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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

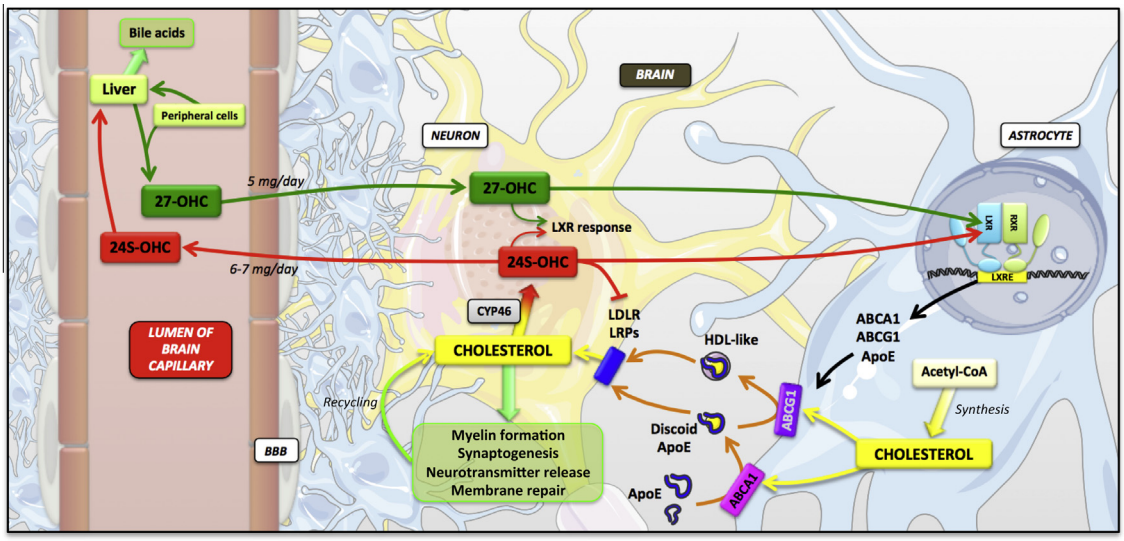

Fig. 1. Brain cholesterol homeostasis. In the adult brain, cholesterol is synthesized by astrocytes and then shuttled to neurons via an ABC-transporter mediated process. In neurons, excess of this sterol is then converted into 24S-hydroxycholesterol (24S-OHC) which may cross the blood–brain barrier (BBB) 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.

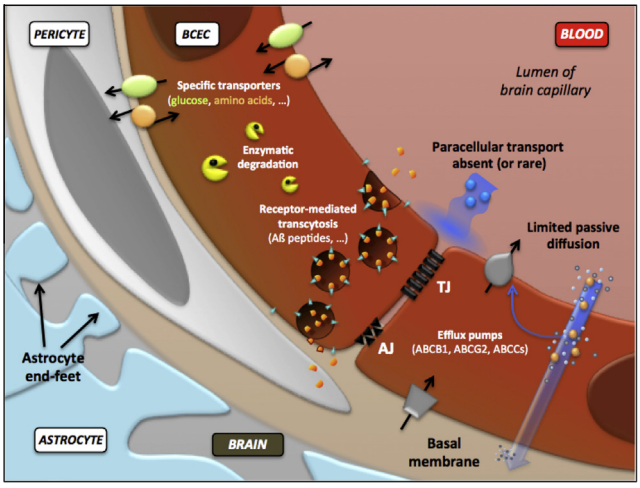

Fig. 2. The blood–brain barrier. The blood–brain barrier is located at brain capillary level and is composed of brain pericytes which are embedded in the same basal membrane as brain capillary endothelial cells (BCECs). In addition, brain capillaries are surrounded by astrocytic end-feet processes. The 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).

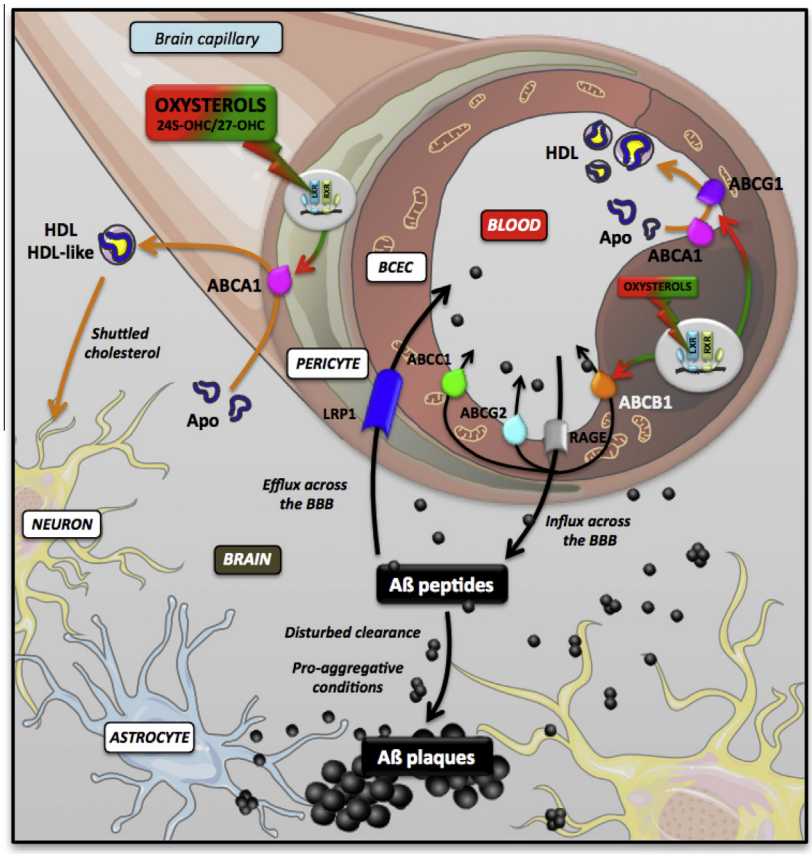

Fig. 3. Potential effects of oxysterols on BBB cells. When oxysterols cross BBB cells, they interact with LXR nuclear receptors which promote the upregulation of ABCB1, ABCA1 and ABCG1. While the upregulation of ABCA1 and ABCG1 promote cholesterol release from cells, the upregulation of ABCB1 observed at the BCEC level, provokes a decrease of Aβ peptide entry into the CNS. Noteworthy, expressions of other receptors and transporters involved in Aβ peptide transport across the BBB are reported as to be not affected by oxysterols.

Using *in vitro* BBB models, we and others have demonstrated an upregulation of the expression of ABCA1 and ABCG1 in BCECs and brain pericytes after treatment with these two oxysterols [34,38–41]. In contrast to neurons and astrocytes [3], no ApoE expression modulation has been reported. While the ABCA1 transporter seems to be preferentially localized at the basolateral (brain side) face, LXR pathway stimulation by oxysterols seems to promote a large luminal expression of this transporter [40]. Consequently, cellular cholesterol release to apolipoproteins (ApoE and ApoA-I) and lipoproteins (HDL) is induced by an ABCA1-mediated process [37,39] to the brain side and also to the peripheral compartment (Fig. 3) [38,40]. This data demonstrates that the BBB, which totals an exchange area of almost 10–18 m^2, can contribute slightly, if not significantly, to HDL particle genesis in the brain.

In return, although the chemical structures of oxysterols permit unhindered diffusion of the latter across biological membranes [42], it is not excluded that an active transport system exists at the BBB level, regulating oxysterol exchange across this barrier. For example, it was recently suggested that the organic anion transporter, transporting polypeptide 2 (oatp2), may mediate the brain's elimination of 24S-OHC [43].

5. BBB, oxysterols and AD

As cited previously, brain cholesterol metabolism dysfunction is intimately linked to neurodegenerative diseases such as AD. Thus, oxysterols, and in particular the 24S-OHC, have been suggested by several researchers as cholesterol turnover markers for this disease [44,45]. AD is characterized by a massive neurodegenerative process resulting mainly from the abnormal accumulation of different forms of the β-amyloid (Aβ) peptides in various areas of the brain and around cerebral microvessels. Interestingly, the BBB is largely involved in regulating the cerebral pool of these peptides. For example, BBB cells are able to synthesize and degrade them [41,46] and some receptors and transporters expressed by BCECs and by pericytes play a role in the elimination of these peptides from the brain to the peripheral circulation or in restricting their entry [31,47]. The most characterized of these transporters, which restrict the entry of Aβ peptides and other xenobiotics to the brain, is an ABC transporter named ABCB1 or P-glycoprotein [47–50], expressed at the luminal side of BCECs. We and others have proven that the 24S-OHC and the 27-OHC increase its expression, which leads to a decrease of these peptides entering the brain compartment (Fig. 3) [38,39,51]. ABCB1 is considered as a promising therapeutical target in AD as a decrease of this transporter expression/activity is reported in microvessels of AD patients [52,53] and its upregulation in mice models decreases the amyloid burden [54,55]. ABCB1 has never been described as an LXR target gene, but it is well-known that other nuclear receptors control its transcription [56]. Therefore, in accordance with previous *in vivo* observations [57], these results suggest that the molecular mechanisms of these oxysterol-mediated effects are probably mediated only partially by LXR and, as such, require further investigation. No effects of these oxysterols were observed in relation to other known receptors and transporters identified as being involved in Aβ peptide transport across the BBB [38]. Interestingly, ABCA1, the major gene regulated by oxysterols, is not directly involved in the Aβ peptide uptake and transport across the BBB (Fig. 3)

[38,39,58]. It is, however, likely that the effect of oxysterols on BBB cholesterol homeostasis modifies the lipoprotein content of the brain and consequently, indirectly Aβ peptide clearance [59,60].

It was also recently demonstrated that oxysterols decrease Aβ peptide biosynthesis by BCECs, by modulating the expression level of enzymes involved in this process [41] and probably, by changing the membrane cholesterol content of these cells [61]. Overall, these data suggest that oxysterol impact on the BBB cells remains underestimated and should be investigated to generate some promising therapeutical perspectives for AD.

6. Conclusion and perspectives

It is now evident that the brain maintains its own cholesterol content but several lines of evidence currently suggest that the BBB could also contribute to this process, in particular through oxysterols. Surprisingly, these latter could also regulate other processes at the BBB level such as Aβ peptide transport. It is likely that other physiological aspects of the BBB may be impacted by oxysterols but this obviously requires further investigation.

These observations open perspectives dealing with the possibility that the BBB may represent a therapeutic target for drugs designed to modulate brain cholesterol homeostasis and/or neurodegenerative diseases.

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