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Perspective

Vascular Risks, Aging, and Late-Onset Dementia: Overlapping Etiologies Point to 'Scavenger Receptor'-Mediated Therapeutics

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Abstract

Early changes in systemic vascular stiffness and endothelial function can contribute to altered cerebrovascular hemodynamics and impaired cognitive function; additionally, these vascular changes point to potential targets for prevention and treatment strategies in people with mild cognitive impairment. Although the pathogenic mechanisms underlying these vascular changes are heterogeneous and complex, one common feature is the development of cerebral blood flow (CBF) dysregulation, resulting in chronic cerebral hypoperfusion (CCH) and subsequently an insufficient blood supply to the brain. However, the incorporation of drugs, or other bioactive molecules, into specifically a "high density lipoprotein-like" ("HDL-like") lipid nanocarrier can result in the production of a multitasking "combination therapeutic" – capable of targeting cell-surface scavenger receptors (mainly SR-BI). Such targeting behavior of this proposed (biomimetic-nanocarrier) therapeutic vehicle can facilitate the nanocarrier's enhanced endocytosis into various target cells which, in turn, increases the likelihood that this multitasking "combination therapeutic" provides some enhanced efficacy at different stages of dementia.

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

1. Introduction

Vascular pathology accompanies the mechanisms underlying aging, Alzheimer's disease, and vascular dementia, all of which serves to indicate cerebrovascular involvement in these pathophysiological processes [1-3]. During the development of the above pathophysiological mechanisms, chronic vascular inflammation further exacerbates vascular dysfunction [2-7]. Early changes in systemic vascular stiffness and endothelial function can contribute to altered cerebrovascular hemodynamics and impaired cognitive function, and point to potential targets for prevention and treatment strategies in people with mild cognitive impairment [1, 3, 5-7]. In summary, vascular dysfunction affects brain structure and function, and leads to cognitive decline and eventually dementia [8].

2. Pulsatile Load to the Brain

The vascular system is a key target of aging, as different researchers have previously explained (e.g., [2, 5-15]). Specifically, the elastic fibers shatter and are then replaced by stiffer collagen, which results in arterial stiffening and the onset of aging in humans. The huge elastic arteries are subjected to a lifelong pulsatile pressure. The amplitude of the pulse pressure wave is subsequently increased due to arterial stiffness, and this pressure wave further penetrates the delicate microcirculation of low-resistance, high-flow organs like the brain. Memory loss and the development of dementia, including Alzheimer's disease, are considered to be promoted by such vascular etiologies [3, 12, 13, 16-20].

More recently, King et al. [6] have further evaluated multiple cardiovascular risk factors to cognitive function; their study concentrates on a variety of latent vascular risk factors, all having independent contributions to cognition. These authors' overall conclusion was that higher pulse pressure is clearly associated with cognitive decline, and the effect was stronger in older adults. Accordingly, these authors assert that controlling pulse pressure may help to preserve cognition, particularly in older adults [6].

Moreover, elevated pulse pressure has a direct effect on cerebral endothelial cells, causing their dysregulation [7]. Specifically, pathological stretch causes increased production of reactive oxygen species (ROS) and inflammatory cytokines by endothelial cells. The increased ROS promotes oxidative tissue damage, while the inflammatory cytokines further activate inflammation in the cerebral microvasculature. Nonetheless, pulse-pressure-induced endothelial dysfunction alone may be enough to cause wide-spread BBB and brain tissue degeneration even in the absence of brain microbleeds. The reviewers (of these cerebral-endothelial studies) draw the conclusion that this central pathogenic mechanism of pulse-pressure-induced cognitive decline into dementia may provide new insights into past failures of dementia treatment strategies, as well as open up new avenues of clinical investigation [7].

3. Parenteral Lipid-Based Nanoparticles for Late-Onset Dementia

In the quest for a more effective therapeutic strategy for treating dementia, an especially intriguing research target for medication delivery is apolipoprotein A-I (or ApoA-I). Specifically, ApoA-I has been used in a number of published (in vivo) drug-delivery investigations (see [21, 22] for reviews). Cell-surface scavenger receptors (primarily SR-BI) have been identified as the primary receptor candidate in relation to the pertinent class of targeting vehicle (i.e., a biobased lipid nanocarrier) utilized. The enhanced endocytosis of "stable" colloidal-lipid nanocarrier particles into a variety of target cells can be facilitated via this major receptor in association with its main apolipoprotein (i.e., via ApoA-I-assisted endocytosis by SR-BI action).

By way of defining "scavenger receptor" in molecular-biology terms, this category of cell-surface receptor falls within a division referred to as "multiligand lipoprotein receptors" [23]. Most other mammalian receptors, which are similarly known to mediate endocytosis, exhibit high binding affinity and narrow specificity. However, the ligand-binding properties of the multiligand lipoprotein receptors do not conform to a narrow binding specificity. Such cell-surface receptors, and in particular many types of scavenger receptors, bind with high affinity to both lipoprotein and *non*lipoprotein ligands and participate in a wide variety of biological processes. The notable similarity of lipid composition between various blood lipoproteins and related lipid nanocarriers [see below] strongly suggests that certain lipid-nanocarrier (nanoemulsion) particles could resemble "modified" lipoprotein particles (in the circulation) and, hence, act as a ligand for cell-surface scavenger receptors [23]. (Since scavenger receptors represent a diverse category (i.e., superfamily) of cell-surface receptors, this receptor category is organized into many different classes (e.g., A-J) usually based on their structural properties. For example, class B scavenger receptors have two transmembrane domains linked with an extracellular loop. A major class B member is the SR-BI (cell-surface) receptor, which is quite widespread (including in arterial wall); accordingly, mutations in SR-BI are known to lead to an increase in atherosclerosis [23].)

A multifunctional "combined treatment" can be created by adding medications, or other bioactive compounds, to the aforementioned "high density lipoprotein-like" ("HDL-like") lipid nanocarrier type [3]. Targeting cell-surface SR-BI should be possible with this therapeutic nanocarrier vehicle. As a result, the therapeutic nanocarrier (nanoemulsion) that is produced is expected to be "multitasking" or able to infiltrate different target cells that carry the important class B of cell-surface scavenger receptors (and in particular SR-BI) [3, 21-23]. This proposed therapeutic's targeting behavior seems likely to offer improved efficacy at various stages of dementia ([24-27]; cf. [28]).

4. Biobased LCM/ND-Lipid Nanoemulsion Safety Studies

Regarding safety, neither in vitro nor in vivo studies have yielded any evidence that the LCM/ND lipid nanoemulsion particles (i.e., the "HDL-like" nanoemulsion particles) aggregate or coalesce into any "superparticle or microbubble-like" structure greater than 5 µm, hence the danger of embolism is minimal [23]. Additionally, this (isotonic) LCM/ND nanoemulsion agent underwent acute intravenous toxicity tests in rabbits and dogs at an independent GLP contractor. [Note that the abbreviation "GLP" denotes that the studies carried out by the aforementioned contractor comply with the Good Laboratory Practices Regulations as stated in 21 CFR Part 58, for submission to the U.S. Food and Drg Administration in support of an Investigational New Drug Application (INDA). As

a result, it is implied by this remark that the GLP guidelines will be followed exactly.] Both species' acute intravenous LD_{50} was found to be higher than 4.8 ml/kg. Additionally, at a dosage of 4.8 ml/kg, no overt toxicity or mortalities were seen [23].

Using the same (isotonic) lipid nanoemulsion agent, it was found in other animal (range-finding subchronic intravenous) toxicology studies that the following toxicology outcomes were seen in rats and rabbits at intravenous doses of 0.14 ml/kg given three times a week for six weeks and 0.48 ml/kg given three times a week for three months: The histology of the adrenals, bladder, brain, heart, kidney, liver, lungs, marrow, pituitary, spleen, testes, thyroid, and ureters did not alter in an unfavorable way, nor did the serum chemistry, liver functions, hematology, or coagulation profile [23].

5. Concluding Remarks

The growing availability of innovative pharmaceutical formulations allowing improved brain targeting ability (and controlled drug release) has thrust the lipid nanocarriers, including nanoemulsions, back to the limelight for overcoming the factors that impede drug delivery through the BBB [3, 29-31]. The key benefit of drug loading into the lipid nanoparticles for brain delivery is the capability to improve the pharmacokinetic profile -- providing higher concentrations, in the brain parenchyma, of drugs that formerly exhibited poor brain disposition [32]. Moreover, the lipid-based nanoparticles described earlier (i.e., the "HDL-like" lipid nanoemulsion type, also known as "LCM/ND nanoemulsions" [3, 20-22]) displayed a natural tendency to target SR-BI receptors (cf. above) and, hence, would serve to increase the total concentration of (targeted) drug in the brain parenchyma – owing to the direct interaction of these lipid-nanocarrier particles with SR-BI receptors on the BBB. Further, such targeting behavior of this proposed (biomimetic-nanocarrier) therapeutic vehicle can facilitate its enhanced endocytosis into various target cells [3, 21-23] which, in turn, increases the likelihood that this multitasking (drug-carrying) therapeutic vehicle provides somewhat enhanced efficacy at different stages of dementia (cf. [28]).

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Competing Interests

Beyond the above employment, the author declares no potential conflicts of interest.

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