

Biobased nanoemulsions for targeted drug delivery to treat dementia and aging

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Abstract

Early changes in cerebrovascular hemodynamics and endothelial function can contribute to altered cognitive function and systemic vascular stiffness later in life. Accordingly, vascular pathology accompanies the mechanisms underlying aging. The development of chronic cerebral hypoperfusion, which leads to a lack of blood flow to the brain, is a common trait despite the various and complex pathogenic mechanisms causing these vascular alterations. Drugs or other bioactive compounds can be incorporated into a "high density lipoprotein-like" ("HDL-like") lipid nanocarrier to create a multifunctional "combination therapeutic" that can target cell-surface scavenger receptors, primarily class B type I (*i.e.*, SR-BI). The enhanced endocytosis of the nanocarrier's drug contents into various target cells, made possible by this proposed (biomimetic-nanocarrier) therapeutic vehicle, increases the likelihood that this multitasking "combination therapeutic" will be more effective at various stages of dementia.

Keywords: Cognitive impairment, dementia, lipid nanoparticles, nanocarrier, nanoemulsion, scavenger receptors, targeted delivery

Introduction

Emerging evidence from numerous animal models indicates that in the development of Alzheimer's disease, cerebrovascular dysfunction frequently precedes both cognitive decline and the start of neurodegenerative alterations [1-4]. In light of this fact, mixed pathology, which displays both Alzheimer's disease and vascular abnormalities has been identified as the most frequent cause of clinical dementia in elderly people. In such mixed dementias, protein tau tangles (in neurons) and [extracellular amyloid-beta (A β) protein] plaques are accompanied by vascular changes [1, 5]. Published data from experiments using transgenic mice and observations in the clinic by MRI scans or at autopsy by neuropathological evaluation provides evidence that tau pathological changes (in neurons) can impact brain endothelial-cell biology, which in turn

induces changes in the brain's microvasculature (including abnormal spiraling morphologies, reduced blood vessel diameters, and increased overall blood vessel density in the cerebral cortex), separate from the effects of senile plaques on vasculature [1]. In comparison, senile plaques (often regarded as the classic lesions of Alzheimer's disease) are extracellular deposits mostly composed of insoluble aggregates of A β protein fibrils and are infiltrated by reactive microglia and astrocytes. A β fibrils cause the production of neurotoxins like reactive oxygen species, by microglia, and have a damaging effect on neurons. Microglia have been implicated as scavenging cells that are responsible for clearing A β fibril deposits of Alzheimer's disease. Accordingly, microglial scavenger receptors have already been described as novel targets for therapeutic interventions in Alzheimer's disease [5].

Targeted nanotherapy for late-onset dementia

A breakdown of the blood-brain barrier (BBB) resulting from structural changes to the cerebral microvasculature are examples of the vascular abnormalities connected to small-vessel illness. Therefore, it is not unexpected that numerous epidemiological studies have found a significant overlap between the risk factors for late-onset Alzheimer's

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disease and small-vessel cerebrovascular illness [3].

As specifically regards drug targeting, it has been documented repeatedly that cell-surface scavenger receptors, primarily class B type I (*i.e.*, SR-BI), allow for the pharmacological targeting [3, 6-13] of endothelial regulation and/or repair [13-15]. Moreover, the earlier reviewed [3, 6] “lipid-coated microbubble/nanoparticle-derived (LCM/ND)” nanoemulsion can conceivably function as a targeted, apoA-I-based (SR-BI mediated) therapeutic agent for common (late-onset) dementias. Specifically, this expectation is based on the fact that SR-BI has already been identified as a major receptor for high-density lipoprotein or HDL [with their major apolipoprotein (apo) A-I] [16-18]. Such LCM/ND nanoemulsions may well be able to partially imitate the heterogeneity of HDL particles due to similarities in the lipid content, which has been documented previously between HDL and these nanoemulsion (drug-carrier) particles [3, 5, 6].

The ongoing discoveries of cerebrovascular pathology [5, 6, 19-29] and an apparent endothelium dysfunction [3, 17, 18, 25, 30-36] in both Alzheimer’s disease and its major risk factors [5, 6, 29-41] provide additional impetus for this particular targeted delivery approach, which uses the proposed LCM/ND lipid nanoemulsion for treating the more prevalent (late-onset) dementias. Adding certain drug molecules to the LCM/ND lipid nanoemulsion type, which are known to be an effective drug carrier [3, 42, 43], would make the following possible: multiple cell types, which are often implicated in Alzheimer’s disease [6], can be simultaneously nanotargeted via cell-surface SR-BI [42, 43].

Biobased lipid nanoemulsion: size distribution and safety studies

Physical characterization of the actual size distribution of the LCM/ND lipid nanoemulsion particles (to be used for treating late-onset dementias) has already been extensively explored [3, 5]. In these studies, the scattered light was measured using five distinct optical particle counters (different models) that were all produced by Particle Measuring Systems (Boulder, CO). Given that all of the data were essentially identical, it can be concluded that the LCM/ND lipid nanoemulsion did not vary in particle size under the various concentration settings. Over a period of time (at least one month), there was no discernible change in the size distribution [3]. When measured with optical particle counters, this nanoemulsion type contains close to 10 billion particles ($< 0.1 \mu\text{m}$) per milliliter. Ninety percent or more of the nanoemulsion particles had diameters of less than $0.2 \mu\text{m}$.

The risk of embolism is negligible because neither *in vitro* nor *in vivo* investigations have demonstrated that the LCM/ND lipid nanoemulsion particles aggregate or coalesce into any “superparticle or microbubble-like” structure more than $5 \mu\text{m}$ [3]. The acute intravenous LD₅₀ for two animal species (rabbits and dogs) was determined to be greater than 4.8 mL/kg. Furthermore, no overt toxicity

or mortalities were observed at a dose of 4.8 mL/kg [3]. Using the same (isotonic) lipid nanoemulsion agent, it was determined in additional animal (range-finding subchronic intravenous) toxicology studies [3] that the following toxicology outcomes were seen at intravenous doses of 0.14 mL/kg given three times a week for six weeks (in rats) and 0.48 mL/kg given three times a week for three months (in rabbits): the blood chemistry, liver functions, hematology, and coagulation profile did not change adversely, and neither did the the histology of the adrenals, bladder, brain, heart, kidney, liver, lungs, marrow, pituitary, spleen, testes, thyroid, and ureters [3].

Biobased LCM/ND nanoemulsion type consists of lipid cubic phases

A noteworthy lipid cubic phase (*i.e.*, Fd3m) is created by a variety of lipid mixtures, when dispersed in water, and is based on packings of discrete inverse micellar aggregates [3, 44-50]. The LCM/ND lipid nanoemulsion (for intended use in treating late-onset dementias) is particularly pertinent to the dispersed Fd3m cubic phase because both of these lipid structures frequently contain cholesterol and three types of (saturated) glycerides, namely tri-, di-, and monoglycerides [51, 52].

Given that these nanoemulsion particles are expected to adsorb apoA-I (see Sect. 2, paragr. 2), it is plausible that they will be effective at their intended targets [3]. Again, when the aforementioned information is combined with the known heterogeneity of HDL particles and the well-documented multiligand capability of SR-BI, this receptor emerges as the top candidate (of all lipoprotein receptors) for major involvement in the enhanced endocytosis of LCM/ND nanoemulsion particles into, and transcytosis across, the endothelial cell layer of the BBB [3].

Concluding remarks

The use of lipid nanocarriers, such as nanoemulsions, to circumvent the barriers that prevent medication transport across the BBB has very recently brought these materials back into the spotlight. As reviewed by Ilic *et al.* (in 2023) [53], among the various strategies studied to overcome the low-water-solubility of various central nervous system (CNS)-active drugs as well as surmount the obstacles in BBB crossing, lipid-based nanoparticles have been recognized as an excellent platform for brain targeting. Conventional dosage forms are associated with a lack of targetability, often resulting in low concentrations within the brain and, hence, a suboptimal therapeutic outcome [53]. In contrast, the “HDL-like” lipid nanoemulsion type (also referred to as “LCM/ND nanoemulsions” [3, 5, 6]) displays a natural tendency to target SR-BI receptors (*cf.* above) and, therefore, would likely act to increase the total concentration of (targeted) drug in the brain parenchyma due to this nanocarrier’s direct interaction with SR-BI receptors on the BBB. Additionally, this particular

targeting behavior can facilitate the drug's enhanced endocytosis into various target cells [3, 5, 6, 54-56], which in turn raises the possibility this "HDL-like" nanoemulsion will be more effective at different stages of late-onset dementia (cf. [28]) when used as a multitasking (drug-carrying) therapeutic vehicle.

In 2022 and 2023, several groups of investigators have published arguments/reviews which support using such a multi-factorial approach for the reversal of cognitive decline in late-onset dementia and mild cognitive impairment: for example, Tarozzi and Angeloni [57] stress that neurological disorders are characterized by a multi-factorial nature that requires treatment with molecules/agents capable of targeting multiple pathogenic events. In addition, Powers and Sahoo [58] point out that SR-BI has been implicated in modulating diabetes risk; this fact is noteworthy since dyslipidemia, diabetes, and atherosclerotic cardiovascular disease are commonly comorbid conditions and are all risk factors for late-onset dementia with aging [58, 59]. Lastly, as specifically concerns late-onset Alzheimer's disease and mild cognitive impairment, Rao *et al.* [60] report that studies have demonstrated that a multi-therapeutic approach is needed to improve/alleviate metabolic abnormalities and Alzheimer's disease-associated cognitive decline. A single-drug approach may delay the progression of memory loss but to date has not prevented or reversed it. Thus, a multi-therapeutic program that simultaneously targets multiple factors underlying the Alzheimer's disease-network may be more effective than a mono-therapeutic approach. Accordingly, this group of investigators further point out that several recent clinical trials and observational studies showed superior outcomes when a multitude of potential contributing pathogenic pathways was addressed simultaneously [60].

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