Mini-Review

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 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

1. 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 [5]. The senile plaques (or characteristic lesions of Alzheimer's disease) are extracellular deposits mostly composed of insoluble aggregates of amyloid-β protein (Aβ) fibrils and are infiltrated by reactive microglia and astrocytes. Aβ 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 Aβ 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].

2. 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 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 [3,5,6], between HDL and these nanoemulsion (drug-carrier) particles.

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 is 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].

3. Biobased Lipid Nanoemulsion: Size Distribution and Safety Studies

Physical characterization of the actual size distribution of the LCM/ND lipid nanoemulsion particles has already been extensively explored [3]. 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 μm) per ml. 90% or more of the nanoemulsion particles had diameters of less than 0.2 μm.

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 μm [3]. The acute intravenous LD_{50} for both species 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].

4. 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 [3,44,45,47-50]. The LCM/ND lipid nanoemulsion 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].

5. 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. Particularly, 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 comcentration 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 [3,5,6,53-

55], which in turn raises the possibility this "HDL-like" nanoemulsion will be more effective at different stages of dementia (cf. [28]) when used as a multitasking (drug-carrying) therapeutic vehicle.

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