Biochemical and Biophysical Research Communications xxx (2013) xxx–xxx

Contents lists available at ScienceDirect

Biochemical and Biophysical Research Communications

journal homepage: www.elsevier.com/locate/ybbrc

Effects of oxysterols on the blood–brain barrier: Implications for Alzheimer's disease

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ARTICLE INFO

Article history:
Available online xxxx

Keywords:
Oxysterols
Blood–brain barrier
ABCA1
ABCB1
Alzheimer's disease
LXR

ABSTRACT

Altered brain cholesterol homeostasis plays a key role in neurodegenerative diseases such as Alzheimer's disease (AD). For a long time, the blood–brain barrier (BBB) was basically considered as a barrier isolating the brain from circulating cholesterol, however, several lines of evidence now suggest that the BBB strictly regulates the exchanges of sterol between the brain and the peripheral circulation. Oxysterols, synthesized by neurons or by peripheral cells, cross the BBB easily and modulate the expression of several enzymes, receptors and transporters which are involved not only in cholesterol metabolism but also in other brain functions. This review article deals with the way oxysterols impact BBB cells. These perspectives open new routes for designing certain therapeutical approaches that target the BBB so that the onset and/or progression of brain diseases such as AD may be modulated.

1. Introduction

Cholesterol is an essential cellular membrane component and is a precursor of several signalling molecules. Neurons and glial cells, within the central nervous system (CNS), are extremely high cholesterol requestors, using the latter to generate and transmit electrical signals. As such, dysfunction of the cholesterol metabolism is intimately linked to abnormal neurological functioning and to neurodegenerative diseases such as Alzheimer's disease (AD) [1,2]. However, the metabolism of this sterol in the CNS is different from its metabolism in the rest of the body and remains partially understood due to the presence of the blood–brain barrier (BBB) which may regulate the exchanges of cholesterol between peripheral and cerebral compartments. This review will highlight the latest data relating to the role of the BBB on complex brain cholesterol homeostasis and, consequently, in AD.

Abbreviations: 24S-OHC, 24S-hydroxycholesterol; 27-OHC, 27-hydroxycholesterol; Aβ peptides, β-amyloid peptides; ABCA1, ABCB1 and ABCG1, ATP-binding cassette (ABC) subfamily A, member 1, ABC subfamily B, member 1 and ABC subfamily G, member 1, respectively; AD, Alzheimer's disease; ApoE, apolipoprotein; BBB, blood–brain barrier; BCECs, brain capillary endothelial cells; CNS, central nervous system; CYP46, cytochrome P450, family 46; HDL, high-density lipoproteins; LXR, liver X receptor.

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2. CNS cholesterol homeostasis

Contrary to the periphery where cholesterol homeostasis is mainly dependent on dietary uptake, brain cholesterol homeostasis seems to depend essentially on de novo synthesis and recycling (Fig. 1). In the adult brain, cholesterol is mainly synthesized by astrocytes from acetyl coenzyme A through a complex series of reactions involving more than 20 enzymes. Then, certain transporters expressed by astrocytes such as the ATP-binding cassette (ABC) transporters (ABC subfamily A, member 1 (ABCA1) and ABC subfamily G, member 1 (ABCG1)) secrete lipoproteins composed of cholesterol and apolipoprotein E (ApoE) *via* a reverse cholesterol transport process [3–5]. These lipoproteins (with a density similar to high-density lipoproteins, HDL) are then shuttled to neurons to be used in synaptogenesis, myelin formation, neurotransmitter release and membrane repair. This cholesterol pool is closely regulated; some of the neurons express the cytochrome P450 enzyme, family 46 (CYP46) which enables excess cholesterol to be converted to 24S-hydroxycholesterol (24S-OHC) [6,7]. This oxysterol (initially named cerebrosterol) is mainly synthesized in the brain, is eliminated into the peripheral circulation, then reaches the liver where it is converted into bile acids. In the peripheral cells where CYP46 is absent or slightly expressed, the major oxysterol synthesized is 27-hydroxycholesterol (27-OHC) [8]. This latter is also able to cross the BBB to reach the brain [9]. Moreover, both these oxysterols are natural ligands for the liver X receptor (LXR) nuclear receptors that modulate the expression of specific

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http://dx.doi.org/10.1016/j.bbrc.2013.11.059

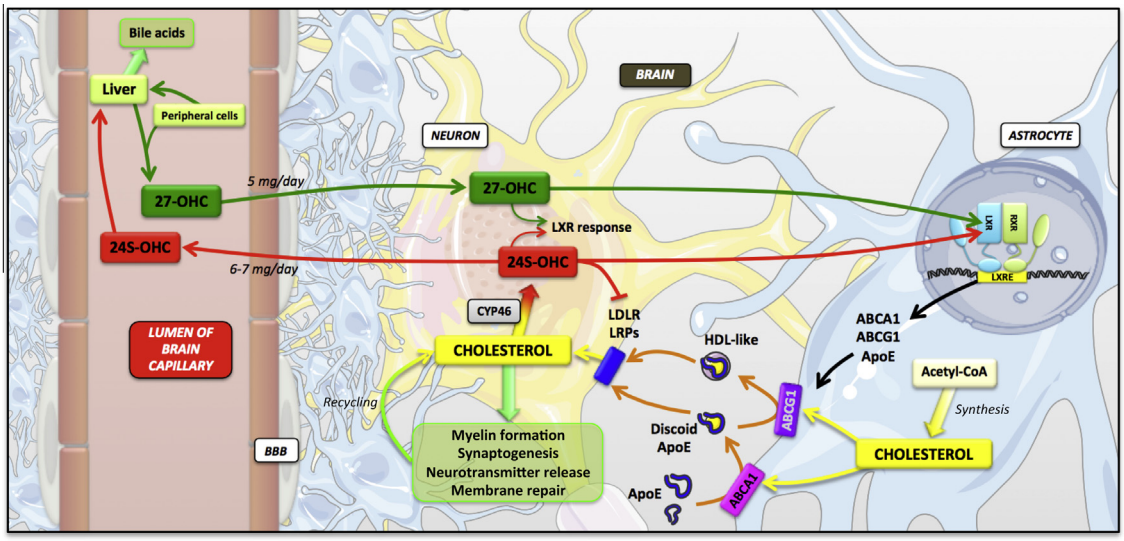

Fig. 1. Brain cholesterol homeostasis. In the adult brain, cholesterol is synthesized by astrocytes and then shuttled to neurons via an ABC-transporter mediated process. In neurons, excess of this sterol is then converted into 24S-hydroxycholesterol (24S-OHC) which may cross the blood–brain barrier (BBB) to be eliminated into the blood circulation. In the brain however, this oxysterol may also interact with the liver X receptor (LXR) nuclear receptors, thus regulating the transcription of their target genes and, therefore, astrocyte/neuron cholesterol turnover. In the periphery, cells convert the excess of cholesterol into 27-hydroxycholesterol (27-OHC) which is also able to cross the BBB and interact with the LXR, thus also participating in brain cholesterol homeostasis.

genes controlling cellular cholesterol pools such as ABCA1, ABCG1 and ApoE [10]. As such, brain cells are able to adapt their own cholesterol turnover based on their requirements and on the peripheral context. For this reason, the brain is consequently considered as quasi-autonomous in terms of cholesterol metabolism.

3. Is the brain isolated from cholesterol peripheral circulation?

Initial animal or human studies in which radioactive lipoproteins/sterols were injected into the blood circulation have observed some slight blood-to-CNS fluxes of cholesterol [11–14] leading to the notion that peripheral cholesterol does not interfere with the cerebral pool. However, more recent evidence shows that peripheral cholesterol may influence the brain cholesterol pool and, therefore, neuronal functions. For example, it was suggested that low levels of circulating cholesterol in adults might be responsible for violent, depressive or even suicidal behaviours [15–17]. Furthermore, clinical and experimental studies have suggested that high levels of circulating cholesterol are closely linked to the onset and evolution of AD [18–23]. Finally, depletion of ABCA1 [24] in the CNS or depletion of cholesterol content in glial cells [25–27] leads to an increase of peripheral cholesterol uptake by the BBB, thus reinforcing the notion that this barrier participates in regulating the complex brain cholesterol homeostasis [28].

4. The blood–brain barrier

The BBB is located at brain capillary network level and is composed of brain capillary endothelial cells (BCECs) surrounded by the brain pericytes embedded in the same basal membrane [29–31] (Fig. 2). In addition, brain capillaries are wrapped by certain astrocytic end-foot processes which connect neurons to the blood circulation [32]. This organization permits a continuous supply of nutrients directly to the brain, depending on neuronal activity. For this reason, it is estimated that almost every human brain neuron has its own capillary. In contrast to peripheral capillary endothelial cells, which allow bidirectional molecule exchange between blood and tissue, BCECs are not fenestrated and are tightly sealed together through junctional complexes such as tight junctions.

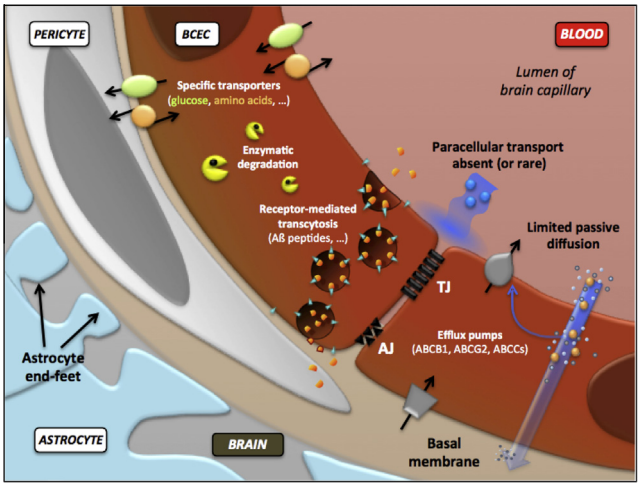

Fig. 2. The blood–brain barrier. The blood–brain barrier is located at brain capillary level and is composed of brain pericytes which are embedded in the same basal membrane as brain capillary endothelial cells (BCECs). In addition, brain capillaries are surrounded by astrocytic end-feet processes. The BCECs are sealed together by tight (TJ) and adherens junctions (AJ) impeding the paracellular passage of molecules between two cells. However, small lipid-soluble molecules can diffuse through BCECs, although some efflux pumps of the ABC family (i.e. ABCB1, ABCG2, ABCC1, etc.) expressed at the blood and/or brain sides of these cells mediate/restrict their entry into the brain. Polar nutrients such as amino acids or glucose are transported into or out of the brain by taking specific solute carriers (transporters). Large macromolecules are delivered intact to the CNS by taking a transcytosis route. Interaction of these macromolecules with their specific receptors leads to triggering an endocytotic process. In addition to these several properties, the BBB cells express several enzymes able to degrade specific substrates such as neurotransmitters, etc.

Thus, to allow bidirectional molecule exchange, these cells express several receptors and transporters in their luminal (blood side) and abluminal (brain side) membranes (Fig. 2). Among them, BCECs and pericytes express ABCA1, ABCG1 and ApoE as well as LXRs [33–37]. Knowing that the brain is cut off from peripheral circulation by the BBB and that 6–7 mg of 24S-OHC [8] and 5 mg of 27-chol [9] cross this barrier every day, it became obvious that the effects of these oxysterols on the BBB cells should be investigated see (Fig. 3).

Please cite this article in press as: F. Gosselet et al., Effects of oxysterols on the blood–brain barrier: Implications for Alzheimer's disease, Biochem. Biophys. Res. Commun. (2013), http://dx.doi.org/10.1016/j.bbrc.2013.11.059