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Review

Biomaterial to Improve Drug Delivery in Alzheimer's Disease: Linking Major Pathogenic Pathways

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Abstract

Aging, hypertension, diabetes, obesity, atherosclerosis, traumatic brain injury, and other factors can all synergistically promote diverse pathological mechanisms. These risk factors trigger widespread inflammation and oxidative stress, both of which can lead to blood-brain barrier (BBB) disruption. These pathological cascades lead to neuronal Ca^{2+} increase, neurodegeneration, gradual cognitive/memory decline, and eventually Alzheimer's disease. In particular, more recent research indicates that chronic inflammatory stimulus in the gut may induce (e.g., via serum amyloid A (SAA)) the release of proinflammatory cytokines. Hence, an effective preventive and therapeutic strategy could be based upon drug targeting toward a major SAA receptor responsible for the SAA-mediated cell signaling events leading to cognitive decline and eventually Alzheimer's disease. In addition, it has already been determined from past studies that drug-carrying lipid nanoparticles can take advantage of physiological receptor-mediated transport processes across the BBB for localized drug delivery in brain tissue.

Keywords
Cognitive impairment; blood-brain barrier; Alzheimer's disease; drug targeting; nanoemulsion; neuroinflammation; proinflammatory cytokines; serum amyloid A

1. Background

Much evidence has been published which indicates that microvascular endothelial dysfunction, due to cerebrovascular risk factors (e.g., atherosclerosis, hypertension, obesity, diabetes, smoking, aging), precedes cognitive decline in Alzheimer's disease and contributes to its pathogenesis (see [1, 2] for reviews). By incorporating appropriate drug(s) into biomimetic (lipid cubic phase) nanocarriers, one obtains a multitasking combination therapeutic which targets certain cell-surface scavenger receptors, and crosses the blood-brain barrier (BBB). Such targeting allows for various Alzheimer's-related cell types to be simultaneously searched out, in vivo, for localized drug treatment [3-6]. This (colloidal-nanocarrier) in vivo targeting advantage may be particularly important when delivering pleiotropic natural substances (e.g., an isoflavone) or for repurposing FDA-approved food additive(s) and/or drug(s), especially one which has shown the added ability to restore some cognitive functions in certain animal models of Alzheimer's disease [4].

2. Endothelial Dysfunction, and Targeted Treatment for Early Dementia

It has been reported repeatedly that *endothelial* modulation and repair is feasible by pharmacological targeting [1, 2, 7-13] of the *SR-BI* receptors (i.e., “scavenger receptor class B, type I”) [13, 14]. Recently, Fung et al. specifically found that SR-BI mediates the uptake and transcytosis of high-density lipoproteins (HDL) across brain microvascular endothelial cells (i.e., across the BBB) [15]. Since SR-BI has already been identified as a major receptor for HDL (with their major apolipoprotein *(apo)A-I) as well as for* the recently reviewed [1, 2] “lipid-coated microbubble/nanoparticle-derived” *(LCM/ND) nanoemulsion* (see below), this multitasking lipid nanoemulsion can arguably serve as a targeted, apoA-I-based, (SR-BI mediated) therapeutic agent for common (late-onset) dementias [16-18].

This targeted (LCM/ND-delivery) type approach receives added impetus from continual findings of cerebrovascular pathology [1, 19-29] and an apparent *endothelium* dysfunction [2, 17, 18, 25, 30-36] in both Alzheimer's disease and its major risk factors [1, 2, 29-41]. By incorporating drug molecules into the LCM/ND lipid nanoemulsion type (yielding particle sizes mostly < 0.1 μm in diameter – see Figure 1), known to be a successful drug carrier [42, 43], one is likely to obtain a multitasking combination therapeutic capable of targeting cell-surface SR-BI.

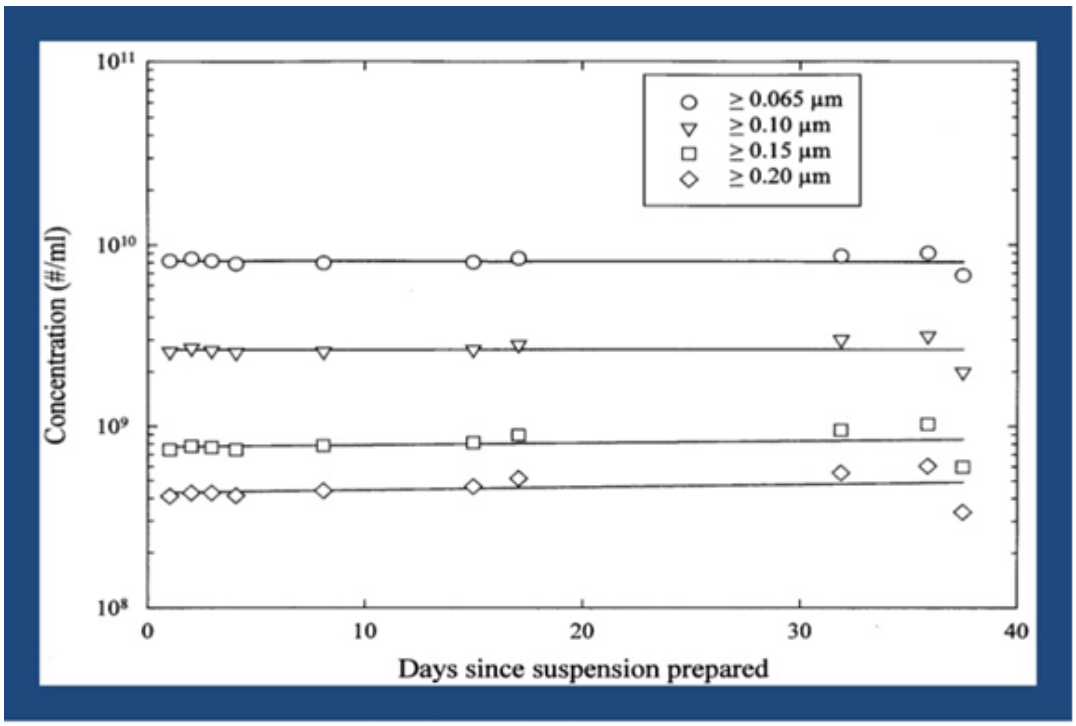

Figure 1 LCM/ND nanoemulsion stability over time. (Adapted from ref. [2]).

3. LCM/ND Nanoemulsion Type, and Targeting via Lipid Cubic Phases

Monoglycerides exhibit different phase behaviors when they are exposed to water [44-50]. Of special interest, the *dispersed Fd3m* cubic phase can represent a lipid/water system which is particularly relevant to the earlier-described (Filmix®) LCM/ND lipid nanoemulsion formulation(s) on account of the fact that the patent claims describing the precise lipid composition of such nanoemulsion formulations (see especially Claim #1 in [51, 52]) specifically include cholesterol and three categories of (saturated) glycerides, that is, tri-, di-, and monoglycerides [51, 52]. In view of the advantageous attributes of monoglycerides (alluded to above), and since (saturated) monoglyceride represents the largest single-lipid fraction of the LCM/ND lipid nanoemulsion type, the monoglyceride content probably plays a dominant role in supporting the evident long-term stability of the liquid-crystalline lipid nanoparticles in such nanoemulsions [42].

In this particular targeted-delivery approach, the self-assembled “lipid particle” structure itself (after intravenous injection) is directed via (adsorption of) plasma lipoproteins, including notably apoA-I, toward the appropriate receptors on the target-cell surface [42].

4. Molecular Mechanism of Colloidal Nanocarrier Formation

Previous reports concerning colloidal nanocarriers [e.g., 5] do not fully explain how various (biobased) lipids, and their mixtures, are able to reliably form self-assembled non-lamellar nanostructures (i.e., lipid cubic phases) – which, in turn, have been observed to serve as colloidally stable nanocarriers for drug(s) in excess water (e.g., in blood plasma) [53]. The answer to this fundamental question resides in the physicochemical tendency of these biobased lipids to adopt a non-lamellar inverse topology. This special tendency, of these surface-active lipids, is itself a function of lipid head-group hydration, acyl chain length, and cholesterol content (see below).

As reviewed by Schwarz and Gompper [54], the predominance of the lamellar phase at ambient temperatures stems from the fact that (in contrast to many synthetic surfactants, which usually have large head groups and form micelles) lipids themselves have rather bulky hydrocarbon chains (e.g., [54-56]). Spontaneous curvature can be increased by changing molecular architecture, that is, by adding lipids with bulkier chains, or by replacing charged lipids with similar ones having only nonionic head groups to avoid Coulombic repulsion between head groups. Lipids with spontaneous curvature are often called "nonbilayer lipids". Hence, with the resulting large spontaneous (negative or inverse) curvature, a cubic phase of inverse spherical micelles is often observed [54].

Notice that there is actual consensus that amphiphilic lipids with weakly hydrated, hydrophilic head groups serve to promote formation of an *Fd3m* cubic phase (also known as phase Q^{227}) ([56]; cf. [57]), -- which is particularly relevant to the earlier-described [3] LCM/ND nanoemulsion formulation(s): Specifically, the saturated glycerides and cholesterol (and its ester derivatives), which together compose the basic Filmix® (LCM/ND) nanoemulsion formulation [42], are *all non*ionic and therefore each amphiphilic lipid in such a lipid mixture would only have a weakly hydrated, hydrophilic head group. Consequently, the above facts considered together support the earlier provisional conclusion that the dispersed *Fd3m* micellar cubic phase represents the most probable or preferred lipid polymorphic form adopted by the particles in the LCM/ND nanoemulsions [3, 42].

As concerns the acyl chain length of the saturated glycerides contained in the LCM/ND nanoemulsion formulations, in relation to promoting formation of an *Fd3m* cubic phase (or Q^{227}), it is useful to also consider related experimental work employing biological amphiphilic lipids having saturated acyl chain lengths (which include) from 12 carbon atoms to 16 carbon atoms long [see below]. Our focus on this specific range of chain lengths stems from the fact that the saturated (nonionic) glycerides in the "particularly preferred" lipid mixture, used to form LCM/ND nanoemulsions, have acyl chain lengths of 12 carbons (e.g., glycerol monolaurate) and 16 carbons (e.g., glycerol tripalmitate) in length [42, 51, 52]. Hence, it is relevant to note a study by Seddon et al. [58] concerning the phase behaviors of a homologous series of saturated phosphoglyceride/fatty acid mixtures having chain lengths of C_{12} and higher, which were analyzed by X-ray diffraction and colorimetry, as a function of water content. These investigators reported that the lamellar phase is suppressed in these lipid mixtures, being replaced by inverse non-lamellar phases for all (saturated acyl) chain lengths greater than C_{12}, and at all levels of hydration ([58]; cf. [59]).

It was also stated earlier (in this section regarding adoption of non-lamellar topology) that cholesterol is another important component in the basic LCM/ND nanoemulsion formulation. This fact is consistent with published data from related experimental studies using phosphoglyceride bilayers: As summarized by Chen and Rand [60], cholesterol has been found to destabilize bilayers of some common biological phosphoglycerides, and to induce the formation of the inverse phase in these systems [61-65]. Specifically, while sterols cannot alone form lamellar structures, sterols like cholesterol appear to have evolved to fill the flickering spaces among the acyl chains in membrane bilayers (e.g., [66]). Furthermore, cholesterol has the unique capability among membrane lipids of rapidly "flip-flopping" (between opposite monolayers of a membrane bilayer), and because of its small (and nonionic) head group, a negative curvature is made easier by an accumulation of cholesterol (see [42] for a review).

In view of all the above considerations concerning the roles of lipid head-group hydration, acyl chain length, and cholesterol content, the dispersed lipid particles of LCM/ND nanoemulsions very likely represent liquid-crystalline inverse-topology nanocarriers, i.e., dispersed lipid cubic phases (cf. [42]).

5. Serum Amyloid A (SAA), SR-BI, and Alzheimer's Disease

Various past studies indicate that inflammation plays an important role in the process of amyloid deposition and, therefore, inhibition of inflammatory cascades may attenuate amyloidogenic processes – such as Alzheimer's disease (e.g., [67]; cf. [68, 69]). Moreover, recent research indicates that chronic inflammatory stimulus in the gut may induce (e.g., via serum amyloid A from the gastrointestinal tract [cf. below]) the release of proinflammatory cytokines. At the same time, increased BBB permeability due to aging (or dysfunction), in turn, allows these proinflammatory cytokines to enter the brain, inducing glia reactivity [70, 71]. (Note too that *un*like other acute phase proteins, which are synthesized primarily in the liver, acute-phase SAA is also markedly expressed at local sites of tissue inflammation. Furthermore, very recent work by other investigators suggest that brain injury can elicit a systemic inflammatory response mediated through SAA that contributes to the pathological outcomes. For example, SAA can induce activation of the inflammasome in microglial cells and give rise to cytokine release which can exacerbate inflammation in the brain following neurological diseases [72-74].) Hence, an effective preventive and therapeutic strategy could be based upon drug targeting toward a major SAA receptor responsible for the SAA-mediated cell signaling events leading to cognitive decline and eventually Alzheimer's disease.

Specifically, earlier research [75] has already confirmed that SR-BI receptors (or its human ortholog CLA-1) function as cell-surface SAA receptors -- which bind, internalize, and mediate SAA-induced proinflammatory effects (cf. [76]). Accordingly, multiple studies suggest that SAA may have profound effects on innate immunity as a result of its chemotactic and cytokine-inducing activities [72]. However, Baranova et al. additionally report that (in cell culture) CLA-1/SR-BI ligands "efficiently *compete"* with SAA for CLA-1/SR-BI binding [75]. For example, it has already been documented repeatedly in the literature that *both* apo A-I and SAA are substrates for SR-BI, which indicates that SR-BI can mediate the transport of *both* proteins across the BBB (e.g., [77]). Not surprisingly, therefore, Robert et al. have recently asserted that many lines of evidence suggest a *protective role* regarding HDL and its major apolipoprotein (apo)A-I in Alzheimer's disease [17]. Accordingly, a similar benefit (of "*competitive binding*" to SR-BI receptors) may well accompany intravenous use clinically of the LCM/ND lipid nanoemulsion vehicle -- which has already been repeatedly described in the peer-reviewed literature (based upon numerous in vivo animal studies) as a targeted, *apoA-I*-based, (*SR-BI* mediated) drug-delivery agent [see Sect. 2].

6. Conclusions

The risk factors for Alzheimer's disease can all synergistically promote diverse pathological mechanisms. In particular, more recent research indicates that chronic inflammatory stimulus in the gut may induce (e.g., notably via serum amyloid A (SAA)) the release of proinflammatory cytokines. At the same time, increased BBB permeability due to aging and/or dysfunction, in turn, allows these proinflammatory cytokines to enter the brain, inducing glia reactivity. Hence, an

effective preventive and therapeutic strategy could be based upon drug targeting toward a major SAA receptor responsible for the SAA-mediated cell signaling events leading to cognitive decline and eventually Alzheimer's disease.

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Competing Interests

The authors declare no conflict of interest. J.S.D. is employed at Cav-Con Inc.

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