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Review

Cholesterol in myelin biogenesis and hypomyelinating disorders ☆

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ABSTRACT

The largest pool of free cholesterol in mammals resides in myelin membranes. Myelin facilitates rapid saltatory impulse propagation by electrical insulation of axons. This function is achieved by ensheathing axons with a tightly compacted stack of membranes. Cholesterol influences myelination at many steps, from the differentiation of myelinating glial cells, over the process of myelin membrane biogenesis, to the functionality of mature myelin. Cholesterol emerged as the only integral myelin component that is essential and rate-limiting for the development of myelin in the central and peripheral nervous system. Moreover, disorders that interfere with sterol synthesis or intracellular trafficking of cholesterol and other lipids cause hypomyelination and neurodegeneration. This review summarizes recent results on the roles of cholesterol in CNS myelin biogenesis in normal development and under different pathological conditions. This article is part of a Special Issue entitled Brain Lipids.

1. Introduction

In the brain, several functions have been attributed to cholesterol, such as neuronal differentiation and synaptogenesis. However, the bulk amount of cholesterol in the brain resides in myelin. About 25% of the unesterified cholesterol of an entire adult mouse is incorporated in myelin membranes. In the brain, myelin even accounts for about 80% of the brain cholesterol content [1–4]. Given that sterol synthesis is a complex and energy consuming process, the animal devotes substantial effort to establish and maintain this large and quite homogenous pool of cholesterol. This suggests that cholesterol in myelin serves essential brain functions. Critical for higher order animals is the accurate and fast transduction of neuronal signals, particularly over long distances, which depends on proper insulation of axons. This insulating function is mediated by the myelin sheath. Myelin is a lipid-rich multilayered stack of membranes that extends from the plasma membrane of oligodendrocytes and wraps around axons. Mechanistic insight into the process of myelin membrane growth has been described recently [5]. The oligodendrocytes synthesize most of the cholesterol needed for myelin membranes [6,7] but they most likely also use external sources [8]. Hence, in addition to synthesis by oligodendrocytes, other cells contribute to myelination by providing the essential constituent cholesterol (see below).

2. Peripheral cholesterol metabolism

To understand the role of cholesterol in myelin, it is important to consider the metabolism and homeostasis of sterols in the brain (Fig. 1) in comparison to the remaining body. Most dietary sterols are absorbed by mucosa cells of the jejunum via NPC1L1 protein (Niemann–Pick type C like protein 1) [9,10]. Together with triglycerides, esterified cholesterol is incorporated into nascent chylomicrons that are released into the lymph. Only after the removal of the majority of triglycerides from chylomicrons by peripheral cells, cholesterol enters blood circulation as part of chylomicron remnants. The liver then is critically involved in adjusting the serum cholesterol level by adapting cholesterol synthesis to the nutritional cholesterol supply. Lipoprotein particles such as VLDL (very low density lipoprotein) and LDL manage the distribution of hydrophobic lipids from the liver to peripheral organs. Reverse transport of cholesterol to the liver is mediated by high density lipoproteins, so called HDL. Each type of lipoprotein contains a specific set of apolipoproteins. Some apolipoproteins are found in several lipoproteins, such as Apolipoprotein E (ApoE) which is present in chylomicrons, VLDL, IDL (intermediate density lipoprotein) and HDL. In contrast, apoAI is restricted to chylomicrons and HDL. However, an exchange of lipids between lipoprotein classes is common

Abbreviations: 7DHC, 7-dehydrocholesterol; ABC transporter, ATP binding cassette transporter; ApoA1, apolipoprotein A1; ApoE, apolipoprotein E; CNS, central nervous system; CYP46A1, cholesterol 24-hydroxylase; CYP51, lanosterol 14 alpha-demethylase; DHCR7, 7-dehydrocholesterol reductase; DHCR24, 24-dehydrocholesterol reductase; HDL, high density lipoprotein; HMGCR, HMG-CoA reductase, 3-hydroxy-3-methylglutaryl-CoA reductase; INSIG, insulin-induced gene; LDL, low density lipoprotein; MBP, myelin basic protein; NP-C, Niemann–Pick disease type C; NPC, Niemann–Pick disease type C protein; PLP, proteolipid protein; PMD, Pelizaeus–Merzbacher disease; SCAP, SREBP cleavage activating protein; SLOS, Smith–Lemli–Opitz syndrome; SNARE, soluble N-ethylmaleimide-sensitive-factor attachment receptor; SREBP, sterol responsive element binding protein; VLDL, very low density lipoprotein

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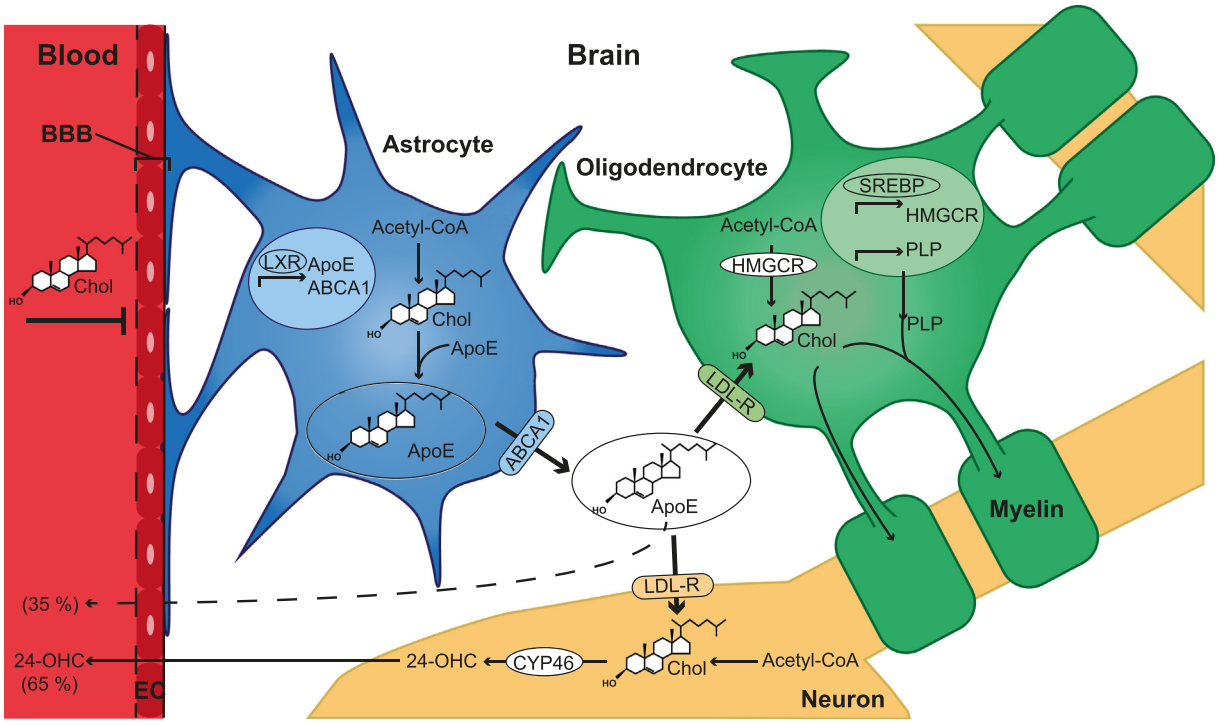

Fig. 1. Model of cholesterol homeostasis in the CNS. Peripheral cholesterol (Chol) entry into the brain is largely precluded by the blood–brain barrier (BBB) which is formed mainly by endothelial cells (EC). In the brain, cholesterol is synthesized de novo by all cells. The cell type of predominant cholesterol synthesis switches from neurons during embryogenesis to oligodendrocytes during postnatal myelination and to mainly astrocytes in the adult. The cholesterol synthesis pathway starts from acetyl-CoA that is converted in a multiple step mechanism to cholesterol, including the rate-limiting enzyme 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMGCR). By a feedback-inhibition mechanism of cholesterol, HMG-CoA reductase expression is regulated, mediated by SREBP (sterol regulatory element-binding protein) transcription factors. Apolipoprotein E (ApoE) facilitates the transport of cholesterol between cells in the brain. ApoE containing lipoproteins are generated by ABC transporter (ABCA1) mediated secretion and further lipidation predominantly in astrocytes. The expression of ApoE and ABCA1 is regulated by the liver X receptor (LXR) family of transcription factors. Lipoproteins are endocytosed by low-density lipoprotein receptors (LDL-R) providing neurons and oligodendrocytes with cholesterol. In the process of myelination, cholesterol associates with the proteolipid protein (PLP) and is integrated into the myelin sheath. One excretion route for cholesterol out of the brain is achieved by conversion to 24(S)-hydroxycholesterol (24-OHC) catalyzed by cholesterol 24-hydroxylase (CYP46). 24-OHC can pass the blood–brain barrier into the blood stream where it gets transported to the bile for degradation. About one third of cholesterol is excreted by another route potentially involving ApoE.

in humans. In hepatocytes, sterols are catabolized by secretion into bile, either as free sterol or after conversion to primary bile acids.

3. Brain metabolism of cholesterol

Although the cholesterol metabolism in the periphery and the CNS follow the same principle, they differ in certain aspects. Because of the very restricted entry of sterols into the CNS, most of the brain cholesterol is synthesized locally. As in the periphery, transport of cholesterol is also mediated by lipoproteins but transport mechanisms are less complex. Turnover of cholesterol in the CNS is limited to hydroxylation. Hydroxylated sterols readily cross the blood–brain barrier for elimination in bile.

3.1. Sterol entry and the blood–brain barrier

Nutritional lipids access the brain only in very limited amounts. The separation of sterol metabolism in the central nervous system (CNS) from the periphery is mediated by the blood–brain barrier. This interface between blood and CNS is formed by endothelial cells of the brain but also astrocytes and pericytes provide inductive signals [11]. The physical barrier is formed by tight junctions between endothelial cells that preclude passive diffusion in and out of the CNS which strongly limits the entry of most hydrophobic molecules including cholesterol [12]. Theoretically, lipoproteins from the circulation could enter the brain to deliver cholesterol to the CNS. However, a study on liver transplantation with donors and recipients carrying different ApoE-isoforms showed that lipoproteins containing ApoE do not enter the brain [13]. In contrast, a plethora of specific transport systems mediate the vivid exchange of small molecules such as water, glucose, amino acids or small peptides over the blood–brain barrier [14]. Even during development, when the blood–brain barrier has not fully formed yet, the brain normally synthesizes the majority of its cholesterol locally [15]. In adults, only few nutritional sterols are stably incorporated in the CNS. Phytosterols including beta-sitosterol and campesterol may add up to 0.1–0.5% of total CNS sterols in adult mice with only little increase upon aging [16–18]. A major contribution of phytosterols to myelin lipids seems unlikely because the peak phase of myelination precedes weaning, and the fraction of plant material to nutrition during early postnatal development is limited. In case of blood–brain barrier impairment, the increased entry of sterols into the brain as well as the increased excretion from the brain demonstrated the imbalance of brain cholesterol homeostasis but the steady state level of cholesterol was not altered [19].

3.2. Cholesterol synthesis

De novo synthesis of cholesterol is divided into two parts. The first mevalonate pathway converts acetyl-CoA to the isoprenoid isopentenyl pyrophosphate. This part also comprises the rate limiting reaction of sterol synthesis: HMG-CoA reductase (3-hydroxy-3-methylglutaryl coenzyme A reductase) catalyzes the formation of mevalonate from HMG-CoA. The second part of the sterol synthesis pathway begins with the first committed step in sterol synthesis that is catalyzed by the farnesyl-diphosphate farnesyltransferase (*FDFT1* gene) and results in the formation of squalene. Squalene epoxidation and cyclization

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