It is now well accepted that the deposition and aggregation of amyloid β (Aβ) peptides are hallmarks of Alzheimer’s disease (AD) [1]. These peptides are constitutively secreted by neurons but (for reasons that remain to be established) Aβ metabolism is altered in AD patients and leads slowly to the neurodegenerative process. With these considerations in mind, the identification of genetic, biochemical, environmental and dietary factors influencing Aβ peptide synthesis, clearance and degradation became a high priority for researchers working on AD. The enzyme responsible for Aβ peptide synthesis was soon identified as a β-secretase called β-site amyloid precursor protein cleaving enzyme 1 (BACE1) [2]. The most important genetic risk factor for late-onset AD was identified as the APOe4 allele [3]. This gene encodes an apolipoprotein, a protein component of the low-density lipoprotein (LDL) particles involved in lipid transport throughout the body; this finding highlighted a probable relationship between AD and cholesterol metabolism. More recently, two other susceptibility loci linked to cholesterol metabolism have been identified in AD: CLU (coding for clusterin, another apolipoprotein) [4] and ABCA7 [5] (coding for the ATP-binding cassette sub-family A member 7 transporter involved in cholesterol homeostasis [6]). This link between AD and cholesterol metabolism was reinforced by the observation that the sterol can modulate BACE1 activity and promote Aβ peptide biosynthesis [7]. Cholesterol was also identified as dietary risk factor in humans; since elevated serum cholesterol is a risk factor for developing AD and amount of Aβ peptide in the brain correlates with serum levels of LDL and total cholesterol [8,9]. Moreover, rabbits and mice on a cholesterol-enriched diet show elevated serum cholesterol levels, increased Aβ peptide deposition and cognitive impairment [10-14]. However, the reasons why serum cholesterol influences AD are difficult to determine, for two main reasons. Firstly, most of the accretion of cholesterol in the central nervous system (CNS) is due to de novo synthesis (reviewed in [15]). Secondly, the brain is isolated from the rest of body by the blood-brain barrier (BBB), a dynamic interface formed by brain capillary endothelial cells (BCECs) and sealed by complex tight junctions that restrict the paracellular pathway [16]. One of the BBB’s main roles is to supply the brain with essential nutrients and mediate the efflux of many waste products. To this end, BCECs express specific receptors or transporters in their luminal (plasma-side) and/or abluminal (brain-side) membranes that force molecules to take the transcellular route.

At present, it is not fully accepted that peripheral cholesterol can cross the BBB and thus influence brain cholesterol homeostasis. Given the lack of in vitro BBB models, initial animal studies have consisted in injecting radioactive sterols and thus estimating the ability of lipoproteins to reach the CNS. No significant blood-to-brain fluxes of radiolabelled LDL-, high-density lipoprotein (HDL)- or free cholesterol were detected in guinea pigs, rabbits, sheep and mice [17,18]. In baboons fed with radioactive sterol and in humans injected with labeled cholesterol, there was a very slight signal in the brain, which was considered to be negligible because it corresponded to a very low fraction of serum cholesterol [19,20]. With the development of new techniques, some recent studies have found that an increase in serum cholesterol levels alters Aβ peptide metabolism – even when there an increase in brain cholesterol content was absent [11,21,22] or slight [12,23,24]. These discrepancies have contributed to the notion that the BBB prevents peripheral cholesterol entry into the brain. However, clinical observations strongly suggest that this exchange between brain and plasma compartments does occur. For example, the cholesterol derivative cholestanol is abnormally produced by the liver in patients with cerebrotendinous xanthomatosis caused by a genetic deregulation in bile acid synthesis [25]. The cholestanol crosses the BBB and accumulates in the brain. Moreover, with the development of capillary extraction methods and in vitro BBB models over the last two decades, other researchers have focused on the BCECs’ ability to transfer cholesterol from the blood to the brain. We and others have demonstrated that BCECs express important receptors and transporters involved in lipoprotein uptake and transcytosis; such as the ATP-binding cassette sub-family A and G members 1 (ABCA1 and ABCG1), ABCA7, scavenger receptor class B member 1 (SCARB1) and the low-density lipoprotein receptor (LDLR) [26-32]. These receptors and transporters promote the movement of LDL and cholesterol across BCECs (our unpublished data and [26,29,31,33]) and the BBB [34]. Moreover, this transport appears to be regulated by glial cells, which can modulate expression of LDLR, ABCA1 and ABCG1 [28,30]. These findings suggest that glial cells communicate with BCECs to compensate for deficiencies or changes in brain cholesterol metabolism. Although ApoE is the major apolipoprotein in the CNS, some studies have revealed the presence of other apolipoproteins (such as ApoA-I). Given that cells from the CNS are unable to synthesize this apolipoprotein, it was suggested that ApoA-I may be imported from the blood into the brain across the BBB by an HDL-mediated process [33,35]. Lastly, one of the strategies developed to deliver molecules to the CNS as a whole involves fusion with apolipoproteins. This approach has proven to be very effective and confirms that a receptor-mediated process lipoprotein deliver occurs at the BCECs’ apical face [36-38]. In conclusion, it is now clear that a very small fraction of serum lipoproteins may enter the brain across the BBB. On the timescale of hours or days, this fraction may be negligible. However, over several decades, this small fraction may influence the brain’s cholesterol.

The Mysterious Link between Cholesterol and Alzheimer’s Disease: Is the Blood-Brain Barrier a Suspect?

Fabien Gosselet1, 2, 3

1Lille Nord de France University, F-59000 Lille, France
2LBHE, University of Artois, F-62300 Lens, France
3IMPRT-IFR114, F-59000 Lille, France

Copyright: © 2011 Gosselet F. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
metabolism and thus the development of neurological diseases like AD. The molecular mechanisms involved in this process remain poorly characterized and need further investigation. Furthermore, in addition to lipoproteins, cholesterol may efficiently cross the BBB after undergoing specific hydroxylation at the 27 and 24 positions by 27-hydroxylase enzyme and 24-hydroxylase (the latter being located exclusively in CNS), respectively [39,40]. These metabolites are called “oxysterols” and are natural ligands for the liver X nuclear receptors that regulate the expression of specific genes controlling cholesterol homeostasis, such as ABCA1 or ABCG1. Oxysterols also seem capable of modulating Aβ peptide synthesis [39,40] but their effects at the BBB level are poorly characterized - demonstrating once again that the barrier’s role in brain cholesterol homeostasis (and thus in AD) has probably been underestimated.

References

nanoparticles targeted with Apo E enter the CNS by transcytosis and are delivered to neurones. J Control Release 137: 78-86.

