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The evolving role of cholesteryl ester transfer protein inhibition beyond cardiovascular disease

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ABSTRACT

The main role of cholesteryl ester transfer protein (CETP) is the transfer of cholesteryl esters and triglycerides between high-density lipoprotein (HDL) particles and triglyceride-rich lipoprotein and low-density lipoprotein (LDL) particles. There is a long history of investigations regarding the inhibition of CETP as a target for reducing major adverse cardiovascular events. Initially, the potential effect on cardiovascular events of CETP inhibitors was hypothesized to be mediated by their ability to increase HDL cholesterol, but, based on evidence from anacetrapib and the newest CETP inhibitor, obicetrapib, it is now understood to be primarily due to reducing LDL cholesterol and apolipoprotein B. Nevertheless, evidence is also mounting that other roles of HDL, including its promotion of cholesterol efflux, as well as its apolipoprotein composition and anti-inflammatory, anti-oxidative, and anti-diabetic properties, may play important roles in several diseases beyond cardiovascular disease, including, but not limited to, Alzheimer's disease, diabetes, and sepsis. Furthermore, although Mendelian randomization analyses suggested that higher HDL cholesterol is associated with increased risk of age-related macular degeneration (AMD), excess risk of AMD was absent in all CETP inhibitor randomized controlled trial data comprising over 70,000 patients. In fact, certain HDL subclasses may, in contrast, be beneficial for treating the retinal cholesterol accumulation that occurs with AMD. This review describes the latest biological evidence regarding the relationship between HDL and CETP inhibition for Alzheimer's disease, type 2 diabetes mellitus, sepsis, and AMD.

1. Introduction

The main role of cholesteryl ester transfer protein (CETP) is to drive the transfer of cholesteryl esters and triglycerides (TG) between high-density lipoprotein (HDL) particles and TG-rich lipoprotein and low-density lipoprotein (LDL) particles. There is a long history of investigations regarding the inhibition of CETP as a target for reducing major adverse cardiovascular events [1]. Initially, the potential effect on cardiovascular events of CETP inhibitors was thought to be mediated by their ability to increase HDL cholesterol (HDL-C), but it is now understood to be primarily due to reducing LDL cholesterol (LDL-C) and apolipoprotein (apo) B [1–4]. It should not be overlooked that several early CETP inhibitors failed in cardiovascular outcome trials due to off-target toxicity, in the case of torcetrapib, or lack of efficacy with dalcetrapib and evacetrapib [5–7]. However, all the CETP inhibitors developed after torcetrapib have had favorable safety profiles [2,6–10]. Furthermore, the most recently completed cardiovascular outcomes trial of a CETP inhibitor, which examined anacetrapib, found that it significantly reduced major coronary events [2,8]. Anacetrapib's development was subsequently discontinued due to its accumulation in adipose tissue because of its high lipophilicity, but another less lipophilic CETP inhibitor, obicetrapib, is currently being investigated in several phase 3 clinical trials [1,9,10].

A multitude of roles for HDL, including its promotion of cholesterol

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efflux, as well as its apolipoprotein (apo) composition and anti-inflammatory, anti-oxidative, and anti-diabetic properties, are hypothesized to play an important part in several diseases beyond cardiovascular disease. Evidence is mounting for the broader potential benefits of CETP inhibition and raising HDL for certain other diseases as described below [11].

Epidemiological evidence and preclinical research support a link between elevated HDL-C and lower risk of Alzheimer's disease (AD) [12,13]. The protective effects of HDL relate in part to its proteome comprising apoA1, apoE, and apoJ [13]. Patients with loss-of-function mutations in the *CETP* gene are protected from the risk of AD associated with also carrying an apoE4 mutation [14–16].

Results from large clinical trials of CETP inhibitors have also demonstrated a reduced risk of type 2 diabetes mellitus (T2DM) and epidemiologic, preclinical, and genetic investigations also support benefit for CETP inhibition and raising HDL for glycemic control [4,17]. Another condition for which CETP inhibition may be relevant is in resolving bacterial infection and sepsis [18,19]. Sepsis causes an acute, profound drop in HDL-C [20–22]. Genetic analyses have identified CETP as a critical regulator of HDL levels and clinical outcomes of sepsis [18,23,24], and CETP inhibition was shown to protect against polymicrobial sepsis in a humanized mouse model [24].

Nordestgaard et al. reported that haplotypes in the CETP gene leading to lower CETP activity were associated with lower absolute risks of cardiovascular mortality, ischemic heart disease, myocardial infarction, peripheral artery disease, and vascular dementia [25]. These were also associated with higher risk of age-related macular degeneration (AMD). Genetic association between CETP and AMD was also previously reported [26] and a larger Mendelian randomization analysis demonstrated that variants that reduced CETP had a moderate hazard ratio (HR) for AMD of 1.3 [27]. Multiple lines of evidence question the accuracy of these data and, most importantly, excess risk of AMD has not been reported in any CETP inhibitor randomized controlled trial [28,29].

The purpose of the present review is to describe the latest mechanistic evidence regarding the relation of CETP inhibition and raising HDL with regards to Alzheimer's, type 2 diabetes mellitus (T2DM), sepsis, and macular degeneration.

2. Alzheimer's disease

AD is characterized by synaptic dysfunction and neurodegeneration as well as vascular dysfunction. Histologically, there is pathogenic accumulation of extracellular amyloid-β protein and hyperphosphorylated intracellular tau filaments in neurons [30]. These result in senile plaques and neurofibrillary tangles and degeneration [30]. The combination of neuronal loss and a heightened state of inflammation is thought to give rise to the eventual cognitive decline observed in patients with AD [31]. Many lines of evidence indicate that lipid metabolism could serve as a bidirectional link between bioenergetic decline and chronic neuro-inflammation, both of which are hallmarks of AD [13,31]. Moreover, given the strong mechanistic connections between amyloid-β, tau protein, apoE and lipid trafficking, lipid metabolism could be the hub where amyloid-β dependent and independent mechanisms of apoE-associated pathologies converge [30,32,33].

In brain there are two pools of cholesterol. The largest (80%) is mostly inert and present in the myelin sheaths of oligodendroglia cells that surround axons. The level of cholesterol synthesis in these cells is very high, especially in the developing brain. The second smaller (20%) pool, is functionally active and more important for brain functions, such as neuronal growth, repair and remodeling of membranes, organelle biosynthesis and synaptogenesis. This pool is localized in neurons and astrocytes, which make up 50% of all brain cells [32]. With age, cholesterol synthesis in neurons is downregulated in humans, and these cells become increasingly dependent on cholesterol produced by astrocytes, which is transported by the apoE-HDL particle to neurons where it is taken up by LDL-receptors (LDL-R) and other LDL-R like proteins (LRP1) [30,34]. Cholesterol synthesis in astrocytes is tightly regulated [30,32–34]. When intracellular cholesterol levels are low, sterol regulatory-element binding proteins rise and promote cholesterol synthesis from acetate and increase cholesterol uptake through the LDL-R. In contrast, when intracellular cholesterol levels are high, cholesterol is converted to oxysterols by cytochrome P450 family 46 subfamily member 1 (CYP46A1) [30]. The oxysterols drive liver X/retinoid X receptors that promote the transcription of ATP binding cassette subfamily A member 1 (ABCA1), subfamily G member 1 (ABCG1) and apoE to upregulate efflux of cholesterol out of neurons to apoE-containing HDL-like particles [30,32–34]. One of the oxysterols, 24S-hydroxycholesterol (24S-HC), which is unique to neurons, can cross the blood-brain barrier to enter the peripheral circulation and be eliminated as bile [30]. Alois Alzheimer reported the presence of "adipose inclusions" in the brain cells of his patients, structures now referred to as "lipid droplets" [32]. These sequester free fatty acids that are cytotoxic in the cytoplasm and also function as an energy-rich storage pool. However, this pool can also be dangerous, because in the presence of reactive oxygen species, peroxidized lipids are generated and, in the presence of hydrolases, oxysterols are generated. In excess, these are cytotoxic. Neurons can mitigate this toxicity by transferring the burden of lipids to astrocytes, but an apoE-HDL particle associated with a substantial amount of lipid is necessary for this to occur.

ApoE has three common isoforms: apoE2, apoE3 and apoE4. ApoE3 is the wild-type allele, apoE2 protects against AD and apoE4 is, by far, the most prominent risk factor for AD [13,34,35]. Of all late-onset sporadic cases of AD, more than 65% carry an apoE4 allele [13]. Along with HDL, apoE forms a particle unique to the brain, apoE-HDL. ApoE is secreted from astrocytes, as well as activated microglia and vascular mural cells in the choroid plexus, and must be sufficiently lipidated to function as lipid/cholesterol transport from astrocytes to neurons in times of shortage and cholesterol efflux from astrocytes and neurons in times of excess, as described above [32–35]. The lipidation of apoE-HDL initially occurs through ABCA1, whereas the last stages of lipidation of the larger apoE-HDL particles occur through ABCG1 and scavenger receptor class B type 1 (SR-B1) [13,30,32]. When HDL-like apoE-containing particles are fully lipidated, key amino acids become "unburied" that interact with LDL-R, LRP1, and the very low-density lipoprotein receptor on neurons [31,36]. ApoE, mainly the apoE2 and apoE3 isoforms, as well as apo J promote endocytosis of apoE-HDL particles through triggering receptor expressed on myeloid cells 2 (TREM-2). In addition, apoE-HDL having a sufficient amount of lipid is important for cerebrovascular integrity and cerebral blood flow, synapse regeneration, immune modulation and clearance and degradation of amyloid-β [32,33,37]. Furthermore, lipidation of apoE prevents the formation of apoE aggregates, which are toxic to neurons.

ApoE4 carriers, however, accumulate more and smaller lipid droplets in astrocytes, exhibit an increase in unsaturated fatty acids in the cytoplasm, and have higher levels of oxidative stress and lipid peroxidation. They also have higher levels of apoE4 aggregates and less removal of lipid debris. In fact, as described previously, in apoE4 carriers, neurons and glial cells have a limited capacity to eliminate cholesterol, and they use their back-up mechanism, CYP46A1, to convert free cholesterol to 24S-HC [30]. Elevated levels of 24S-HC and another oxysterol from the periphery, 27-hydroxycholesterol, suggest an increase in cerebral cholesterol load as observed in AD brains post-mortem [30,33]. This is supported by data from CETP transgenic mice that have both an increased cholesterol load and AD [38], and further by a study demonstrating that when CETP transgenic mice were crossed with amyloid precursor protein (APP) transgenic mice (a standard AD model), the progression of AD was augmented in the double transgenic mice [39]. Also, evacetrapib slowed that progression [39]. An imbalance of cholesterol homeostasis is the key feature in brains of apoE4 carriers. Insufficiently lipidated apoE-HDL particles, which are smaller than such particles in apoE3 carriers, are a hallmark of apoE4

carrier status. When apoE is not lipidated to a large enough extent, cholesterol accumulates in astrocytes and neurons leading to cytotoxicity, a proinflammatory transcriptome and alteration of membrane composition. Therefore, in apoE4 carriers, removal of amyloid-β is obstructed and deposition is stimulated [34,37]. ApoE co-deposits with β-amyloid in amyloid plaques [33,35,37]. These effects are the consequence of dysregulated expression of genes in cholesterol biosynthesis and of impaired lysosomal cholesterol degradation by acidic lipases. Thus, apoE4 has consequences for lipid homeostasis, cholesterol efflux, removal of amyloid-β, and neuro-inflammation. These characteristics of apoE have led to the formulation of the ApoE Cascade Hypothesis, by which apoE has become a disease target itself, especially the apoE4 isoform [32,40].

In the brain, all of the transporters and enzymes necessary for remodeling of apoE-HDL particles, such as lecithin-cholesterol acyltransferase and phospholipid transfer protein, are present, but at very small percentages of their concentration in the periphery [30,36,41]. Expression of CETP in the brain is not certain. (See Fig. 1, reproduced from Borras, et al. [30]). However, patients with loss-of-function mutations in the *CETP* gene are protected from the risk of AD associated with also carrying an apoE4 mutation [14,16]. Patients with AD who have an apoE4 allele have lower HDL-C and apoA1 levels, and diminished CSF cholesterol-efflux capacity [42]. Peripheral overexpression of apoA1 preserves cognitive function, reduces neuroinflammation and protects mice from cerebral amyloid angiopathy, suggestive of a role for peripheral HDL in the clearance of brain amyloid-β [43,44]. ApoA1 in CSF comes from the periphery [30] and, theoretically, could substitute for dysfunctional apoE4. Both apoA1 Milano and the apoA1 mimetic peptide 4 F, which upregulates ABCA1 activity, have been infused into mouse models and results demonstrated reduced amyloid-β levels and neuro-inflammation [30,43,45]. However, whether these actions may also function in the human central nervous system is still unclear.

Martinez et al. demonstrated that having more small, functional apoA1-containing HDL particles in CSF is better for cognition [44]. Research findings suggest that apoA1 in the brain is a chaperone of amyloid-β and the larger the concentration of apoA1, the more soluble amyloid-β becomes, making it ready for transport out of the brain through the CSF [37,42,43,46]. As described above, in brains with apoE4, the apoE-HDL particle is not adequately lipidated and therefore the transport of cholesterol ester from astrocyte to neuron is hampered, which damages the synapses, since neurons cannot synthesize their own cholesterol. However, apoA1 can substitute for that dysfunction of apoE that leads to mitochondrial uncoupling, hampering energy production and removal of toxic sterols. Oligodendrocytes normally function to produce the myelin sheath, however, in the presence of apoE4, multiple metabolic processes are deranged, and the oligodendrocytes stop making myelin which further leads to neurodegeneration.

Loss of function in ABCA1, the cholesterol efflux protein, is a risk factor for AD, signifying that insufficient efflux lies at the heart of AD and repairing that efflux might be an important strategy for its treatment [47]. Based on the effect of CETP inhibitors on systemic pre-beta HDL levels and apoA1 [3], and their ability to promote cholesterol efflux, including ABCA-1-mediated cholesterol efflux [48–50], mechanistically, pharmacological CETP inhibition might be expected to increase apoA1 levels in the brain and be beneficial for protecting against AD.

Based on all of the previous lines of evidence and recent investigations in CETP transgenic mice [51], we hypothesize that inhibiting CETP might be a therapeutic target for AD in humans by reducing the overall content of cholesterol, oxysterols or, specifically, the apoE4 concentration in the brain, or, alternatively, by increasing apoA1/pre-beta HDL in the circulation and in the choroid plexus, which might restore cholesterol metabolism in the neurovascular unit.

3. Diabetes

While trials of CETP inhibitors produced mixed effects on coronary heart disease reduction, CETP inhibition has been shown to reduce new-onset T2DM across all large trials of this drug class [52,53]. Furthermore, reduced risk of T2DM consequent to CETP inhibition is supported by epidemiological, preclinical, and genetic work evaluating HDL and glycemic control. CETP inhibitors notably act by raising HDL-C, and HDL-C is negatively correlated with T2DM risk [54] adding predictive value to T2DM risk-assessment tools [55]. There is significant mechanistic evidence for a bidirectional relationship between dyslipidemia and T2DM in which dyslipidemia causes lipid accumulation and inflammation spurring insulin resistance, while insulin resistance changes HDL composition, reduces apoA1 exacerbating dyslipidemia, and increases non-enzymatic glycation of apoA1 by reactive alpha-oxaldehydes causing impaired HDL function (e.g., increased inflammation, all contribute to a vicious cycle [56–61]. (See Fig. 2, reproduced from Dangas, et al. [52].) However, the precise chronology remains unresolved. A genetic link between dyslipidemia and T2DM is well-established through evidence of loss-of-function genotypes at proprotein convertase subtilisin kexin type 9 (*PCSK9*) and 3-hydroxy-3-methylglutaryl coenzyme A reductase (*HMGCR*) associated with T2DM risk [62]. Early Mendelian randomization studies yielded mixed results [63,64], but a recent, larger Mendelian randomization study genetically validated CETP inhibition for T2DM prevention [27].

The likely mechanisms through which CETP inhibitors affect glucose metabolism and subsequently T2DM risk are multi-fold [53,56]. In pancreatic ß-cells, cellular and rodent studies have characterized multiple glucose-lowering actions such as inhibiting apoptosis [65,66], reducing inflammation [67], and promoting insulin secretion [67–70], supported by impaired insulin secretion in carriers of *ABCA1* loss-of-function mutations [71,72]. One such study found that CETP knock-in mice had higher β-cell cholesterol and free cholesterol, less β-cell insulin, lower plasma fasting insulin levels, and secreted less insulin after a glucose challenge when compared to wild-type mice [73]. In the periphery, HDL-mediated cholesterol-efflux increases insulin sensitivity [74], thereby increasing glucose uptake. Together, these mechanisms reduce plasma glucose. Accordingly, in T2DM patients, reconstituted-HDL was shown to stimulate insulin secretion and reduce plasma glucose in a double-blind, placebo-controlled crossover study [75]. Plasma glucose was reduced at 30 min whereas insulin secretion rose after 1.5 h, suggesting an insulin-independent glucose-lowering role for HDL, such as AMP-activated protein kinase-dependent glucose uptake [61,75], which appears to be enhanced by apoA1 [76]. Importantly, this study evaluated acutely altered HDL-C. Thus, the suggested mechanisms may be unrepresentative of clinically relevant chronic HDL-C changes. Furthermore, they lacked power ($n = 13$), so no causation can be derived. These studies cannot distill the true effect of HDL from complex interactions controlling glycemic status, leaving the precise mechanism unclear.

The mechanisms for T2DM reduction of the CETP inhibitor drug class have also been specifically investigated. Cellular (dalcetrapib [77] and anacetrapib [78]) and in vivo rodent studies (torcetrapib [79]) of CETP inhibitors suggest that these drugs may stimulate reverse cholesterol transport at ß-cells encouraging insulin secretion and promoting survival of these cells, but evidence is still preliminary.

In summary, there is significant genetic and mechanistic evidence that the effect of CETP inhibitors on T2DM risk is mediated by HDL modulation of glucose metabolism and increased ß-cell function. However, the exact chronology of these mechanisms and precise translation to humans remain uncharacterized. Further work using gold-standard methods to evaluate insulin sensitivity, glucose uptake, and insulin secretion in humans is warranted to further clarify the clinical relevance of these proposed mechanisms.

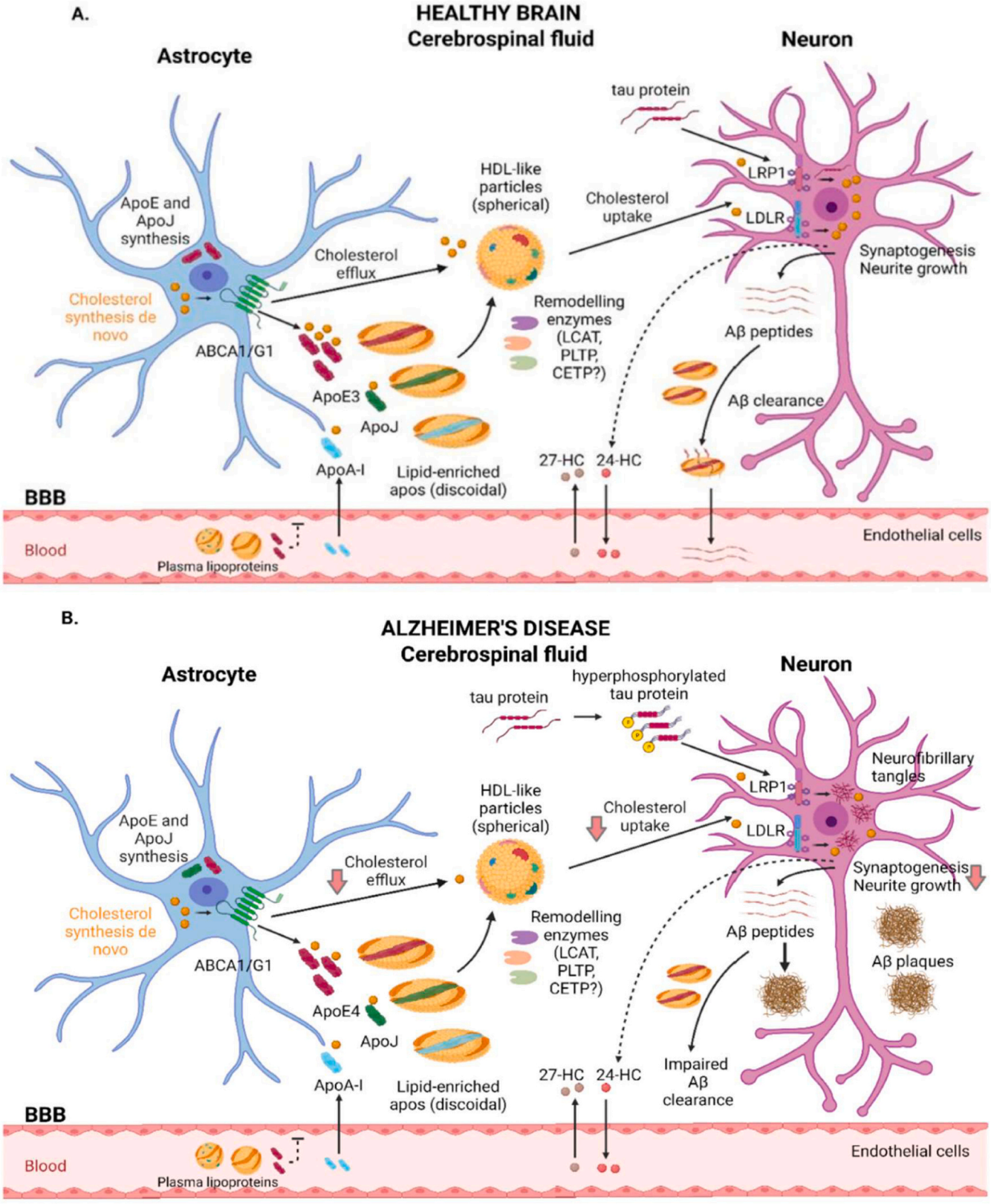

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Fig. 1. Schematic representation of the main steps involved in cholesterol trafficking in the brain (A) In healthy subjects, astrocytes are responsible for de novo cholesterol and ApoE synthesis, with ApoE3 being the predominant isoform. Cholesterol efflux from astrocytes occurs, in part, through the ABCA1 and ABCG1 transporters. Lipid-free ApoE and, in smaller amounts, ApoA1 and ApoJ can be further lipidized by remodeling enzymes, resulting in spherical mature HDL-like particles that can interact with membrane receptors such as LRP1 and LDLR, leading to cholesterol uptake by neurons and guaranteeing essential functions such as synaptogenesis and neurite growth. Oxysterols can flux across the BBB. Neurons convert excess cholesterol in 24-HC, which can be eliminated to the bloodstream. In contrast, 27-HC enters the brain, where it promotes various functions. ApoE also contributes to the clearance of Aβ peptides. (B) In AD subjects, the pathological accumulation of hyperphosphorylated tau protein and Aβ plaque deposition may alter physiological functions in the brain. ApoE4, the predominant isoform in AD patients, is poorly lipidated and barely removes Aβ peptides. LRP1 plays a critical role in neuronal tau endocytosis. Recent works suggest alterations regarding cholesterol transport, including reduced HDL-like mediated cholesterol efflux and impaired cholesterol uptake, leading to cell dysfunction. Abbreviations: Aβ, amyloid beta; ABC, ATP-binding cassette; AD, Alzheimer's disease; Apo, apolipoprotein; BBB, blood-brain barrier; CETP, cholesteryl ester transfer protein; HC, hydroxycholesterol; HDL, high-density lipoprotein; LCAT, lecithin-cholesterol acyltransferase; LDLR, low-density lipoprotein receptor; LRP1, LDLR-related protein 1. From Borras C, et al. [30]

4. Sepsis

Sepsis is a life-threatening, dysregulated host response leading to organ dysfunction [80]. The global burden of sepsis is astonishingly high. It affects almost 50 million people per year worldwide [81]; 20% of all deaths worldwide are due to sepsis. Despite the high prevalence of morbidity and mortality, no effective therapies exist yet beyond antibiotic therapy and supportive care [82]. Therefore, novel therapies are in high demand.

Interestingly, sepsis greatly impacts HDL metabolism by causing an acute, large drop in HDL-C [20–22]. Decreases in HDL-C and several HDL apolipoproteins (apoA1 and apoC1) are associated with increased risk of multiorgan dysfunction, prolonged hospital admission, and mortality [83–85]. Both apoA1 and apoC1 can bind and initiate elimination from plasma of lipopolysaccharide (LPS), a component of the outer shell of Gram-negative bacteria [86,87]. Binding of LPS to HDL particles is thought to be part of the innate immune response. The critical role of HDL and apoA1 in sepsis pathogenesis is supported by preclinical mouse models. Both infusion of HDL and transgenic overexpression of apoA1 reduce inflammation and improve survival rates after intra-abdominal sepsis [88].

The potential role of CETP was further elucidated in a recently published article which showed that a relatively common gain-of-function variant in CETP (missense variant in *CETP*; rs1800777-A) is associated with an exaggerated decline in HDL-C levels during sepsis [23]. Carriers of this variant had more organ failure, greater need for organ support during sepsis, and increased mortality, in two independent cohorts. These findings were subsequently replicated in the Vasopressin Versus Norepinephrine Infusion in Patients with Septic Shock and the Septic Shock Trial (VASST) and St. Paul's Intensive Care Unit Version 2 (SPIHICU2) cohorts [23]. Mendelian randomization utilizing the same cohorts was consistent with the conclusion that genetically reduced HDL levels are a causal factor for decreased sepsis survival. These results suggest a novel gene-environment interaction between CETP and systemic inflammation that contributes to changes in HDL-C levels and survival from sepsis [23].

In full accordance, this CETP gain-of-function variant was significantly associated with increased risk of acute sepsis mortality (HR, 1.44; 95% confidence interval [CI], 1.22–1.70) in a recent meta-analysis of seven human cohorts including the large UK Biobank and the Copenhagen General Population Study [24]. In favorable contrast, a genetic score for decreased CETP function was associated with significantly decreased sepsis mortality in the UK Biobank (HR, 0.77; 95% CI, 0.59–1.00 per 1 mmol/L increase in HDL-C) and in the Identification of Single Nucleotide Polymorphisms Predisposing to Altered Acute Lung Injury Risk (iSPAAR) cohort (HR, 0.60; 95% CI, 0.37–0.98 per 1 mmol/L increase in HDL-C) [24]. Taken together, these genetic approaches identified CETP as a critical regulator of HDL-C levels and clinical outcomes of sepsis [23,24], which led to the hypothesis that CETP inhibition is a promising pharmacological strategy to prevent mortality in sepsis [18].

A role of CETP in innate immunity is in full accordance with the finding that plasma CETP is predominantly derived from Kupffer cells, the resident macrophages within the liver, as evidenced from human liver biopsies as well as studies in APOE* 3-Leiden.CETP mice [89]. Subsequent studies in APOE* 3-Leiden.CETP mice showed that CETP is expressed by a resting subset of Kupffer cells [90]. LPS has long been known to reduce hepatic CETP expression and plasma CETP levels [91,92]. This effect appears to be caused by activation of resting Kupffer cells, leading to reduced CETP expression, and consequently raising HDL-C [90].

A recent groundbreaking study demonstrated that CETP inhibition prevents septic death in an experimental setting [24]. A single administration of anacetrapib to APOE* 3-Leiden.CETP mice at 6 h after induction of intraabdominal polymicrobial sepsis induced by cecal ligation and puncture (CLP) preserved plasma levels of HDL-C and apoA1 and increased survival relative to placebo (70.6% vs. 35.3%), while no effect of anacetrapib on CLP-induced HDL changes and survival was observed in APOE* 3-Leiden mice that do not express CETP [24].

A recent study showed that low numbers of small and medium HDL particles associate with increased infectious disease morbidity and mortality, based on which the authors suggested to apply infusion of reconstituted HDL rather than CETP inhibition in sepsis [93]. However, even if the smaller HDL particles would explain protection in sepsis, it should be noted that a Mendelian randomization approach based on a CETP genetic score has shown that CETP affects medium HDL in addition to large and extra-large HDL [94], and CETP inhibition does result in an increase in small and medium HDL [48,50].

As a working hypothesis, the increase in HDL caused by pharmacological CETP inhibition 1) increases HDL-mediated scavenging of endotoxins [95], thereby preventing excessive endotoxemia that underlies sepsis-induced mortality, and 2) activates macrophages towards an antibacterial response that is required to combat the underlying infection [96]. (See Fig. 3, reproduced from Blauw, et al. [18].) Future studies should aim at revealing whether CETP inhibition effectively treats the various causes of sepsis using clinically relevant models of, e.g., Gram-negative, Gram-positive, and viral sepsis. In addition, human studies need to be initiated to reveal whether CETP inhibition attenuates endotoxin-induced inflammation and at the same time activates macrophages towards an antimicrobial response. Human studies should reveal whether the increase in HDL induced by CETP inhibition is sufficient to have therapeutic benefit. If so, pharmacological inhibition of septicemia, e.g., with the CETP inhibitor obicetrapib, has great potential in the treatment of sepsis.

5. Age-related macular degeneration, Bruch's membrane, and HDL

Evidence from Mendelian randomization analyses suggested that haplotypes in the CETP gene leading to lower CETP activity were associated with higher risk of AMD [25,27,97]. However, results from Mendelian randomization analyses cannot be used for estimating the potential for adverse drug reactions or as evidence for a *causal* relationship between a genetically instrumented exposure and an observed outcome [28,29]. There was no association between *CETP* allele carrier status and any stage of AMD. Furthermore, if genetically determined low

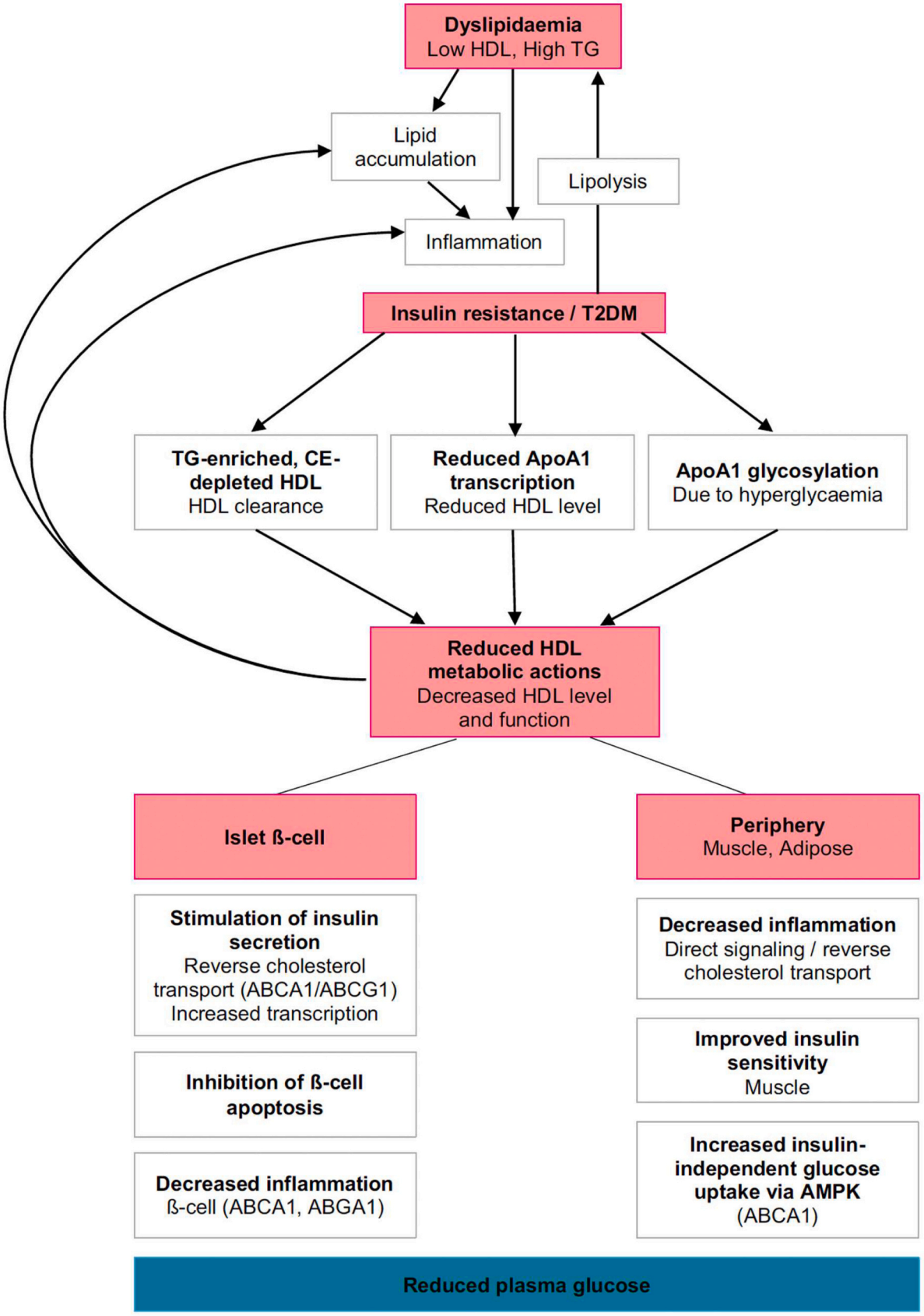

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Fig. 2. Mechanisms linking HDL-C and diabetes. Dyslipidemia (low HDL) causes lipid accumulation and inflammation propagating insulin resistance and T2DM. T2DM increases apoA1 glycation (non-enzymatic) by reactive alpha-oxoaldehydes, such as methyglyoxal and glycoaldehyde, has been shown to reduce apoA1 transcription in animal models and cell cultures, and changes HDL composition to increase its clearance and reduce HDL levels and function [57–59]. HDL is normally involved in reverse cholesterol transport and has anti-inflammatory actions at the level of the beta-cell and in the periphery resulting in decreased plasma glucose [56]. HDL promotes insulin secretion via apoA1 [68] and ABCA1/ABCG (1) or through stimulating insulin transcription. HDL-C may inhibit ER-stress-induced beta-cell apoptosis [66] and islet cell inflammation via ABCA1 and ABCG [67]. Loss of HDL particles and function exacerbates lipid accumulation and inflammation and increases plasma glucose in a vicious cycle. Abbreviations: ABC, ATP binding cassette; apo, apolipoprotein; HDL, high-density lipoprotein; HDL-C, high-density lipoprotein cholesterol; T2DM, type 2 diabetes mellitus.
From Dangas K, et al. [52]

CETP activity were a causal pathway for macular degeneration, then persons with loss-of-function variants in *CETP* would be expected to be at increased AMD risk. However, there are no case reports of AMD in patients with homozygous or heterozygous CETP deficiency [98,99].

Results from randomized controlled trials also indicate there is no excess risk of AMD associated with CETP inhibition. All cardiovascular outcome trials of CETP inhibitors testing torcetrapib [5], dalcetrapib [6], evacetrapib [7], and anacetrapib [2,8] reported no difference from control for any eye disorder, e.g., loss of visual acuity or blindness. The Randomized Evaluation of the Effects of Anacetrapib Through Lipid Modification (REVEAL) trial alone enrolled 30,000 patients and demonstrated no difference in the incidence of AMD between anacetrapib- and placebo-treated patients, whereas first major coronary events were reduced by 9% during the median follow-up of 4.1 years (12% proportional reduction when including an extended follow-up period; median overall follow-up of 6.3 years) [2,8].

AMD occurs when disruption of the macular surface, the photoreceptor-rich, central part of the retina, is infiltrated by focal or diffuse lipoprotein-rich deposits called drusen. These drusen form either under the neurosensory retina called sub-retinal drusenoid deposits or under the retinal pigment epithelium (RPE) [100]. The RPE is a monolayer of polarized epithelial cells serving as the interface between the neural retina and the choroid, the main blood supply to the outer layer of the retina [101]. The basement membrane of RPE cells form Bruch's membrane (BrM), a pentalaminar structure consisting of the endothelial cells of the choriocapillaris and the matrix, which fills the space between the RPE and BrM. BrM is not a membrane per se, and therefore discoidal apoA-containing lipids (e.g., HDL) easily pass through BrM [102]. Fig. 4, reproduced from Kjeldsen, et al. [97], illustrates the movement of cholesterol across the BrM and within the retina.

Thus, the body's natural cholesterol homeostatic processes of reverse cholesterol transport and cholesterol efflux open a window of opportunity to treat cholesterol accumulation within the RPE and BrM [103]. In fact, smaller, discoidal HDL which cross the RPE and BrM may be size matched for such a purpose. Therefore, therapies which increase pre-beta, small discoidal HDL, or directly deliver apoA to the site of cholesterol accumulation, provide a unique potential target to treat AMD especially because RPEs express SRB-1 receptors providing the natural ligand of apoA1 to initiate cholesterol removal [104]. Research findings have suggested potential for treating retinal neovascularization with apoA1. An in vitro investigation of primary human retinal vascular endothelial cells transfected with apoA1-GFP recombinant lentiviral demonstrated that overexpression of apoA1 inhibited angiogenesis and suppressed placental growth factor expression [105].

In the CETP Inhibition by Obicetrapib in Patients with Mild Dyslipidemia (TULIP) trial, which administered obicetrapib 1, 2.5, 5, or 10 mg obicetrapib or matching placebo, HDL-C was increased by 75.8%, 124.3%, 157.1%, and 179.0%, respectively [48]. Compared with placebo, total, non-ABCA1- and ABCA1-specific cholesterol efflux capacity increased dose dependently by up to 38%, 72%, and 28%, respectively, at the 10 mg dose [50]. Furthermore pre-beta-1 HDL, which is the primary acceptor for ABCA1-driven cholesterol efflux, was increased by 36% and pre-beta-2 HDL by 66%. These particle levels correlated significantly with the total and ABCA1-driven cholesterol efflux increase. Similarly, the CETP inhibitor, evacetrapib, administered as monotherapy and combined with statins to dyslipidemia patients, was shown to significantly increase total and ABCA1-specific cholesterol efflux capacity and pre-beta-1 HDL [49]. These results suggest that AMD might potentially be treated with small discoidal HDL particles and, furthermore, because CETP inhibitors robustly increase pre-beta-1 HDL, CETP inhibition might constitute a future therapy for the lipid deposition in AMD.

Another potential benefit of raising HDL with CETP inhibition is to increase xanthophyll bioavailability, which may be protective against AMD [106–108]. As documented by McGwin et al., a large body of preclinical and clinical evidence supports the idea that delivering lipophilic antioxidants to the macula may serve to protect against AMD [109]. The Age-Related Eye Disease Study (AREDS and AREDS2) demonstrated that lutein/zeaxanthin supplementation reduced neovascular AMD [108,110]. Given that HDL particles are the major carriers of xanthophylls, it is hypothesized that increasing HDL may result in enhanced circulation of xanthophylls (Data on file, NewAmsterdam Pharma; [111]). Analyses of samples from the Randomized Study of Obicetrapib in Combination with Ezetimibe (OCEAN; NCT04770389) demonstrated that obicetrapib increased the plasma level of pre-beta-1 HDL, as well as total plasma lutein, zeaxanthin and tocopherol, mainly due to a dramatic increase in HDL-carried antioxidants (Data on file, NewAmsterdam Pharma; [50]).

Thus, multiple lines of evidence from individuals with loss-of-function variants and randomized controlled trials of CETP inhibitors, along with supportive evidence suggesting the possibility of benefits for raising HDL on eye health, indicate there is no excess risk of AMD associated with CETP inhibition [28].

6. Discussion and perspectives

For over two decades there has been interest in developing CETP inhibitors with the preliminary focus placed on their ability to raise HDL-C concentrations [1,3]. The majority of the clinical trials aimed at detecting benefits on cardiovascular risk reduction failed, for a variety of compound or study-related reasons [1,3]. Torcetrapib increased cardiovascular events and death due to structure-related off-target effects that increased blood pressure, aldosterone, steroid, and endothelin-1 levels, and was associated with electrolyte abnormalities, whereas the cardiovascular outcome trials of dalcetrapib and evacetrapib were terminated early due to lack of efficacy [5–7]. For dalcetrapib, this was due to its modest effect on LDL-C, but for evacetrapib, the trial was likely simply too short to demonstrate clinical benefit [6,7]. The clinical development program for anacetrapib indicated it was able to significantly reduce cardiovascular events, but it was discontinued due to accumulation in the adipose tissue because of its high lipophilicity [2]. During the cardiovascular outcomes trial of anacetrapib, patients receiving the drug compared with placebo had slightly higher systolic and diastolic blood pressures (0.7 and 0.3 mm Hg, respectively), and more subjects developed an estimated glomerular filtration rate of < 60 mL/min/1.73 m^2 of body surface area (11.5% vs. 10.6%, respectively), however there were no significant differences in serious adverse events attributed to hypertension or renal failure during the main trial or in an extended follow-up period [2,8].

Results are promising for obicetrapib, a selective CETP inhibitor with a more polar structure, which is in clinical development for reducing LDL-C and the incidence of major adverse cardiovascular events [1,3,9,

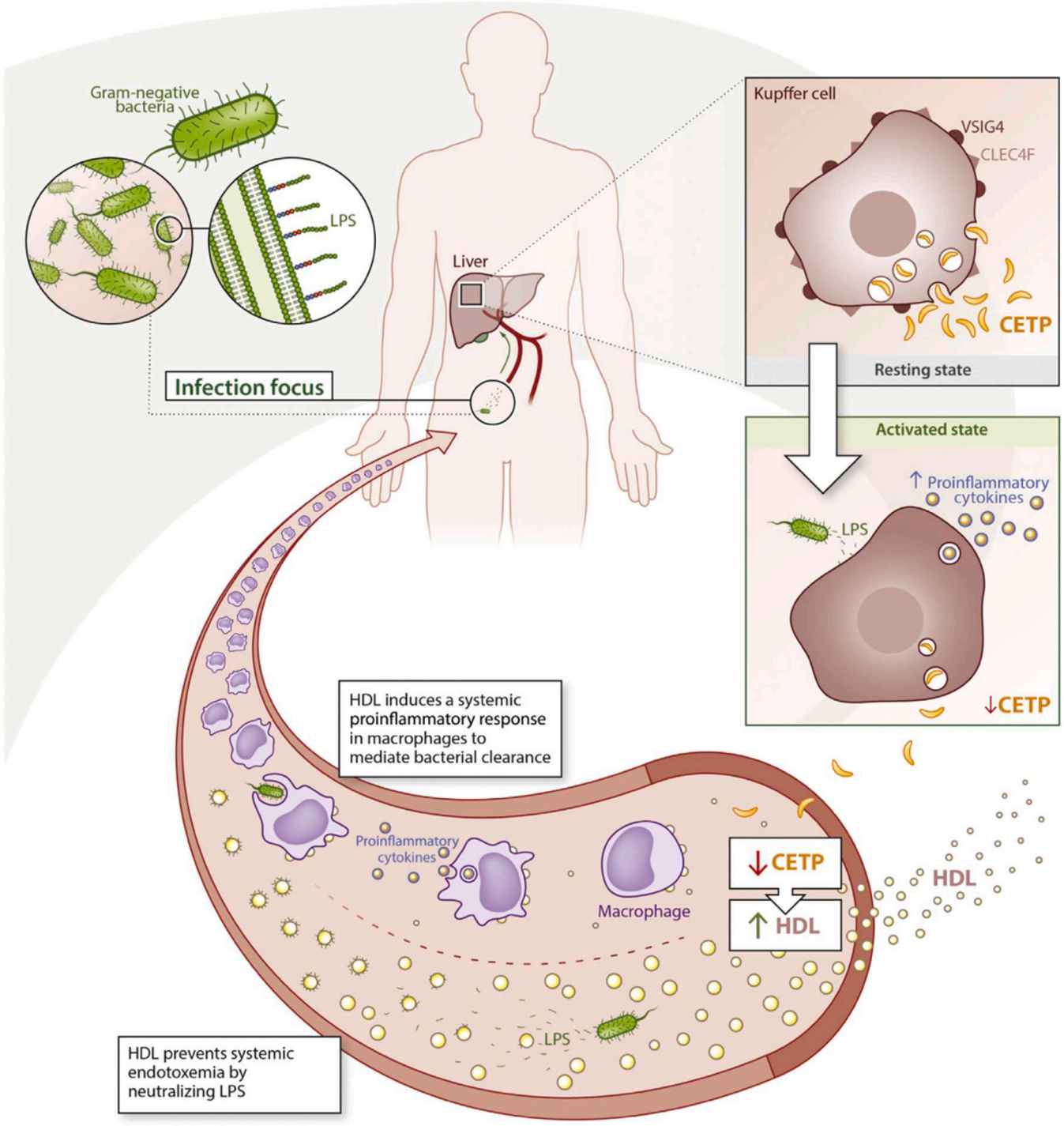

Fig. 3. HDL and CETP and their relation to bacteremia. In a noninfectious state, CETP is mainly produced by Kupffer cells, the resting macrophages in the liver. When Gram-negative bacteria invade the blood, as occurs in sepsis, they release the endotoxin LPS that triggers Kupffer cells to become activated and induce an antibacterial response via the release of proinflammatory cytokines. Concomitantly, Kupffer cells lose their expression of CETP, which increases HDL levels in the circulation. This rise in HDL prevents systemic endotoxemia by neutralizing LPS and induces a systemic proinflammatory response in macrophages to mediate bacterial clearance. Abbreviations: CETP, cholesteryl ester transfer protein; HDL, high-density lipoprotein; LPS, lipopolysaccharide.
Reprinted from Blauw et al. [18]

10,48,112]. Both the Randomized Study of Obicetrapib as an Adjunct to Statin Therapy (ROSE) and the Study to Evaluate the Effect of Obicetrapib in Combination with Ezetimibe as an Adjunct to High Intensity Statin Therapy (ROSE2) phase 2 trials met their primary endpoints of significantly lowering LDL-C [1,9,10]. In ROSE, obicetrapib dose dependently lowered LDL-C and apoB by up to 50.8% and 29.8%, respectively, and raised HDL-C by up to 165% at the 10 mg dose. There were no major side effects with obicetrapib in either trial. Three phase 3 trials of obicetrapib are ongoing, including the Cardiovascular Outcome Study to Evaluate the Effect of Obicetrapib in Patients with Cardiovascular Disease (PREVAIL, NCT05202509), which will enroll 9000 patients with results expected late in 2026. The primary objective of PREVAIL is to evaluate the effect on risk of major adverse cardiovascular events, including cardiovascular death, non-fatal myocardial infarction,

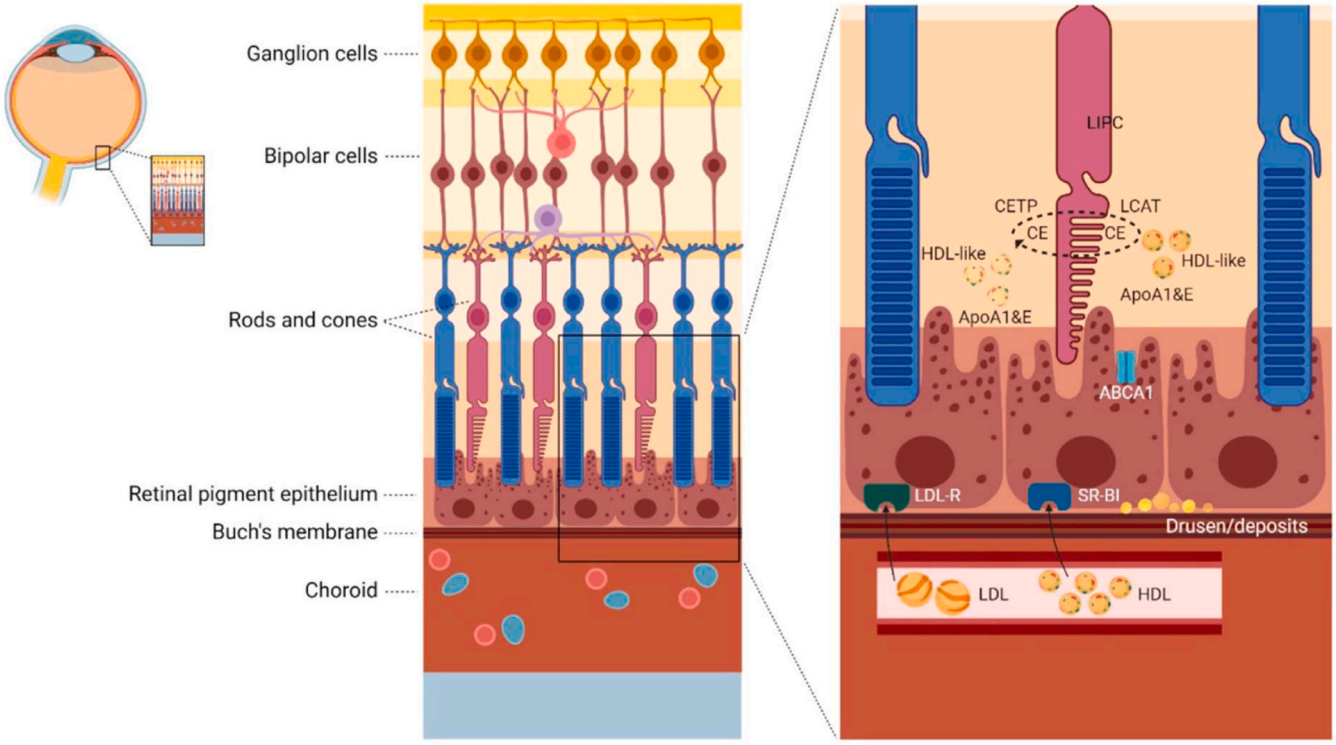

Fig. 4. Suggested mechanism of lipid transport in the retina. HDL, with apoA1 as its major apolipoprotein component, delivers cholesterol to the retina via scavenger receptors, and LDL delivers cholesterol via members of the LDL-R family. ApoA1 mediates the interaction of HDL with ABCA1 transporters, which aid in moving cholesterol through the RPE into the interphotoreceptor matrix. Enzymes within the retina (LCAT and LIPC) remodel the HDL particles by converting free cholesterol into cholesteryl esters and hydrolyzing phospholipids. CETP has a potential role in transferring esterified cholesterol between lipoproteins and photoreceptor membranes. Photoreceptor discs are lipid-rich, and HDL may work as a transporter of cholesterol and phospholipids between the RPE and the interphotoreceptor matrix, supporting their synthesis and degradation. The RPE maintains its lipid balance by transporting lipoproteins with an abundance of esterified cholesterol back to Bruch's membrane. Abbreviations: ABC, ATP-binding cassette; Apo, apolipoprotein; CE, cholesterol ester; CETP, cholesteryl ester transfer protein; HDL, high-density lipoprotein; LCAT, lecithin:cholesterol acyltransferase; LIPC, hepatic lipase; LDL, low-density lipoprotein; LDL-R, LDL receptor; RPE, retinal pigment epithelium; SR-BI, scavenger receptor BI.
From Kjeldsen et al. [97]

non-fatal stroke, or non-elective coronary revascularization. Secondary endpoints include its ability to lower LDL-C, prevent new-onset diabetes mellitus, and long-term safety. Based on genetic and preclinical evidence indicating that CETP inhibition can reverse cholesterol accumulation and associated cognitive impairment in mice, a phase 2, proof-of-concept, open-label study in patients with mild cognitive impairment and early AD is underway to evaluate the pharmacodynamics, pharmacokinetics, and safety of obicetrapib therapy (NCT05161715). Results are expected in mid-2023.

Despite HDL-C concentration being largely abandoned as a potential therapeutic target for cardiovascular disease risk reduction, insights from recent studies suggest new applications for raising HDL, specifically with CETP inhibition, on different vascular and non-vascular endpoints, including diabetes, AD, and sepsis [113]. CETP inhibition has been shown, both genetically and in clinical trials, to reduce diabetes risk and evidence indicates that this is mediated by HDL's modulation of glucose metabolism. More work is needed to fully understand these mechanisms. Further research, including human studies, is also needed to explore whether increasing HDL as induced by CETP inhibition has therapeutic benefit in the treatment of sepsis. Investigations are also needed to further address whether there is a cause-effect relationship between HDL and AD and the mechanism by which CETP inhibition may protect from the occurrence of AD.

Although not discussed in this article, dysfunctional HDL has also been reported in patients with COVID-19, where it is associated with increased disease severity and poor clinical outcomes [114]. Furthermore, dalcetrapib has been shown to have an inhibitory effect on SARS-CoV-2 3CL protease and viral replication, suggesting another emerging area of interest for investigating the potential benefit of CETP inhibition for raising HDL [115].

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CRediT authorship contribution statement

N.M., K.D., M.R.D., P.C.N.R., M.R.D: Writing-Original Draft, Writing-Reviewing and Editing; J.J.P.K.: Conceptualization, Writing-Original Draft, Writing-Reviewing and Editing.

Declaration of Competing Interest

N.M. is Founder and Chief Executive Officer of Mobius Scientific, Inc. M.D. is Vice President of Research & Development for NewAmsterdam Pharma. M.R.D. as an employee of Midwest Biomedical Research has received consulting fees from NewAmsterdam Pharma. J.J.P.K. is founder and Chief Science Officer of NewAmsterdam Pharma, and Emeritus Professor of Medicine at the University of Amsterdam, The Netherlands. K.D. and P.C.N.R. have no relevant conflicts of interest.

Data availability

No data were used for the research described in this article.

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