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Review

The impairment of cholesterol metabolism in Huntington disease ☆

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ABSTRACT

Huntington disease (HD), an autosomal dominant neurodegenerative disorder caused by an abnormal expansion of CAG trinucleotide repeat in the *Huntingtin* (*HTT*) gene, is characterized by extensive neurodegeneration of striatum and cortex and severe diffuse atrophy at MRI.

The expression of genes involved in the cholesterol biosynthetic pathway and the amount of cholesterol, lanosterol, lathosterol and 24S-hydroxycholesterol were reduced in murine models of HD. In case of HD-patients, the decrease of plasma 24OHC follows disease progression proportionally to motor and neuropsychiatric dysfunction and MRI brain atrophy, together with lanosterol and lathosterol (markers of cholesterol synthesis), and 27-hydroxycholesterol. A significant reduction of total plasma cholesterol was observed only in advanced stages.

It is likely that mutant HTT decreases the maturation of SREBP and the up-regulation LXR and LXR-targeted genes (SREBP, ABCG1 and ABCG4, HMGCoA reductase, ApoE) resulting into a lower synthesis and transport of cholesterol from astrocytes to neurons via ApoE. In primary oligodendrocytes, mutant HTT inhibited the regulatory effect of PGC1α on cholesterol metabolism and on the expression of MBP.

HTT seems to play a regulatory role in lipid metabolism. The impairment of the cholesterol metabolism was found to be proportional to the CAG repeat length and to the load of mutant HTT. A dysregulation on PGC1α and mitochondria dysfunction may be involved in an overall reduction of acetyl-CoA and ATP synthesis, contributing to the cerebral and whole body cholesterol impairment. This article is part of a Special Issue entitled Brain Lipids

1. Cholesterol

Cholesterol is a structural element of mammal cellular membrane and regulates the fluidity of lipid bilayers. It is the precursor of bile acids, steroid hormones and oxysterols. The cellular needs are covered by de novo synthesis or by the uptake from circulating lipoproteins. All the cells are able to synthesize, release and take up cholesterol to maintain their cholesterol homeostasis: some produce an excess of cholesterol to provide other cells, some others need exogenous cholesterol because of limited synthetic capacity. In humans, 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. Cholesterol, together with the other lipids, is absorbed by small intestine, loaded on chylomicrons and delivered to the liver. The exogenous cell supply is covered by very low density lipoprotein (VLDL)–low density lipoprotein (LDL) cycle. Since an excess of free cholesterol is toxic to the cells, a number of strategies have been evolved either to export it (via lipoproteins), to store it in an esterified form or release it after oxidation into oxysterols.

A major fraction of the exceeding is exported by the reverse cholesterol transport mechanism involving the high density lipoprotein (HDL) and the ATP-binding cassette (ABC)-transporter family.

Abbreviations: 24OHC, 24S-Hydroxycholesterol; 27OHC, 27-Hydroxycholesterol; ABC, ATP-binding cassette transporter; ACAT, Acyl-Coa:cholesterol acyltransferase; AD, Alzheimer disease; ApoE, Apolipoprotein E; BACHD, Bacterial artificial chromosome HD; BDNF, Brain-derived neurotrophic factor; Cav1, Caveolin-1; CNS, Central nervous system; CSF, Cerebrospinal fluid; CYP7A1, Cholesterol 7α-hydroxylase; CYP27A1, Sterol 27-hydroxylase; CYP46A1, Cholesterol 24-hydroxylase; CYP51, Lanosterol 14-alpha demetylase; DHCR24, 24-Dehydrocholesterol reductase; ER, Endoplasmic reticulum; HD, Huntington disease; HDL, High density lipoproteins; HMGCoA, 3α-Hydroxy-3-methylglutarylcoenzyme A; HMGCoAR, HMGCoA reductase; HMGCoAS, HMGCoA synthetase; HTT, Huntingtin; Insig, Insulin induced gene; LDL, Low density lipoproteins; LDL-R, LDL-receptor; LRP, LDL-related protein; LXR, Liver X receptor; MBP, Myelin basic protein; MM, Mitochonrial membrane; MRI, Magnetic resonance imaging; MS, Multiple sclerosis; NPC, Niemann–Pick type C; NS, Neural stem; PGC1α, Peroxisome proliferator-activated receptor-gamma co-activator 1 alpha; PLP, Proteolipid protein; PPARγ, Peroxisome proliferator-activated recepetor gamma; SCAP, SREBP cleavage-activating protein; ST, Striatal; TCA, Tricarboxylic acid; SRE, Sterol responsive element; SREBP, Sterol responsive element binding protein; VLDL, Very low density lipoprotein; YAC, Yeast artificial chromosome

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Cholesterol is synthesized from acetyl-CoA that is converted into 3-hydroxy-3-methylglutaril-CoA (HMGCoA) through two condensation steps (Figs. 1 and 2). Microsomal HMGCoA reductase (HMGCoAR) catalyzes the reduction of HMGCoA into mevanolate in endoplasmic reticulum (ER). Mevalonate is phosphorilated into isopentyl-pyrophosphate and other isoprenoids and then by condensation of six units is formed squalene which is cyclized into the parental steroid, lanosterol. Two alternative ways proceed with the cholesterol synthesis: the Block pathway (desmosterol as the main intermediate) and the Kandutsch–Russell pathway (lathosterol and 7-dehydrocholesterol, the two main intermediates). The quantification of the cholesterol precursors lanosterol, lathosterol and desmosterol is considered as surrogate marker for tissue or whole body cholesterol synthesis [1–3].

The HMGCoAR reaction is recognized as the rate limiting step of cholesterol synthesis [4]. Cholesterol and oxysterols are directly involved in a negative feedback mechanism of the enzyme regulation both at the protein and the transcriptional level. Oxysterols modulate lipid synthesis by acting on sterol responsive element (SRE) binding proteins (SREBPs). These transcription factors regulate lipid homeostasis in vertebrate cells by activation of more than 30 genes involved in the synthesis and uptake of cholesterol, fatty acids, triglycerides and phospholipids as well as NADPH [5]. SREBPs are expressed as inactive 120 kDa precursors (pSREBPs) integral to the ER membrane. When intracellular cholesterol levels are low, pSREBPs are translocated from the ER to the Golgi by an escort protein, SREBP cleavage-activating protein (SCAP), where they are cleaved into a 67 kDa active transcription factors, not membrane bound. These shorter mature SREBPs (mSREBPs) enter the nucleus and modulate transcription of genes containing a SRE in the promoter region. When intracellular cholesterol levels are in excess, SCAP, which has a cholesterol-sensing domain, binds insulin induced gene (Insig) and the Insig-SCAP-pSREBP is retained in the ER reducing cholesterol synthesis [6,7]. SREBPs exist in three isoforms: SREBP-1A activates cholesterol, fatty acid and triglycerides synthesis, SREBP-1C enhances fatty acid synthesis and SREBP-2 is primarily involved in cholesterol synthesis [6].

About 1 g of cholesterol is eliminated from the body every day. Approximately half of this is excreted into the feces after conversion into bile acids; the remainder is excreted as non-metabolized cholesterol

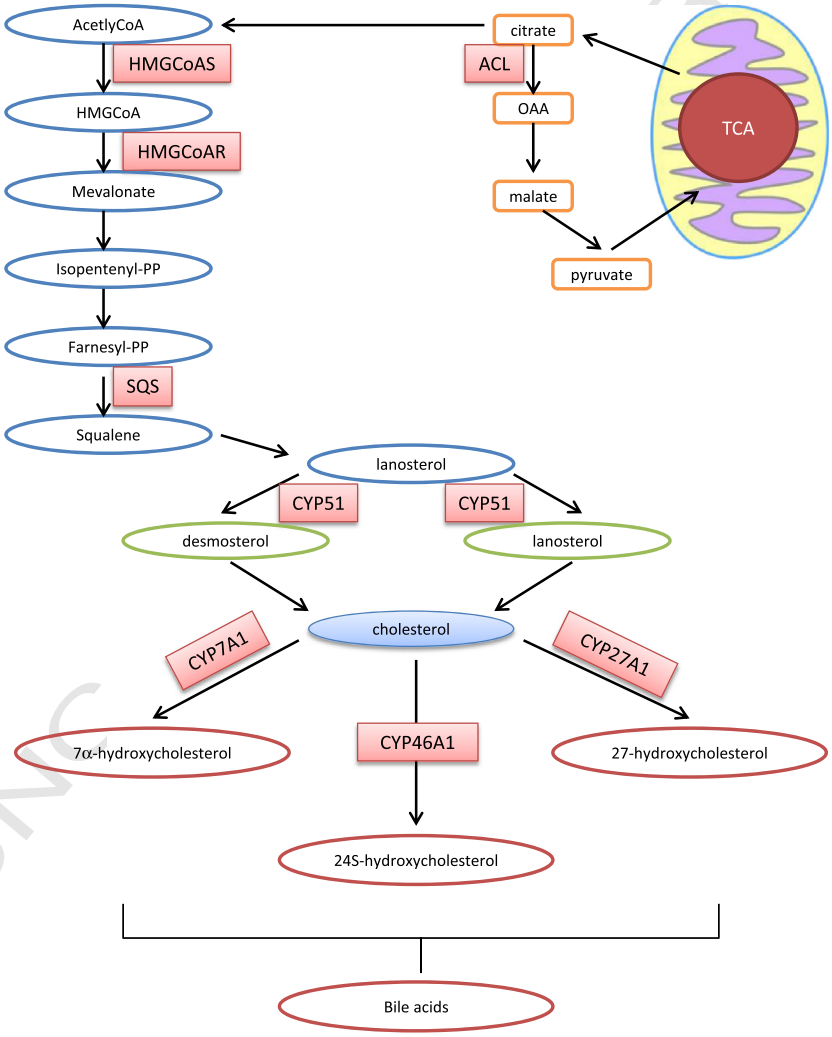

Fig. 1. Simplified diagram of cholesterol metabolism in the cells. The formation of acetyl-CoA is the first step of cholesterol and fatty acids synthesis. The acetyl-CoA enters in cytosol in form of citrate by the tricaboxylate transport system. ATP-citrate-lyase (ACL) converts citrate into acetyl-CoA and oxaloacetate in an ATP-driven reaction. HMGCoAS catalyzes the condensation of 3 acetyl-CoA into HMGCoA. The rate limiting step occurs at the HMGCoAR 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 cyclized by squalene synthetase (SQS) then the first sterol, lanosterol is formed. Two alternative pathways (Block and Kandush–Russel) lead to cholesterol formation. Liver CYP7A1 converts cholesterol into 7 α-hydroxycholesterol (7αOHC), the main precursor of the neutral bile acid pathway. Cholesterol 27-hydroxylase (CYP27A1), expressed in different cell types, converts cholesterol into 27-hydroxycholesterol (27OHC), precursor of the acidic bile acid pathway. Neuronal specific cholesterol 24-hydroxylase (CYP46A1) is responsible for 24S-hydroxycholesterol (24OHC) formation.

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