Review

Is Alzheimer's Disease a Liver Disease of the Brain?

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Abstract. Clinical specialization is not only a force for progress, but it has also led to the fragmentation of medical knowledge. The focus of research in the field of Alzheimer's disease (AD) is neurobiology, while hepatologists focus on liver diseases and lipid specialists on atherosclerosis. This article on AD focuses on the role of the liver and lipid homeostasis in the development of AD. Amyloid-β (Aβ) deposits accumulate as plaques in the brain of an AD patient long before cognitive decline is evident. Aβ generation is a normal physiological process; the steady-state level of Aβ in the brain is determined by balance between Aβ production and its clearance. We present evidence suggesting that the liver is the origin of brain Aβ deposits and that it is involved in peripheral clearance of circulating Aβ in the blood. Hence the liver could be targeted to decrease Aβ production or increase peripheral clearance.

Keywords: Alzheimer's disease, apolipoprotein E, circadian, hepatitis C virus, liver, metabolic syndrome, small interfering RNAs

INTRODUCTION

In an ever more algorithmically-driven world, medical super-specialization often leads to blinkered thought and academic compartmentalization of medical care. Those with multisystem disorders are often looked after by a clutch of different specialists, while the rush to medical specialization leaves little time for those giving care to think laterally. Few neurologists or neuropsychiatrists dual accredit in General Internal Medicine and time precludes them following advances in other specialties. Among hepatologists, little thought is given to the extrahepatic sequelae of liver disease, while still fewer in the discipline recognize that many diseases which traditionally are thought to be specific to other organs may actually have a major hepatic component. Alzheimer's disease (AD), the most common form of dementia, is a case in point. In the second most common neurodegenerative disorder, Parkinson's disease, new research is suggesting a role for the microbiota-gut-brain axis in alpha-synuclein pathology in the brain (reviewed in [1]).

This review of AD, written from the perspective of hepatology and lipidology, presents evidence suggesting that the liver is the origin of brain amyloid-β

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(Aβ) deposits and that it is involved in peripheral clearance of circulating Aβ in the blood. Furthermore, useful new drugs for dementia may be focused on decreased hepatic production or increased peripheral clearance of Aβ protein.

AD affects more than 40 million people globally and is expected to hit 75.6 million by 2030. AD is the sixth leading cause of mortality in the United States, accounting for 3.6% of all deaths in 2014 [2]. In the United Kingdom, almost one in eight people (12.8%) died from AD in 2018; it is the biggest killer in women at 15.3% and the second biggest killer in men at 8%. The most common form of AD, which occurs sporadically late in life (late-onset AD, LOAD) is typified by deposition of Aβ within the brain [3, 4]. Aβ generation is a normal physiological process; the steady-state level of Aβ in the brain is determined by the balance between Aβ production and its clearance and an imbalance in the Aβ production/excretion rate is the basis of increased Aβ levels in AD.

AMYLOID-β HOMEOSTASIS

Altered production or clearance of a protein might be a trait (that is, lifelong) marker that precedes build-up of the protein in inclusions or aggregates.

Production

Three loci that modify Aβ accumulation and deposition in the brains of a mouse model of AD have been previously described: amyloid-β protein precursor (AβPP), presenilin 1 (PSEN1), and presenilin 2 (PSEN2). Mutations in these loci result in abnormal processing of AβPP and increased generation of $A\beta_{42}$, which aggregates as insoluble β-pleated sheets [5]. One of these, the *PSEN2* gene encoding presenilin 2, a component of the γ-secretase activity is responsible for generating Aβ by proteolysis. Activity of mouse PSEN2, as measured by levels of mRNA accumulation, has unexpectedly been shown to be heritable in the liver, but not the brain, suggesting that the liver is the origin of brain Aβ deposits [6]. Sutcliffe and colleagues showed that peripheral administration of the anticancer drug, Imatinib, commonly known as Gleevac (a specific inhibitor of a number of tyrosine kinase enzymes), resulted in a 50% reduction in plasma and brain Aβ levels. As Imatinib does not cross the blood-brain barrier (BBB), this provided evidence that Aβ produced peripherally was contributing to brain Aβ. Imatinib lowers Aβ levels through indirect inhibition of γ-secretase activity [7]. Imatinib also renders AβPP less susceptible to proteolysis by β-secretase (BACE) without inhibiting BACE enzymatic activity or the processing of other BACE substrates [8]. However, plasma levels of $A\beta_{42}$ did not change in patients with chronic myeloid leukemia treated with Imatinib [9], bringing into question whether it may have a role in individuals with Aβ dyshomeostasis.

The important study by Sutcliffe et al. [6] built on earlier findings that peripherally derived $A\beta_{40}$ and $A\beta_{42}$ can cross the BBB and that circulating Aβ could thus contribute to neurotoxicity [10, 11]. The implication that Aβ homeostasis was an interconnected system involving the liver and BBB to regulate brain Aβ was discussed at the time [12] but needs re-emphasizing now, with the addition of new data from the last decade.

The *AβPP* gene is located at chromosome 21q21 and individuals with Down's syndrome, which results from trisomy of chromosome 21, develop AD neuropathology (reviewed in [13]). Individuals with partial trisomy of chromosome 21, which does not include the *AβPP* gene, fail to develop AD neuropathology, demonstrating that excess Aβ production is sufficient to cause AD (Fig. 1). In addition, recent tissue-specific metabolomic analysis revealed that the liver was the earliest affected organ in AβPP/PS1 mice during amyloid pathology progression [14]. Genetic variants affecting AβPP and Aβ processing are associated not only with early-onset autosomal dominant AD but also with LOAD [15].

Generation of the AβPP by β- and γ-secretases occurs in early endosomes, followed by routing of Aβ to multivesicular bodies in HeLa and N2a cells and subsequently, a minute fraction of Aβ peptides can be secreted from the cells in association with exosomes [16]. Exosomes are extracellular membrane vesicles actively secreted by cells into the circulation that are involved in cell-to-cell communication in normal homeostasis. They can carry cargo across the BBB [17] and are carriers of Aβ in AD [18]. The BBB keeps neurotoxic plasma derived components out of the central nervous system, but recent studies suggest an early BBB breakdown in AD [19]. The receptor for advanced glycation end products (RAGE) has been implicated in the transport of Aβ across the BBB [11, 20]. Inhibiting RAGE has been shown to have significant therapeutic benefit in AD models [21]. High dietary advanced glycation end products have also been found to accelerate Aβ deposition in an AD murine model mediated by overexpression of RAGE [22].

Amyloid Aβ dyshomeostasis

Factors favoring increased Aβ production:

- Mutations in presenilin 1
- Mutations in presenilin 2
- Mutations within and flanking the Aβ region of AβPP
- Individuals with Trisomy 21 (Down's syndrome) who harbor 3 copies of AβPP

CLEARANCE

PRODUCTION
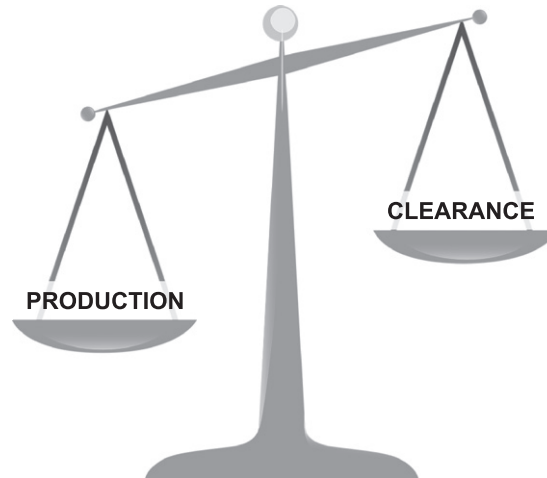
Factors favoring decreased Aβ clearance:

- Loss-of-function variants in ABCA7
- ApoE4 inhibits Aβ clearance via LRP1 and LDLR
- P-gp dysfunction/inhibition
- Poor sleep/disturbance of circadian rhythm including peripheral liver clock

Fig. 1. Some factors altering the balance between amyloid Aβ production and clearance leading to dyshomeostasis. Peripheral clearance can remove 40–50% of Aβ burden in the brain [25, 26]. Aβ, amyloid-β; AβPP, amyloid-β protein precursor, LRP1, low-density lipoprotein receptor-related peptide 1; LDLR, low-density-lipoprotein receptor; P-gp, P-glycoprotein.

Clearance

LOAD, the common form of AD, is characterized by an overall impairment in Aβ clearance [23]. Aβ clearance is a complex event that involves more than neurons and microglia [24]. Peripheral clearance of brain-derived Aβ exists physiologically. Efflux of Aβ to peripheral blood accounts for 50% of total brain Aβ clearance in humans [25], suggesting that the physiological Aβ clearance capacity of the peripheral system provides an important mechanism against Aβ accumulation in the brain. Hence, dysfunction of peripheral Aβ clearance may contribute to the development of AD.

In a murine model of AD using parabiosis (the anatomical joining of two animals for physiological research), it has been shown that parabiosis reduces brain Aβ burden through clearance by peripheral tissues and organs, including the liver [26]. In this model, it was calculated that the periphery can remove 40% of Aβ burden in the brain, similar to other estimates of the importance of peripheral physiological Aβ clearance [25]. Studies in another model system found a short half-life of both $A\beta_{40}$ and $A\beta_{42}$ after injection of only 2.5–3.0 min with the liver being the major organ responsible for plasma clearance, accounting for > 60% of the peptide uptake. Indeed, it was suggested that the capability of the liver to take-up, catabolize, and excrete large doses of Aβ, several orders of magnitude above its physiologic concen-

tration may explain not only the femtomolar plasma levels of Aβ, but also the minor fluctuation observed with age and disease stages [27].

There are several potential pathways for the efflux of brain Aβ into the periphery. These include clearance via the glial-lymphatic (glymphatic) system [28] and transport across the BBB, mediated by low-density lipoprotein receptor-related peptide 1 (LRP1) [29, 30] and the low-density-lipoprotein receptor (LDLR). In animal models of AD, lack of LDLR enhances amyloid deposition in the brain [31], while LDLR overexpression increases the rate that Aβ enters the blood from the brain [32].

In plasma, a soluble form of LRP1 (sLRP1) is the major transport protein for peripheral Aβ [33]. Improving the binding of Aβ to a sLRP1 variant has been shown to increase the efficiency of Aβ clearance [34], suggesting that this binding prevents re-entry of Aβ to the brain. Impaired sLRP1 binding of plasma Aβ has also been reported to be an early biomarker for mild cognitive impairment preceding AD [35]. Brain-derived Aβ in the arterial blood is cleared physiologically when it goes through the capillary bed of the peripheral organs and tissues, including the liver [26]. LRP1 is the major receptor responsible for the saturable uptake of plasma free $A\beta_{40}$ by the liver [36]. The remarkable therapeutic effect of the ayurvedic agent, *Withania somnifera* (also known as poison gooseberry or winter cherry, from the nightshade family), mediated through upregula-

tion of liver LRP indicates that targeting the periphery offers a unique mechanism for Aβ clearance as this therapy reverses the behavioral deficits and pathology seen in AD models [37]. Atorvastatin has also been shown to upregulate liver LRP1 and this effect is mediated by the sterol response element-binding protein-2 (SREBP-2) *in vitro* and *in vivo* [38]. Statins can reduce AD risk and the effect varies with statin molecule, sex, and race/ethnicity [39].

Transthyretin, a protein involved in the transport of thyroid hormones and retinol, has been proposed as a protective protein in AD [40]. Transthyretin acts as a carrier of Aβ at the BBB and liver using LRP1 [41].

Thus, LRP1 is involved in three stages of the homeostatic control of Aβ clearance including 1) cell-surface LRP1 at the BBB and cerebrovascular cells, mediating brain-to-blood Aβ clearance, 2) circulating LRP1 providing a key endogenous peripheral 'sink' activity for plasma Aβ which prevents free Aβ access to the brain [42], and 3) LRP1 in the liver mediating systemic Aβ clearance [43] (Fig. 2).

In a human study using amyloid PET with [^{11}C]PiB, the C667T polymorphism of the LRP1 gene has been shown to be moderately, but significantly associated with global and regional amyloid deposition [44]. This finding is compatible with the Aβ hypothesis that impaired amyloid clearance contributes to amyloid deposition in LOAD.

LRP1 is capable of recognizing a wide variety of structurally-distinct ligands; Apolipoprotein E (ApoE) is one. ApoE polymorphic alleles are major genetic determinants of AD. Individuals carrying the epsilon (ε) 4 allele (*APOE ε*4) are at increased risk of AD, compared to those carrying the more common ε3 allele, whereas the ε2 allele decreases risk. Thus, at age 85 years, the lifetime risk of AD without reference to *APOE* genotype is 11% in males and 14% in females, compared to 51% for male *APOE4* homozygotes and 60% for female *APOE4* homozygotes, consistent with autosomal co-dominant inheritance of a moderately penetrant gene variant [45]. In a murine model, Aβ was mainly sequestered in the liver and its peripheral clearance was by influenced by ApoE [46]. A number of subsequent studies suggest that ApoE4 inhibits Aβ clearance and/or is less efficient in mediating Aβ peripheral clearance compared with ApoE3 and ApoE2 [47] (reviewed in [48, 49]). A biologically inspired nanostructure, ApoE3-reconstituted high-density lipoprotein, with high binding affinity to Aβ, rescues memory loss of mice with AD by accelerating the clearance of Aβ [50].

ApoE expression is transcriptionally induced through the action of the nuclear receptors peroxisome proliferator-activated receptor gamma (PPARγ) and liver X receptor (LXR) in coordination with retinoid X receptors (RXRs).

In the liver, LRP1 functions in concert with LDLR in the clearance of ApoE-containing particles circulating in plasma [51]. Biliary clearance of Aβ is not only mediated by LRP1, but also by the drug efflux pump, P-glycoprotein encoded by *ABCB1* gene [52]. P-glycoprotein dysfunction in BBB active efflux of xenobiotics has been shown by imaging studies in individuals with early AD [53]. This raises the possibility that common pharmacological inhibitors of P-glycoprotein, such as amiodarone, lansoprazole, omeprazole, and other proton-pump inhibitors, tamoxifen and verapamil [54], could impact on Aβ clearance. A recent *in vitro* study using synthetic fluorescein-labelled Aβ$_{40}$ and Aβ$_{42}$ spiked into human liver homogenates has shown that Aβ degradation rates are lower in AD-derived homogenates as compared with those from non-demented control subjects, even after accounting for the covariates of age, sex, and *APOE* genotype. The authors conclude that their results "support the possibility that impaired hepatic Aβ degradation could be a factor contributing to increased brain Aβ accumulation and AD" [55]. In addition, serum-based bile acid metabolites are associated with AD biomarkers, providing further evidence that bile acid pathways play a role in AD pathophysiology [56].

Plasma assays as screening tests for AD

Plasma Aβ levels tend to be nearer the lower limits of detection, but there is emerging consensus that "recent improvements in technologies to assess plasma levels of amyloid beta indicate that a single sample of blood could provide an accurate estimate of brain amyloid positivity" [57]. For example, measurement of plasma Aβ biomarkers by immunoprecipitation coupled with mass spectrometry has recently been shown to correlate with brain Aβ burden and levels of Aβ$_{42}$ in cerebrospinal fluid (CSF) [58]. The biomarkers measured were ratios of AβPP$_{669-711}$/Aβ$_{42}$ and Aβ$_{40}$/Aβ$_{42}$ and their composites, confirming that plasma Aβ might reflect brain amyloid deposition. Another group has shown that the secondary structure distribution of Aβ in blood plasma, measured by an immuno-infrared sensor, is an excellent biomarker for AD, reflecting the Aβ burden in the brain [59]. The performance
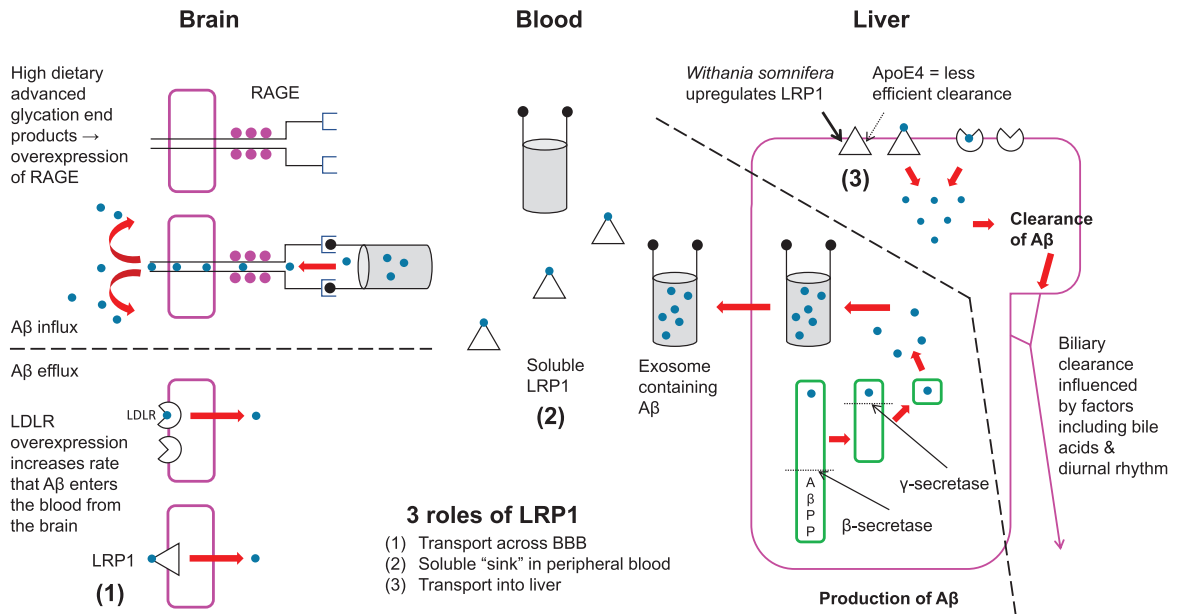
Fig. 2. Schematic representation of Alzheimer's disease homeostasis showing amyloid-β (Aβ) production from amyloid-β protein precursor (AβPP) in the liver, dysregulated influx/efflux across blood-brain barrier (BBB) (1), transport in serum via soluble LRP1 (2) and exosomes [61] and saturable uptake of Aβ by liver via low-density lipoprotein receptor-related peptide 1 (LRP1) and low-density-lipoprotein receptor (LDLR) (3) with subsequent biliary clearance. RAGE, receptor for advanced glycation end products.

of Elecsys (Roche Diagnostics, Basel, Switzerland) immunoassays to measure plasma $A\beta_{42}$ and $A\beta_{40}$ has also recently been shown to predict Aβ status in all stages of AD and their accuracy can be increased by analyzing *APOE* genotype [60]. A recently reported promising approach is measuring exosome-bound Aβ; this has shown to better reflect PET imaging of brain amyloid plaques than unbound or total circulating Aβ and hence enable early diagnosis and disease monitoring [61].

Circadian rhythm

A rapidly growing body of research suggests that disturbances in the circadian system precede the emergence of the characteristic cognitive and motor symptoms of AD [62]. Aggregation of Aβ into extracellular plaques in the brain likely begins 20 years before the onset of dementia. Aβ concentrations in both humans and mouse models show Aβ concentrations rise during wakefulness and fall during sleep, that is, an Aβ diurnal pattern. Studies on sleep raise the possibility that altering sleep quality might impact Aβ deposition and may also regulate the clearance of Aβ from the brain [63]. Indeed, sleep has been identified as a factor which alters the production and/or clearance of Aβ in stable isotope labelling kinetic (SILK) studies measuring Aβ turnover in blood and within the brain [64]. SILK studies have shown that the $A\beta_{42}$:$A\beta_{40}$ turnover rate positively correlates with amyloid plaque load and demonstrate that understanding Aβ dynamics in different compartments including CSF, blood, and brain tissue is crucial to improving therapy. Thus, studies showing significantly lower levels of CSF $A\beta_{42}$ in AD patients with more severe cognitive impairment [65] are unable to provide information on changes in Aβ turnover occurring either during the circadian cycle or during the progression of disease.

The clearance of amyloid from the brain during sleep is primarily via the glymphatic pathway [66, 67]. These lymphatic vessels exit the cranium along veins and arteries associated with the middle meningeal arteries, transporting waste via the deep cervical lymph nodes to the systemic circulation (reviewed in [68]). Initial functional studies in the sleeping brain have shown the importance of the glymphatic pathway in animal models. More recent research has demonstrated glymphatic efflux in patients with AD [69].

Proper functioning of the circadian system is determined by the orchestration of the suprachiasmatic nucleus in the hypothalamus and synchronized peripheral clocks in local tissues, including the

liver. Mass spectrometry analyses of the mouse liver proteome has shown that many secreted proteins accumulate with a diurnal rhythm [70]. Circadian post-transcriptional and post-translational mechanisms play a key role in the temporal orchestration of liver-specific metabolic pathways [71]. Among those enriched in the liver cycling proteome are primary bile acid biosynthesis, bile secretion, protein processing in the ER, PPAR signaling pathway, and metabolism of xenobiotics. Hence poor sleep may be impacting on the hepatic production and biliary clearance of Aβ, as well as directly on the brain. The unfolded protein response (UPR) and circadian rhythm are intimately linked in the liver [72] and the UPR is emerging as a pharmaceutical candidate to combat neurodegenerative diseases [73]. It would hence be of interest to measure the diurnal pattern of plasma biomarkers of AD in relation to therapy.

THERAPEUTIC IMPLICATIONS OF PERIPHERAL PRODUCTION AND CLEARANCE OF Aβ

The aim of the G8 summit held in London in 2013 was "to create disease modifying treatment to stop, slow, or reverse the condition", but, under the current conditions, only drugs currently in late phase I or later will have a chance of being approved by 2025 [74]. Drug development is costly, as is exemplified by anti-Aβ monoclonal antibodies (mAbs), some of which have progressed to evaluation in phase II and phase III trials [75]. To date, the most promising is Aducanumab (BIIB037; Biogen, Inc., Cambridge, MA), a fully human IgG1 mAb, which selectively reacts with Aβ aggregates, including soluble oligomers and insoluble fibrils [76]. This mAb has been shown to enter the brain, bind parenchymal Aβ, and reduce soluble and insoluble Aβ in a dose-dependent manner. However, some medications that are already licensed for other indications may be beneficial in AD by altering the peripheral pathways involved in the physiological homeostasis of Aβ. Therapies which could be repurposed include both licensed drugs and herbal remedies, for example:

Tauroursodeoxycholic acid (TUDCA) is the taurine conjugate of ursodeoxycholic acid (UDCA), a US Food and Drug Administration (FDA)-approved hydrophilic bile acid for the treatment of certain cholestatic liver diseases [77]. There is a growing body of research on the mechanism(s) of TUDCA and its potential therapeutic effect on a wide variety of non-liver diseases [78], including amyotrophic lateral sclerosis [79]. In a mouse model of AD, TUDCA supplementation has been shown to reduce hippocampal and pre-frontal amyloid deposition [80]. TUDCA affects biliary excretion and may predominantly act by altering the production/clearance dynamics of Aβ in the periphery. In AD patients an altered bile acid profile (increased ratio of deoxycholic acid:cholic acid, which reflects 7α-dehydroxylation of cholic acid by gut bacteria), has been shown to associate with cognitive decline, suggesting a possible role of gut-liver-brain axis in the pathogenesis of AD [81], analogous to Parkinson's disease [1]. TUDCA is now being used in a phase II trial in combination with another repurposed drug, sodium phenylbutyrate, produced by Amylyx Pharmaceuticals Inc. (Cambridge, Mass, USA) (AMX0035), supported by the Alzheimer's Drug Discovery Foundation and the Alzheimer's Association.

Bile acids (chenodeoxycholic acid and cholic acid) are physiological ligands/activators of the nuclear receptors, farnesoid-X-receptor, pregnane-X-receptor (PXR) and constitutive androstane receptor, while lithocholic acid is a ligand for the Vitamin D receptor (VDR) and PXR [82]. These receptors generally form heterodimers with RXR [83].

Other nuclear receptor agonists

PPARγ may act as a master regulator of the transcription of several genes involved in LOAD pathogenesis [84]. PPARγ agonists such as the glitazone, **pioglitazone**, prescribed for the treatment of type 2 diabetes, promote amyloid clearance in animal models of AD [85]. A phase II study of pioglitazone in AD showed that it is safe and well tolerated and two large phase III trials are ongoing [86]. In patients with diabetes, pioglitazone treatment is a time- and dose-dependent protective factor against dementia [87]. **Cilostazol** enhances LRP1 expression in liver by activating PPARγ through the peroxisome proliferator response element in the LRP1 promoter [88]. In mice, combined PPARγ /LXR agonist treatment also reduces soluble and deposited forms of Aβ [89].

The **RXR** agonist, **bexarotene** (brand name: Targretin), which is approved by both the FDA and European Medicines Agency (EMA) for use in cutaneous T cell lymphoma, stimulates physiological Aβ clearance mechanisms, resulting in the rapid reversal of a broad range of Aβ-induced deficits in mouse models [90].

VDR - 1,25-dihydroxyvitamin D3 (1,25(OH) 2D3) treatment has been shown *in vitro* to enhance both $A\beta_{40}$ efflux across the BBB and hepatic uptake by HepG2 cells, accompanied by increased LRP1 expression. It was suggested that the effect was exerted via the nuclear VDR and could explain how 1,25(OH)2D3 exerts neuroprotection against AD [91].

Flavonoids

Genistein is an isoflavone derived from the dyer's broom plant, *Genista tinctoria*, which activates PPARs. Treatment of an AD mouse model with genistein results in improvement in various parameters of cognition, associated with a lowering of $A\beta$ levels in brain and in the number and the area of amyloid plaques [92]. The authors conclude that "our results strongly suggest that controlled clinical trials should be performed to test the effect of genistein as treatment of human AD".

Newly identified flavonoids which selectively target another nuclear receptor/pathway, $LXR\beta$ have also been found to reduce total brain $A\beta$ and plaque burden in $A\beta PP/PS1$ double transgenic mice [93].

Silymarin, the main flavonoid extracted from milk thistle, has long been used as a medicinal herb for liver diseases. In a mouse model, it has been shown that Silymarin treatment was associated with a decline in $A\beta$ oligomer production [94]. Silymarin can control the production of $A\beta$ by inhibiting the precursor substance of $A\beta$, $A\beta PP$, and has potential for the treatment of AD [95].

Gene silencing and genome editing

The property of a therapeutic agent in AD to penetrate the BBB has generally been regarded as a prerequisite for new drugs [96]. Recognition of the importance of the liver in $A\beta$ production and clearance means that targeting the liver might be a promising therapeutic approach.

The last decade has witnessed renewed interest in novel therapeutic agents aiming to prevent the production of disease-causing proteins at the level of mRNA, reviewed in [97]. Broadly, two oligonucleotide-based technologies are being deployed in this way, antisense oligonucleotides (ASO) and small interfering RNAs (siRNA), which respectively prevent translation or trigger RNA induced silencing complex (RISC)-dependent cleavage of a specific RNA target. A large number of

disease targets reside in the liver where they are susceptible to modulation by oligonucleotide therapies [98]. The ASO mipomersen, targeting apolipoprotein B in the liver to treat familial hypercholesterolemia, was among the first such agents to be marketed [99]. The recent entry of large numbers of gene silencing agents into clinical trials owes much to the development of conjugates that enable specific delivery of the oligonucleotide to the cytoplasm of the desired target cell, allowing lower doses with fewer side effects. In particular, addition of *N*-Acetylgalactosamine conjugates, which bind with high specificity and affinity to the asialoglycoprotein receptor on hepatocytes has elicited robust gene silencing *in vivo* [100].

Proof of concept for silencing the production of a form of aberrant amyloid by the liver in order to prevent or reverse damage to the nervous system is provided by the rare metabolic disease, hereditary transthyretin amyloidosis. In this condition, mutant transthyretin is produced in the liver resulting in amyloid fibril deposition in various organs and heterogeneous clinical symptoms including peripheral neuropathy and cardiomyopathy [101]. Patirisan, a gene silencing agent delivered to the hepatocyte in a lipid nanoparticle, reduces the production of abnormal transthyretin and can halt or even reverse the process. Both Patirisan, an siRNA and Inotersen, an untargeted ASO, are approved by the FDA and EC for this disorder [102].

Whereas gene silencing provides a temporary fix, all be it with single dose duration of action above six months now regularly achievable, the ability to permanently alter the human genome remains an attractive possibility for patients with deleterious genetic mutations. This has been made possible by a series of technologies collectively known as genome editing for which CRISPR-Cas9 was the archetype. In murine models, liver-directed somatic genome editing with CRISPR-Cas9 is a novel and versatile approach with therapeutic potential in metabolic disorders [103]. The proof of principle that a gene can be targeted in mammalian hepatocytes *in vivo* would suggest that sequence-specific gene editing might be viable in humans [104–107]. In the future, liver-specific gene editing may be used to alter hepatic gene transcription for therapeutic purposes in AD. It is tempting to speculate that mutations in $A\beta PP$, PSEN1 [108], and ApoE4 [109] could be targeted with these technologies. In addition, as lifelong overexpression of wild-type $A\beta PP$ causes AD in individuals with trisomy 21 (Down's syndrome), so the normal hepatic $A\beta PP$ gene could be targeted in AD to decrease

production and alter the balance in favor of $A\beta_{42}$ clearance.

LIVER DISEASES AND DEMENTIA

It is recognized that hepatic functionality should be considered when $A\beta$ balance is addressed [24]. This is reflected in the situation of orthotopic liver transplantation (OLT) where the recipient passes through an anhepatic phase to reperfusion of the new organ. Postoperative cognitive dysfunction is observed in 11% to 44% of OLT patients and is unrelated with the success of a surgery. It is associated with an increase in the serum biomarkers of dementia including $A\beta$ protein 24 h after surgery [110], presumably reflecting alterations in the clearance of $A\beta$ as a result of OLT.

90% of people who die from liver disease are under the age of 70, but the majority of AD cases occur late in life (>65 years). However, a recent large epidemiological study demonstrated that comorbidities significantly associated with mild cognitive impairment and dementia were cirrhosis (OR 3.29, CI 1.29–8.41), cerebrovascular disease (OR 3.35, CI 2.62–4.28), asthma (OR 1.56, CI 1.07–2.27), and diabetes mellitus (OR 1.24, CI 1.07–1.44) [111]. In addition, some studies have shown associations of AD with specific liver diseases.

Hepatitis C virus (HCV)

Chronic HCV infection has been found to be associated with dementia in a large population-based cohort (Hazard ratio 1.36 [95% CI 1.27–1.42]) [112]. More recently, a predictor of cirrhosis in chronic HCV infection, an elevated aspartate aminotransferase to alanine aminotransferase ratio, has been reported to be associated with AD diagnosis (Odds ratio: 7.932) [113]. ApoE, a critical player in $A\beta$ homeostasis, is intimately involved in production of infectious HCV particles [114] and is important in HCV cell entry. HCV may cross the BBB leading to neuroinflammation and neuropsychiatric symptoms [115]. We have reported ApoE deficiency in HCV associated depression [116]. Interestingly low plasma levels of ApoE are associated with increased risk of future AD and all dementia in the general population, independent of $\varepsilon2/\varepsilon3/\varepsilon4$ *APOE* genotype [117].

NAFLD, metabolic syndrome, and type 2 diabetes

Non-alcoholic fatty liver disease (NAFLD) is a chronic liver disease which is increasing in preva-lence, in tandem with the obesity epidemic. NAFLD defines a spectrum of conditions from simple steatosis to non-alcoholic steatohepatitis and cirrhosis and is regarded as the hepatic manifestation of the metabolic syndrome. Hepatic insulin resistance is associated with NAFLD and is a major factor in the pathogenesis of type 2 diabetes and the metabolic syndrome [118].

Various epidemiological studies have shown that metabolic syndrome and type 2 diabetes [119] [120] are correlated with AD. In addition, short sleep duration and poor sleep quality are associated with an increased risk of both NAFLD [121] and AD [62].

In murine models, correlations between a high fat diet and elevated brain and serum $A\beta_{42}$ have been observed [122], and NALFD induces signs of AD in wild-type mice and accelerates pathological signs of AD [123]. Advanced glycation end-products exacerbate progression of experimental NAFLD [124] and AD [22].

SUMMARY

An imbalance in the $A\beta$ production/excretion rate underlies the increased brain concentrations of $A\beta$ in AD. There is evidence suggesting that the liver is the origin of brain $A\beta$ deposits and that it is involved in peripheral clearance of plasma $A\beta$. LRP-1 is the major receptor responsible for the saturable uptake of plasma free $A\beta$ by the liver. A number of medications that are already licensed for other indications and herbal remedies that are currently available improve the $A\beta$ balance in animal models via decreased hepatic production or increased biliary clearance. Hepatic functionality should be considered when $A\beta$ balance is addressed and future developments could include liver-directed somatic genome editing and/or therapeutic gene silencing. Cirrhosis, chronic hepatitis C infection, and NAFLD, the hepatic manifestation of metabolic syndrome, are associated with an increased risk of AD, despite chronic liver disease leading to an early death (under the age of 70 years) in 90% of patients and LOAD manifesting after the age of 65 years.

Clinical specialization, subspecialization, and sub-subspecialization has some advantages in terms of creating standards but could be said to be leading to a growing fragmentation of medical care [125]. Hence, when a variant in the ATP-binding cassette A7 (*ABCA7*) gene which encodes for a phospholipid transporter, is shown to be associated with

LOAD [126], subsequent research focuses on brain mRNA and protein expression [127]. Conversely, hepatologists, who have highly focused knowledge and skills, do not see patients with dementia or keep abreast with the scientific progress in the field of AD. Most patients with long-term conditions and co-morbidities want physicians who see them as a whole person and can deliver holistic care. Perhaps the time has come for a more physiological approach to AD, looking at the integrative function of organs and a multidisciplinary approach to reversing the epidemic?

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