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The LXR/RXR Approaches in Alzheimer's Disease: Is the Blood-Brain Barrier the Forgotten Partner?

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Alzheimer's disease (AD) is a neurodegenerative pathology mainly associated with amyloid-β (Aβ) peptide aggregation and deposition in brain parenchyma and perivascular spaces [1]. This hallmark results from altered natural processes of clearance of these peptides from brain [2]. Finding a treatment for AD has become the main challenge of the 21st century for the scientific community due to the progressive increase of people affected and the rising costs of care [3]. Since the last decade, a new promising therapeutical strategy based on the stimulation of liver X receptors (LXRs) by agonists has arisen to slow down the evolution of AD. LXRs are ligand-activated transcription factors which are involved in cellular cholesterol metabolism by regulating the expression of target genes [4]. These nuclear receptors have been linked with the onset and progression of AD since APP/PS1 mice deficient for LXRs showed a greater number of Aβ plaques in brain parenchyma and an accelerated cognitive decline [5]. The close relationship between LXRs and AD is associated with the transporter ATP Binding Cassette sub-family A member 1 (ABCA1) [6] which regulate the cerebral cholesterol release to apolipoprotein E (ApoE) [7]. Indeed, ABCA1 depletion in AD-related mice models led to an increased deposition of Aβ peptides in brain [8-11] whereas its overexpression reduced the cerebral Aβ burden [12]. Moreover, the stimulation of LXRs with synthetic agonists such as T0901317 or GW3965 in AD-related mice models demonstrated a significant decrease of cerebral Aβ burden [13-18] associated with the increased expression of ABCA1 and ApoE which contribute to the degradation of Aβ peptides by microglial cells. Indeed, the ABCA1-mediated lipidation of ApoE promotes the formation of Aβ -ApoE complexes which are degraded by the microglial cells through a phagocytic process [7]. In addition to this effect on cerebral Aβ burden, 24S-hydroxycholesterol (24S-OHC) and 27-hydroxycholesterol (27-OHC), two oxysterols known to be natural endogenous agonists of LXRs, have been described to decrease the activity of β-site amyloid precursor protein cleaving enzyme 1 (BACE1), the key secretase involved in Aβ peptide production [19-21]. Thus, stimulating the LXR pathway appears to be an attractive therapeutic approach in AD.

As a type II nuclear receptor, LXR forms an obligate heterodimer with a retinoid X receptor (RXR) to be functional. Moreover, LXR is a permissive RXR partner, i.e. the stimulation of RXR induces the activation of LXR pathway with or without LXR agonists, and therefore promotes the expression of LXR target genes [22,23]. Since the LXR pathway is an attractive therapeutic target in AD, it was postulated that stimulating RXRs could also have an effect on Aβ peptide deposition and clearance through the activation of LXR target genes [24]. In February 2012, Landreth's team published that bexarotene, a RXR agonist initially used in cutaneous T-cell lymphoma treatment, not only decreased the cerebral Aβ burden by stimulating Aβ plaques phagocytosis by microglial cells following an ABCA1/ApoE-mediated process, but also improved the cognitive function of AD-related mice models after unique or chronic treatments [25]. However, some comments and studies published one year later reported divergent results in different AD-related mice models [26-30] and beagle dogs [29] even if the same dose of bexarotene were used. Indeed, excepting a slight decrease of brain soluble or insoluble Aβ peptide levels [26,30], these studies showed that bexarotene modified neither the size nor the number of Aβ plaques [26,28-30]. Moreover, the initial benefit effect of bexarotene on cognitive functions was either not reproduced [26,27], or questionable [29] in view of the induced adverse effects such as cutaneous irritation, weight loss, dyslipidemia, hypersensitivity, hypothyroidism or leukopenia [29,31]. These divergent observations are currently explained by the different preparations for bexarotene which could alter its affinity for the RXRs, the different periods of treatment and the different animal models used [32]. However, none of these studies have taken into account the blood-brain barrier (BBB) despite its key roles in AD [33,34] and its alteration observed in some AD-related mice models [35,36] which could explain the previous discrepancies.

The BBB, located within the brain capillaries and formed by the brain capillary endothelial cells (BCECs) surrounded by brain pericytes and astrocytes which are necessary to induce and maintain the BBB phenotype [37,38], is involved in Aβ peptide exchanges, synthesis and degradation mechanisms [33]. Indeed, BCECs express the amyloid precursor protein (APP) [39,40] and the secretases involved in its amyloidogenic cleavage such as BACE1 [40]. BCECs are therefore able to secrete soluble fragments of APP and Aß peptides mainly in their abluminal side (i.e. cerebral side) which could exacerbate the perivascular amyloid deposition [33,40,41]. BCECs express also the enzymes responsible for Aβ peptide degradation such as insulin degrading enzyme (IDE) or neprilysin (NEP) [33,42]. Moreover, the BBB regulates the cerebral pool of Aβ peptides by bidirectional exchanges between blood and brain through influx (from blood to brain) and efflux (from brain to blood) transport processes [34]. Aβ peptide influx across the BBB is driven by the receptor for advanced glycation end-products (RAGE) and restricted by the transporters ABCB1 and ABCG2. These receptor/transporters are expressed at the luminal side (i.e. blood side) of BCECs [43-46]. Aβ peptide efflux across the BBB is commonly associated with the low density lipoprotein receptor-related protein 1 (LRP1) and other members of the low density lipoprotein receptor (LDLR) family [34,47,48]. Some ABC

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transporters have been described to take part in this efflux process such as ABCC1 (also named multidrug resistance associated protein 1 or MRP1) [49] and ABCG4 [50]. Very few studies focused on the effects of LXR or RXR stimulation in terms of amyloid metabolism at the BBB level, the latter therefore appears as the forgotten partner in LXR/RXR approaches in AD. This lack of data is surprising knowing that oxysterols such as 24S-OHC and 27-OHC cross daily this barrier [19] and promote cholesterol efflux from BBB cells [51-54]. A study led by Panzenboeck's team demonstrated in vitro that both 24S-OHC and 27-OHC induced the non-amyloidogenic cleavage of APP in BCECs and reduced Aβ secretion and oligomerisation in abluminal (i.e. cerebral) compartment [40]. Furthermore, we demonstrated in vitro in BCECs and in brain pericytes that ABCA1 expression is increased after LXR stimulation with 24S-OHC and 27-OHC but is not directly involved in accumulation or transport of soluble Aβ peptides [53,54]. The latter point highlights that ABCA1 is not able to transport Aβ peptides as previously described [55], however this transport is modified after LXR stimulation. Indeed, 24S-OHC and 27-OHC decreased Aβ peptide influx across BCECs that is associated with the increased expression and functionality of ABCB1 [53]. Even if ABCB1 is not a LXR target gene, a previous study in C57BL/6 mice has also shown that T0901317 and GW3965 induced its expression [56]. Knowing that ABCB1 expression and functionality are drastically decreased in brain microvessels of AD patients [57-60], these data suggest that LXR stimulation at the BBB level could restore/optimize ABCB1 expression and function by restricting the entry of Aβ peptides into the brain following an ABCB1-mediated process, and could therefore limit their deposition in perivascular spaces. In addition to our previous results on the LXR-based approach, the first studies focused on the RXR stimulation at the BBB level demonstrated promising effects in terms of Aβ peptide exchanges. In fact, bexarotene enhanced Aβ peptide clearance from brain to blood across the BBB following an ApoE and probably a LRP1-mediated process in a human in vitro BBB model [61,62]. Thus, the LXR/RXR stimulation studies at the BBB level reinforce the therapeutical interest of both nuclear receptors in AD by restricting Aβ peptide entry in brain and by optimizing the Aβ peptide clearance from brain.

Altogether, these observations underline the complementarity and the need of both brain- and BBB-focused studies in the LXR/RXR therapeutic approaches, and highlight once again how underestimated the BBB is in this disease.

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