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Review

24S-hydroxycholesterol in plasma: A marker of cholesterol turnover in neurodegenerative diseases

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ABSTRACT

Brain cholesterol is mainly involved in the cell membrane structure, in signal transduction, neurotransmitter release, synaptogenesis and membrane trafficking. Impairment of brain cholesterol metabolism was described in neurodegenerative diseases, such as Multiple Sclerosis, Alzheimer and Huntington Diseases. Since the blood–brain barrier efficiently prevents cholesterol uptake from the circulation into the brain, de novo synthesis is responsible for almost all cholesterol present there. Cholesterol is converted into 24S-hydroxycholesterol (24OHC) by cholesterol 24-hydroxylase (CYP46A1) expressed in neural cells.

Plasma concentration of 24OHC depends upon the balance between cerebral production and hepatic elimination and is related to the number of metabolically active neurons in the brain. Factors affecting brain cholesterol turnover and liver elimination of oxysterols, together with the metabolism of plasma lipoproteins, genetic background, nutrition and lifestyle habits were found to significantly affect its plasma levels.

Either increased or decreased plasma 24OHC concentrations were described in patients with neurodegenerative diseases. A group of evidence suggests that reduced levels of 24OHC are related to the loss of metabolically active cells and the degree of brain atrophy. Inflammation, dysfunction of BBB, increased cholesterol turnover might counteract this tendency resulting in increased levels or, in some cases, in unsignificant changes.

The study of plasma 24OHC is likely to offer an insight about brain cholesterol turnover with a limited diagnostic power.

1. Cholesterol

Cholesterol is present in all vertebrate cells and, as structural element, regulates the fluidity of lipid bilayers. It is also a precursor of bile acids, steroid hormones and oxysterols. De novo synthesis and uptake from circulating lipoproteins cover the cholesterol needs of the cells. In general, cells 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 of free cholesterol may be toxic to the cells and a number of strategies have been 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

Abbreviations: 24OHC, 24S-hydroxycholesterol; 27OHC, 27-hydroxycholesterol; Aβ, amyloid beta; ABC, ATP-binding cassette transporter; ACAT, acyl-Coa:cholesterol acyltransferase; AD, Alzheimer disease; Apoe, apolipoprotien E; APP, amyloid precursor protein; BACE, β-secretase 1; CE, cholesteryl ester; CETP, cholesteryl ester transfer protein; CNS, central nervous system; CoA, coenzyme A; CRP, C reactive protein; CSF, cerebrospinal fluid; CYP27A1, sterol 27-hydroxylase; CYP46A1, cholesterol 24-hydroxylase; CYP51, 14-alpha-demetylase; DHRC24, delta 24-reductase; ER, endoplasmic reticulum; HD, Huntington Disease; HMG, 3α-hydroxy-3-methylglutarylcoenzyme A; HMGCR, HMG-Coa reductase; HTT, Huntingtin; Insig, insulin induced gene; LDL, low density lipoproteins; LXR, liver X receptor; MBP, myelin basic protein; MCI, mild cognitive impairment; MRI, magnetic resonance imaging; MS, multiple sclerosis; NFT, neruofibrillary tangles; NS, neural stem; nss, statistically not significant; OCD, other cognitive dementia; PD, Parkinson's Disease; PGC1a, peroxisome-proliferator-activated receptor gamma co-activator 1 alpha; PLP, proteo-lipid protein; PPMS, primary progressive MS; P-Tau, hyper-phosphorylated tau protein; RRMS, relapsing remitting MS; SCAP, SREBP cleavage-activating protein; SRE, sterol responsive element; SREBP, sterol responsive element binding protein; ss, statistically significant; T-Tau, total tau protein; VD, vascular dementia; WMH, white matter hyperintensities; YAC, yeast artificial chromosome.

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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 biosynthesis of cholesterol may be divided into five stages: 1) synthesis of mevalonate from acetyl-coenzyme A (CoA); 2) synthesis of isoprenoid units from mevalonate by loss of CO_2; 3) condensation of six isoprenoid units to form squalene; 4) cyclization of squalene to give the parental steroid, lanosterol; 5) formation of cholesterol by rearranging the lanosterol molecule. The most important rate limiting step is the conversion of the 3α-hydroxy-3-methylglutarylcoenzyme A (HMG-CoA) into mevalonate, catalyzed by the microsomal HMG-CoA reductase (HMGCR) (Fig. 1) [1]. The activity of the enzyme is regulated by a negative feedback mechanism both at the protein and 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 and desmosterol are further precursors synthesized in later steps (Kandutsch-Russell and Bloch pathways, respectively). In humans, lanosterol and lathosterol are regarded as plasma surrogate markers for whole body cholesterol synthesis [2–4]. 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 solubilization and absorption of fats, cholesterol, vitamins and drugs. About 95% of the bile acids are reabsorbed from the intestine and reach the liver via the portal vein (entero-hepatic cycling).

Two are the major pathways in bile acid synthesis. The neutral pathway is initiated by the rate-limiting enzyme cholesterol 7α-hydroxylase which is mainly expressed in hepatocytes. Under normal conditions the neutral pathway dominates in healthy adult humans [5]. 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. 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 3β-hydroxy-5-cholestenoic acid. The latter acid may be further converted into 7α-hydroxy-3-oxo-cholesten-4-cholestenoic acid and then proceeds 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 [6,7].

Cholesterol can be also absorbed by small intestine and loaded on chylomicrons together with other lipids and plantosterols, a group of molecules of vegetable origin similar to cholesterol. Plasma levels of plantosterols (i.e. campesterol and sitosterol) are regarded as marker of cholesterol absorption [8].

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 [9]. Within the brain about 70% of cholesterol is present in myelin where it plays mainly a structural role as element of the cell membrane. The remaining 30% of brain cholesterol is divided between glial cells (20%) and neurons (10%), mainly located in cellular membranes [10]. Cholesterol is organized

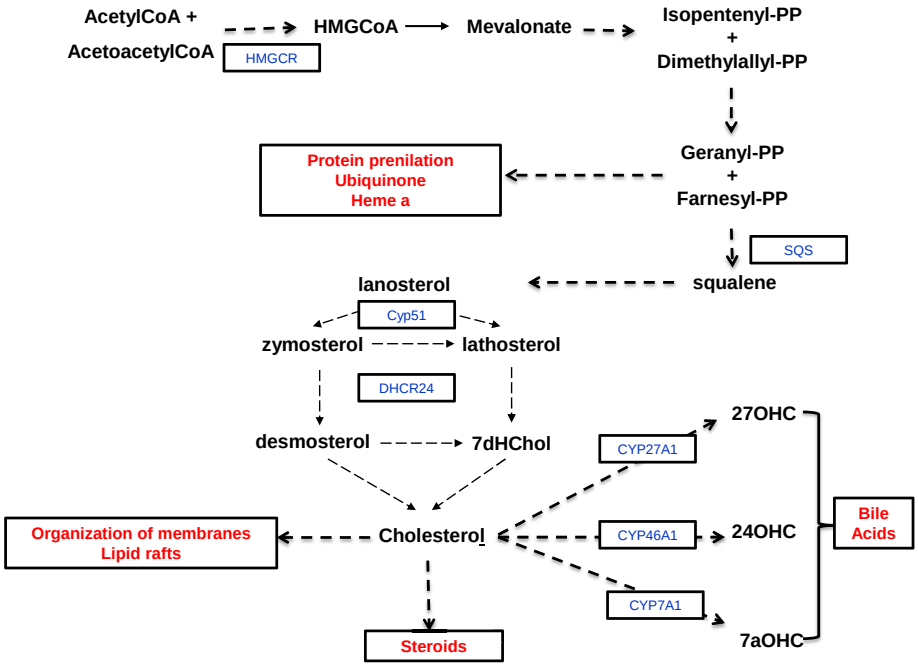

Fig. 1. Simplified diagram of cholesterol metabolism in the cells. Filled arrows mean direct enzymatic reaction, dot arrows mean metabolic reactions not presented in the figure. Cholesterol synthesis begins with the transport of acetyl-CoA from mitochondria into the cytosol. Rate limiting step occurs at the 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase (HMGCR) 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. Precursor sterols can be converted by 3β-hydroxycholesterol Δ24 reductase (DHCR24). Cholesterol is involved in structure, organization and function of cellular membranes and is precursor of oxysterols, bile acids and steroids. Liver CYP7A1 converts cholesterol into 7α-hydroxycholesterol (7aOHC), the main precursor of the neutral bile acid pathway. Cholesterol 27-hydroxylase (27OHC) 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.