which cholesterol metabolism is disturbed but not likely to be the primary pathogenetic factor are Alzheimer's Disease and Parkinson's Disease. For a detailed review see Björkhem et al. 2010. The most obvious link between Alzheimer's Disease and cholesterol metabolism is the fact that presence of the E4 isoform of the cholesterol transporter ApoE as well as hypercholesterolemia are important risk factors for the disease.

4. Brain cholesterol in Huntington's Disease

Huntington's Disease (HD) is an inherited dominant neurodegenerative disorder characterised by a glutamine expansion within the N-terminus of the huntingtin protein (HTT) (Walker, 2007). The CAG trinucleotide repeats are located within the coding region of exon 1 of the HTT gene. HTT is widely expressed throughout the body and has been ascribed numerous roles in various intracellular functions including protein trafficking, vesicle transport, endocytosis, postsynaptic signalling, transcriptional regulation and an anti-apoptotic function (Gil & Rego, 2008). Gradual atrophy of the striatum (caudate nucleus and putamen) together with astrogliosis (Vonsattel et al., 1985) is a pathological characteristic of the disease. According to MRI investigations there is also a severe cortical atrophy combined with striatal degeneration (Aylward, 2007).

Cholesterol metabolism is affected in HD (Valenza & Cattaneo, 2011). The expression of some genes involved in the cholesterol biosynthetic pathway: hydroxy-methyl-glutaryl-CoA reductase, sterol 14- α demethylase (CYP51) and 7-dehydrocholesterol 7-reductase (DHCR7), were found to be reduced in inducible mutant HTT cell lines as well as in striatum and cortex of transgenic R6/2 HTT-fragment mice (Valenza et al., 2005; Valenza et al., 2007a)

Impairment of cholesterol metabolism in HD was confirmed in other additional studies.

The brain amount of the cholesterol precursors lanosterol and lathosterol, considered as markers for cholesterol synthesis (Xie et al., 2003) were found to be reduced. Also the levels of cholesterol were found to be significantly reduced in the brain of different rodent models for Huntington's Disease such as the R6/2 mice (Valenza et al., 2007a), the yeast artificial chromosome (YAC) mice, the (HdhQ111/111) Hdh knock-in mice and others (Valenza et al., 2007b; Valenza et al., 2010).

Reduced levels of 24OHC were found in whole brain, striatum and cortex in the rodent models of Huntington's Disease, suggesting an impairment of cholesterol elimination by the metabolically active neuronal cells in the brain (Valenza et al., 2010).

The reductions of cholesterol synthesis, accumulation and turnover were found to be more marked with increasing length of the CAG repeats. In addition to the length of the repeats, the impairment of cholesterol synthesis was affected by the amount of mutated huntingtin. Finally, there was also an age-dependent effect. Thus the levels of cholesterol and cholesterol precursors were only slightly reduced in young animals during the process of maturation and much more reduced in older animals (Valenza et al., 2010).

A possible explanation for the molecular mechanism involved in the impairment of cholesterol metabolism is a mutant HTT-dependent decrease in the amount of active SREBP. The role of this factor is to translocate from the cytosolic compartment to the cell nucleus where, in presence of low cholesterol levels, it activates the transcription of SRE-controlled genes. Reduced SREBP translocation was thus found in cellular models of HD and in brain striatum collected from R6/2 mice (Valenza et al., 2005). A reduced entry of SREBP into the nucleus would be expected to lead to decreased cholesterol synthesis.

As referred to above cholesterol is critical for neurite outgrowth (Pfrieger, 2011). Neurite loss is an early manifestation of various neurodegenerative disorders, including HD, in which morphological abnormalities of the brain and defects in synaptic activity have been documented (Li et al., 2003; Levine et al., 2004; Schulz et al., 2004).

Wild type HTT is able to bind to some nuclear receptors involved in lipid metabolism: Liver-X-Receptor (LXR), PPAR γ and vitamin D receptor (Futter et al., 2009). Overexpression of HTT was shown to activate LXR while a lack of HTT led to an inhibition of LXR-mediated transcription. The possibility must be considered that the mutated form of HTT is less able to up-regulate LXR and LXR-targeted genes, including SREBP. Such a mechanism could be a possible link between the HTT-mutation and the disturbances in cholesterol metabolism. Further work is needed, however, to establish this.

The mRNA levels of genes involved in cholesterol biosynthesis (hydroxy-methyl-glutaryl-CoA reductase, sterol 14-alpha demethylase, 7-dehydrocholesterol 7-reductase) and in cholesterol efflux (*abca1* and *abcg1*) were found to be significantly reduced in primary astrocytes from both R6/2 and YAC 128 mice as compared to wild type controls or YAC18. Thus, astrocytes bearing a HTT mutation synthesized and secreted less ApoE than control cells. In accordance with this, the levels of HDL-like ApoE-lipoproteins present in CSF collected from YAC128 mice were reduced as compared to CSF from wt mice (Valenza et al., 2010). The results are consistent with a reduced ApoE mediated cholesterol transport.

In theory, the impairment of astrocyte cholesterol metabolism might be due to a combination of reduced activity of LXRs as a consequence of the reduced levels of 24OHC (Valenza et al., 2010) and a reduced SREBP activation. According to the study by Shafaati et al., however, the levels of 24OHC may be less important for LXR activation under *in vivo* conditions (Shafaati et al., 2011). It seems likely that there are other yet uncovered HTT-sensitive mechanisms that are of importance for synthesis, transport and delivery of cholesterol from astrocytes to neurons .

Both MRI and pathological investigations demonstrated abnormalities in oligodendrocytes and white matter in HD brains (Myers et al., 1991; Gomez-Tortosa et al., 2001; Fennema-Notestine et al., 2004; Paulsen et al., 2008; Tabrizi et al., 2009; Nopoulos et al., 2011; Rosas et al., 2010) even in pre manifesting subjects (Gomez-Tortosa et al., 2001; Bartzokis et al., 2007; Tabrizi et al., 2009). Pathological alteration of white matter may represent an early event in HD pathogenesis.

In primary oligodendrocytes, mutant HTT was found to inhibit the regulatory effect of Peroxisome-proliferator-activated receptor-gamma co-activator 1 alpha (PGC1 α) on HmgCoA synthetase and HmgCoA reductase, expression of myelin basic protein and cholesterol metabolism (Xjiang et al., 2011). Brains from R6/2 and BACHAD mice had abnormal myelination, reduced expression of myelin basic protein and PGC1 α (Xjiang et al., 2011). In a PGC1 α knock out mice model defective myelination, reduced expression of myelin basic protein and reduction of cholesterol synthesis and accumulation has been demonstrated. The expression of HMGCoA reductase and HMGCoA synthetase and myelin basic protein was found to be reduced in this model (Xjiang et al., 2011). Peroxisome-proliferator-activated receptor gamma co-activator 1 alpha (PGC1 α) plays a role in the transcriptional regulation of energy metabolism and has been implicated in several neurodegenerative disorders (Finck & Kelly, 2006), including HD (Cui et al., 2006; Weydt et al., 2006; Chaturvedi et al., 2009; Chaturvedi et al., 2010; McConoughy et al., 2010). PGC1 α knockout mice exhibited vacuolar abnormalities in the CNS that were primarily associated with the white matter (Lin et al., 2006; Leone et al., 2005). It is likely that PGC1 α is involved in regulation of cholesterol synthesis by direct or indirect interaction with SREBP and LXR affecting, thus, myelination.

5. Study of peripheral and cerebral cholesterol metabolism in neurodegenerative disorders

5.1 Huntington's Disease

Plasma concentration of 24OHC was found reduced in HD patients compared to healthy subjects. Both in two populations (an Italian and an English cohort), as well as in the combined two cohorts, 24OHC levels were significantly reduced at any disease stage (Leoni et al., 2008). The reduction of plasma 24OHC was found to parallel the degree of caudate atrophy (measured as reduction of caudate volume at MRI). A significant positive correlation was found between 24OHC levels and degree of caudate atrophy as measured by morphometric MRI (Leoni et al., 2008). These results support that reduction of plasma 24S-hydroxycholesterol is related to the loss of metabolically active neuronal cells in the brain and thus to the degree of brain atrophy (see also Leoni & Caccia, 2011).

Total plasma cholesterol was found to be reduced in pre-manifesting subjects and in HD patients compared to controls (Markianos et al., 2008). In other studies (Leoni et al., 2008; Leoni et al., 2011) a slight reduction was found with the progress of the disease stage. A significant reduction of cholesterol levels were however found only in the most advanced cases (stage 3-5).

In a more detailed study on cholesterol homeostasis in HD it was reported that the cholesterol precursors lanosterol and lathosterol were reduced in plasma collected from HD patients at any disease stage. Also the level of the bile acid precursor 27-hydroxycholesterol was significantly reduced. Thus both whole-body and brain cholesterol homeostasis appear to be impaired in HD (Leoni et al., 2011).

HD gene positive carriers (named pre-manifest individuals) have been shown to present significant cognitive and neuropsychiatric dysfunction in parallel with changes in whole-brain volume, regional grey and white matter, at a stage prior to motor onset of disease. (Paulsen et al., 2008; Tabrizi et al., 2009). The plasma levels of 24OHC in pre-manifest subjects were similar to those of controls and higher than those of HD patients. However the gene positive pre-manifest subjects were heterogeneous: some subjects were very close to the motor onset with advanced neurodegeneration, others were far from onset. In subjects close to motor onset, 24OHC levels were found to be lower compared to those far from onset, and similar to the levels observed in manifest HD patients (Leoni et al., 2008). Interestingly, the markers of cholesterol synthesis lathosterol and lanosterol, and the marker of cholesterol elimination (27-hydroxycholesterol) were found to be reduced in pre-manifest subjects while the levels of 24S-hydroxycholesterol were reduced in patients proportionally to the degree of brain atrophy observed at MRI.

Presence of huntingtin mutations appears to be associated with a general global effect on cholesterol synthesis. Thus it is tempting to suggest that the huntingtin protein has a regulatory role in the normal cerebral as well as extracerebral biosynthesis of cholesterol (Valenza & Cattaneo, 2011). The production of 24OHC by the neuronal cells is likely to be dependent both on the numbers of such cells and on availability of substrate cholesterol. Both these factors are likely to be affected by HTT mutations.

5.2 Plasma sterols and oxysterols in neurodegenerative disease

Impairment of cholesterol metabolism were described also in animal models and patients affected by Multiple Sclerosis and Alzheimer's Disease.

Multiple Sclerosis (MS) is the most common autoimmune and demyelinating disorder of the CNS. Axonal damage and neurodegeneration is commonly found in the brains of patients with MS in both lesions and in normal-appearing white matter (Miller et al., 2002). Substantial neuronal loss and volume loss were demonstrated in grey matter, resulting in brain atrophy measured at Magnetic Resonance Imaging (MRI) (Cifelli et al., 2002). Plasma 24OHC was significantly reduced in relapsing-remitting and in primary progressive MS patients with a long story of disease (Leoni et al., 2002; Teunissen et al., 2003). The reduction of plasma 24OHC may reflect the total spatiotemporal burden of disease (i.e. the cumulative effects of its dissemination in space and its duration in time) since a significant correlation between plasma 24OHC and the volume of T2-weighted hyperintense lesions in relapsing-remitting and in primary progressive patients (Danylaitė Karrenbauer et al., 2006). A significant direct correlation was observed between the plasma 24S-hydroxycholesterol and the Grey Matter Fraction (MRI marker of brain atrophy) of MS patients (Leoni & Caccia, 2011). Lathosterol was found reduced in patients affected by MS (Teunissen, 2003) as well in animal model of MS (Teunissen et al., 2007). Also 27-hydroxycholesterol was found reduced in plasma collected from patients (Leoni et al., 2002; Teunissen et al., 2003) suggesting that whole body cholesterol metabolism may be altered in MS.

In AD the annual rate of global brain atrophy is 2-3% as compared with 0.2-0.5% in healthy controls (Fox et al., 1999; Jack et al., 2010). There is a prominent early involvement of medial temporal lobe structures, especially the entorhinal cortex and hippocampus (Jack et al., 1998). The progressive extensive atrophy is associated to a progressive reduction of the brain (Heverin et al., 2004) and plasma levels of 24OHC, and the latter is negatively correlated to the Mini Mental Score (Papassotiropoulos et al., 2000; Solomon et al., 2009b). A significant correlation of 24OHC with the hippocampal volume (Koschack et al., 2009) or the direct or fractional volumes of grey matter was found in mid-age or aged individuals (Solomon et al., 2009b). Such correlation was missed in case of Mild Cognitive Impairment (MCI) or AD patients: a possible explanation could be the abnormal expression of the CYP46 enzyme in glial cells that was shown in the brain of patients affected by AD (Brown et al., 2004; Bogdanovic et al., 2001), which occurs as a compensatory mechanism in neuronal degeneration.

Finally it was found that the reduction of plasma 24OHC correlated with the severity of dementia or the degree of brain atrophy (Papassotiropoulos et al., 2000; Solomon et al., 2009b).

Epidemiological studies showed an association between elevated total cholesterol at midlife and increased risk of AD (Kivipelto & Salomon, 2006). Long-term studies reported that a decline in plasma total cholesterol levels from midlife to late-life is associated with early stages in dementia development. It is likely that while high midlife cholesterol is a risk factor for AD, decreased cholesterol later in life may instead reflect an ongoing pathological processes in the brain and should be considered as a frailty marker, predictive of worse cognitive functioning (Stewart et al., 2007; Mielke et al., 2005; Solomon et al., 2009a; Solomon et al., 2009b). A large 21-year follow-up study presented an association between serum total cholesterol changes from midlife to late-life and late-life cognitive status: a moderate decrease is associated with increased risk of a more impaired late-life cognitive status after adjusting for major confounders (Solomon et al., 2007).

No correlation between serum total cholesterol or LDL-C and CSF biomarkers was reported (Solomon et al., 2009a). No significant differences about total or LDL-cholesterol were found

between aging individuals, MCI and AD patients but significant reductions of cholesterol precursors lathosterol and lanosterol and 27-hydroxycholesterol were instead observed in AD patients compared to MCI and aging individuals. As expected $A\beta_{1-42}$ changed in the same way while tau and P-tau in the opposite one. Thus, the CSF biomarkers signature in aging population with cognitive decline was found associated with reduction of whole body cholesterol metabolism (Solomon et al., 2009a). In AD patients (but not in case of MCI or control individuals) lower plasma total cholesterol and LDL-C were found related to lower brain volumes/higher CSF volumes (Solomon et al., 2009a). In contrast, in the control group lower levels of the cholesterol precursors lanosterol and lathosterol (considered as marker of a lower rate of endogenous cholesterol synthesis) were related to higher brain volumes/lower CSF volumes. The positive correlations between lanosterol, lathosterol, total cholesterol and LDL-C with brain volumes in patients with AD compared to MCI and controls are consistent with the hypothesis of a central nervous system (CNS)-induced depressing effect of neurodegeneration on extracerebral cholesterol metabolism (Solomon et al., 2009).

Very recent studies on patients with Parkinson's Disease have reported a markedly decreased level of 24OHC in the plasma, which is consistent with the finding of correlation between brain atrophy, CNS neuronal mass and its plasma levels (Björkhem et al., 2009).

In addition to the above diseases, brain tumours and some severe central nervous system infections also have reduced levels of 24OHC in the circulation (Bretillon et al., 2000b).

6. Conclusion

A clear link has been established between the glutamine expansion in the huntingtin gene and cholesterol metabolism. The mechanism behind this is still unknown. Since the effect on cholesterol synthesis is global it seems likely that the huntingtin gene is of regulatory importance for cholesterol synthesis also under normal conditions. It should be noted that unexplained global effect on cholesterol homeostasis has been observed also in other neurodegenerative diseases such as Alzheimer's Disease.

Liver integrity and clearance, presence of CNS pathology, therapies, cholesterol recommended levels, body mass index, diet were found to affect significantly the whole body cholesterol metabolism and plasma levels of 24OHC (Bretillon et al., 2000; Björkhem et al., 2009; Björkhem, 2006; Brown & Jessup, 2009; Leoni & Caccia, 2011). The criteria of selection of the control population, the pre-analytical factors of sample collection and handling, the methodology used for the study of sterols and oxysterols may affect the final findings. The use of sterols and side-chain oxidised cholesterol as biomarker for the diagnosis of neurodegenerative diseases seems to be still limited. However, the plasma level of a neuronal metabolite of cholesterol, 24S-hydroxycholesterol, appears to be a valuable biomarker for the progression of Huntington's Disease.

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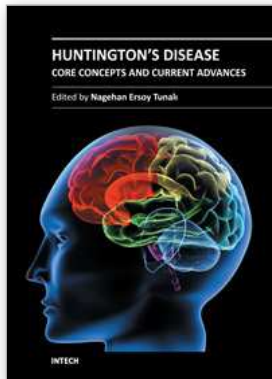
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Huntington's Disease is one of the well-studied neurodegenerative conditions, a quite devastating and currently incurable one. It is a brain disorder that causes certain types of neurons to become damaged, causing various parts of the brain to deteriorate and lose their function. This results in uncontrolled movements, loss of intellectual capabilities and behavioural disturbances. Since the identification of the causative mutation, there have been many significant developments in understanding the cellular and molecular perturbations. This book, "Huntington's Disease - Core Concepts and Current Advances", was prepared to serve as a source of up-to-date information on a wide range of issues involved in Huntington's Disease. It will help the clinicians, health care providers, researchers, graduate students and life science readers to increase their understanding of the clinical correlates, genetic aspects, neuropathological findings, cellular and molecular events and potential therapeutic interventions involved in HD. The book not only serves reviewed fundamental information on the disease but also presents original research in several disciplines, which collectively provide comprehensive description of the key issues in the area.

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