



Research Article

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Drug Nanotargeting for Treating Vascular Dementia and Alzheimer's Disease

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Abstract

Microvascular endothelial dysfunction precedes, often by decades, the cognitive decline associated with Alzheimer's disease. Hence, preservation of a healthy cerebrovascular endothelium can be an important therapeutic target. By incorporating appropriate drug(s) into biobased (lipid cubic phase) nanocarriers, one obtains a multitasking combination therapeutic which targets certain cell-surface scavenger receptors, mainly class B type I (i.e., SR-BI), and crosses the blood-brain barrier. Such colloidal-nanocarrier targeting allows for various Alzheimer's-related cell types to be simultaneously searched in a holistic integrative approach, *in vivo*, for localized drug treatment. Using various biobased lipids and their mixtures to form self-assembled non-lamellar nanostructures, it has continually been reported possible to successfully obtain stable colloidal dispersions of (liquid-crystalline) lipid cubic phases with well-defined particle size and morphology. In particular, monoglyceride-based lyotropic liquid-crystalline phases are relatively unique owing to their rich polymorphism in water and potential application as drug nanocarriers. This (colloidal-nanocarrier) *in vivo* targeting advantage may be particularly important when delivering pleiotropic natural substances (e.g., an isoflavone) or for repurposing an FDA-approved drug.

Keywords

Alzheimer's disease, Blood-brain barrier, Cognitive impairment, Drug targeting, Lipid cubic phases, Nanoemulsion, Scavenger receptors, SR-BI, Vascular dementia

Introduction

Vascular brain lesions are very common in people over 70-years-old, and recent reviews [1,2] provide much evidence that a large proportion of dementia cases may be attributable to cerebrovascular disease [3,4]. Accordingly, vascular cognitive impairment and dementia (VCID) is the second leading cause of dementia behind Alzheimer's disease, and is a frequent co-morbidity in the Alzheimer's patient [5,6]. Furthermore, growing data from brain imaging studies and various animal models suggest that cerebrovascular dysfunction may well precede cognitive impairment and the onset of neurodegenerative changes in Alzheimer's disease [2,4].

Endothelial dysfunction and targeted nanotherapy for early dementia

Small-vessel disease is commonly found in patients who have other brain pathologies, such as plaques and tangles associated with neurodegenerative disease. The vascular changes associated with small-vessel disease include alterations in density and morphology of cerebral microvasculature, and a blood-brain barrier (BBB) breakdown with leakage of blood-borne molecules [4]. It is no surprise, therefore, that multiple epidemiological studies have shown a marked overlap among risk factors for small-vessel cerebrovascular

disease and late-onset Alzheimer's disease.

It has been reported repeatedly that *endothelial* modulation and repair is feasible by pharmacological targeting [1,2,7-13] via SR-BI receptors [13]. As the detailed review by Mahringer, et al. [14] points out, the BBB is equipped with several endocytic receptors at the luminal surface (i.e., the capillary endothelial membrane), including SR-BI. Recently, Fung, et al. [15] 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). 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

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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]. Documented similarities in lipid composition - among HDL and the biomimetic (nanoemulsion) nanocarrier particles - can partially simulate or mimic the known heterogeneity (i.e., subpopulations or subspecies) of HDL particles [1,2].

This targeted-delivery-approach, using the proposed LCM/ND lipid nanoemulsion for treating the more common (late-onset) dementias, 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), 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. This (intravenous) combination therapeutic would make it possible for various cell types, all potentially implicated in Alzheimer's disease, [1,2] to be simultaneously sought out and better reached for localized drug treatment of brain tissue *in vivo* [42,43].

LCM/ND nanoemulsion type and targeting via lipid cubic phases

Importantly, monoglyceride is the largest single-lipid fraction (by wt. %) of the powdered solid lipid surfactants used to produce the (Filmix[®]) LCM/ND nanoemulsions [42] As a group, monoglycerides exhibit different phase behaviors when they are exposed to water [44,45]. In particular, the self-assembly of varied and useful dispersed cubic phases (among other liquid-crystalline phases) depends heavily on the acyl chain length of the glycerides (primarily monoglycerides) placed in contact with water [42]. The (lyotropic or solvent-induced) cubic liquid-crystalline phases may be classified into two distinct classes: Bicontinuous cubic phases [46] and micellar or discontinuous (e.g., type Fd3m) cubic phases [47].

A noteworthy lipid cubic phase of the latter category is based upon packings of discrete inverse micellar aggregates and is formed by a variety of lipid systems [47]. Seddon, et al. [48] point out that the most frequently observed such (inverse micellar cubic) structure is a cubic phase of crystallographic space group Fd3m. Luzzati and coworkers have reported that this Fd3m cubic phase evidently requires a heterogeneous mixture of polar lipids [49,50]. 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 (recounted 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 nanopar-

ticles in such nanoemulsions [42].

In this particular targeted-delivery approach, the self-assembled "lipid particle" structure itself (upon intravenous injection of the LCM/ND nanoemulsion) is apparently successfully utilized as the "active" targeting ligand -which is directed via (adsorption of) plasma lipoproteins (including notably apoA-I) toward the appropriate receptors on the target-cell surface. These dispersed liquid-crystalline lipid particles, of the LCM/ND nanoemulsion formulation, are colloiddally stable nanocarriers which very likely represent liquid-crystalline inverse-topology nanotransporters (nanocarriers), i.e., dispersed lipid cubic phases [42].

Amyloid- β ion channel hypothesis of Alzheimer's disease

As explained in many reviews [53,54] by different investigators, it has been recognized for over two decades that disturbance of the intracellular calcium homeostasis is central to the pathophysiology of several neurodegenerative disorders. As concerns Alzheimer's disease, it is believed by many researchers that enhanced calcium load may be brought about by extracellular accumulation of amyloid- β (A β) in the brain. Such studies have laid the foundation for the popular idea that amyloid- β peptides (39-42 amino acid molecules) are, in part, toxic to brain tissue because they form aberrant ion channels in cellular membranes and thereby disrupt Ca²⁺ homeostasis in brain tissue and increase intracellular Ca²⁺ [53,54].

Historical support for the above amyloid- β ion channel hypothesis, or so-called "calcium hypothesis", has also been observed at the clinical level [55]. Namely, there is little correlation between the amounts of fibrillar (insoluble) deposit at autopsy and the clinical severity of Alzheimer's disease. In contrast, a good correlation exists between early cognitive impairment and levels of soluble forms of A β in the brain [56]. (Aggregation of A β proceeds from formation of soluble (low molecular weight) spherical oligomers toward eventually assuming a final and stable conformation as insoluble fibrils from which amyloid- β plaques are constituted.) Hence, neurotoxicity is associated with soluble aggregates (i.e., oligomers) of A β rather than with the plaques themselves [56].

As summarized by Di Scala, et al., [55] the structure of amyloid pores has been extensively studied by ultrastructural methods. In particular, one group of investigators recently applied strategies (widely used to examine the structure of membrane proteins) to study the two major A β variants, namely, A β (1-40) and A β (1-42). Under the optimized detergent micelle conditions: 1) A β (1-40) aggregated into amyloid fibrils, 2) Contrariwise, A β (1-42) assembled into oligomers that inserted into lipid bilayers as well-defined pores [57] (These amyloid pores adopted characteristics of a β -barrel arrangement). Because A β (1-42), relative to A β (1-40), has a more prominent role in Alzheimer's disease, the higher propensity of A β (1-42) to form β -barrel pore-forming oligomers is an indication of their importance in Alzheimer's disease [57] Very recently, a different research group reported very similar findings [58]. As background for their study, these latter authors point out that: -elevated A β (1-42) plasma levels have

been correlated with the progression of late-onset forms of Alzheimer's disease, A β (1-42) is significantly more neurotoxic than A β (1-40) both *in vivo* and in neuronal cell culture, and memory impairment is believed to be driven by A β (1-42) disruption of long-term (hippocampal) potentiation. In accordance with these considerations, these authors' own detailed experimental data [58] indicated that A β (1-42) assemblies in oligomeric preparations form ion channels (in membranes excised from cells of neuronal origin). In contrast, A β (1-40) oligomers, fibrils, and monomers did not form channels. Moreover, ion channel conductance results suggested that A β (1-42) oligomers, but not monomers and fibrils, formed pore structures. The authors concluded that their findings demonstrate that only A β (1-42) contains unique structural features that facilitate membrane insertion and channel formation, now aligning ion channel formation with the neurotoxic effect of A β (1-42) compared to A β (1-40) in Alzheimer's disease [58].

Brain injury, edaravone, and Alzheimer's disease

Besides the above considerations about amyloid pore formation, another important pathophysiological overlap is described, in the literature, existing between brain injury and Alzheimer's-disease brain. Wang, et al. [59] have pointed out that non-neuronal brain cells, especially astrocytes (the predominant cell type in the human brain), may exert an active role in the pathogenesis of traumatic brain injury (TBI). Activated astrocytes may contribute to increased oxidative stress and neuroinflammation following neurotrauma. Interestingly, the drug Edaravone has been used successfully, in past research, due to its neuroprotective and antioxidative effects on the brain after TBI. Wang, et al. [59] extended this research and found that, after intravenous administration (in rats), Edaravone treatment significantly decreased hippocampal neuron loss, reduced oxidative stress, and decreased neuronal programmed cell death as compared with control treatment. The protective effects of Edaravone treatment were also related to the pathology of TBI on non-neuronal cells, as Edaravone decreased both astrocyte and microglia activation following TBI. These authors conclude that the likely mechanism of Edaravone's neuroprotective effect in the rat model of TBI is via inhibiting oxidative stress, leading to a decreased inflammatory response and decreased glial activation, and thereby reducing neuronal death and improving neurological function. [59] Similarly, Itoh, et al. [60] have reported that intravenous Edaravone administration (in rats), following TBI, inhibited free radical-induced neuronal degeneration and apoptotic cell death around the damaged area. Hence, Edaravone treatment improved cerebral dysfunction following TBI, suggesting its potential as an effective clinical therapy [60].

In view of the above description of TBI, the effects of the drug Edaravone, and the pathophysiological overlap of TBI with many characteristics of Alzheimer's disease brain (cf. above), it is logical and consistent that Jiao, et al. [61] have recently reported that Edaravone can also ameliorate Alzheimer's disease-type pathologies and cognitive deficits of a mouse model of Alzheimer's disease. Specifically, besides reducing amyloid deposition and tau hyperphosphorylation,

Edaravone was found to alleviate oxidative stress and, hence, attenuates the downstream pathologies including glial activation, neuroinflammation, neuronal loss, and synaptic dysfunction, and rescues the memory deficits of the mice [61]. (Note that Edaravone is a small-molecule drug, which is known to function as a free-radical scavenger, it currently is being used clinically in Japan to treat (acute ischemic) stroke patients. [59,61]) Jiao, et al. [61] further state that their above findings suggest that Edaravone is a promising drug candidate for Alzheimer's disease by targeting multiple key pathways of the disease pathogenesis. This recommendation by Jiao, et al. of Edaravone (for treating Alzheimer's disease) fits well with the initial drug candidates suggested elsewhere, [1] based on low-molecular-weight and sufficient lipophilicity, for incorporation into the LCM/ND lipid nanoemulsion (as again proposed here) to treat Alzheimer's disease. Since the Jiao, et al. recommendation is based in part on knowledge of failed clinical trials indicating that a single target or pathway does not work on this complex disease, [61] these investigators are understandably encouraged by a drug like Edaravone which targets multiple pathways of Alzheimer's disease pathogenesis.

While the risk factors for dementia trigger widespread inflammation and oxidative stress (e.g., [62,63]), it is also true that these two processes can result in more biological effects than enhanced calcium load in brain tissue and neurodegeneration (cf. [64]). In fact, oxidative stress and inflammation each involve pathophysiological cascades associated with a wide range of pathologies and especially aging. However, these two processes/cascades are not always associated with biological damage. (For example, oxidative stress constitutes an important mechanism in many physiological processes, such as adaptations to physical exercise and cell signaling.) Yet, when oxidative stress and/or inflammation are dysregulated, their action is harmful [64,65]. (In this situation, one corresponding example [of many] occurs in Alzheimer's disease, where growing evidence links the "reactive oxygen species" (ROS)-mediated damages with molecular targets including mitochondrial dynamics/function, autophagic pathways, and proteostasis balance. [66]) Accordingly, Khalil, et al. [67] found that Alzheimer's disease impaired the interaction of HDL (and ApoA-I) with the SR-BI receptor, and their experimental results indicated that such patients had higher levels of oxidative stress [67,68]. The authors concluded that their clinical study provides evidence for the first time that the functionality of HDL is impaired in Alzheimer's disease, and that this alteration may be caused by Alzheimer's disease-associated oxidative stress and inflammation [67,68]. This conclusion is consistent with earlier work where SR-BI was identified on astrocytes and vascular smooth muscle cells in Alzheimer's disease brain, and has been demonstrated to mediate the adhesion of microglia to aggregated A β (cf. [68]). Moreover, these authors further report that SR-BI mediates perivascular macrophage response, and regulates A β -related pathology and cerebral amyloid angiopathy, in an Alzheimer's-disease mouse model [68].

Concluding Remarks

Microvascular endothelial dysfunction precedes, often by

decades, the cognitive decline associated with Alzheimer's disease. The cardiovascular risk factors for this disease trigger widespread inflammation and oxidative stress, both of which can lead to BBB disruption. Past studies (e.g., [69,70]) have shown that low-grade inflammation and endothelial dysfunction contribute to reduced information processing speed and executive functioning in an older population. These interacting processes involve pathophysiological cascades which lead to neuronal (intracellular) Ca^{2+} increase, neurodegeneration, gradual cognitive/memory decline, and eventually (late-onset) dementia. By incorporating appropriate drug(s) into biomimetic (lipid cubic phase) nanocarriers, one obtains a multitasking combination therapeutic which targets certain cell-surface scavenger receptors, mainly class B type I (i.e., SR-BI), and crosses the BBB. Such biomedical application of colloidal drug-nanocarriers can potentially be extended to the treatment of complex medical disorders like vascular dementia and (late-onset) Alzheimer's disease [69,70]. Recent reviews (e.g., [66,71,72]) of human Alzheimer's-disease studies have noted a significant elevation in inflammatory mediators in the cerebral microcirculation, crucially, inflammation has a key role in linking several types of vascular and neuronal damage (in Alzheimer's-disease brain) to cardiovascular risk factors, such as arterial stiffness and hypertension [66]. Lastly, it has been reconfirmed in the current literature that receptor-mediated endocytosis/transcytosis via lipoprotein receptors, particularly scavenger receptors including SR-BI, remains a major route for drug delivery across the blood-brain barrier, namely, recently published work has demonstrated that nanocomplexes can be readily transported into brain capillary endothelial cells (bovine and porcine) via SR-BI receptor-mediated endocytosis [7] (see also [73-75]). Accordingly, endothelial modulation and repair become feasible by pharmacological targeting [8-12,76-79] via SR-BI receptors (cf. [13]). The proposed multitasking combination therapeutic appears likely to display greater efficacy at different stages of Alzheimer's disease [41]. Moreover, the effects of the various cell types targeted (via SR-BI) may be additive, multiplicative, or otherwise synergistic.

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Conflicts of Interest

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

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