

Treating early dementia: Drug targeting and circumventing the blood-brain barrier

Joseph S. D'Arrigo*

Cavitation-Control Technology Inc., Farmington, CT 06032, USA

Abstract

Over past decades, a frequent co-morbidity of cerebrovascular pathology and Alzheimer's disease pathology has been observed. Accordingly, much evidence has been reported which indicates that microvascular endothelial dysfunction, due to cerebrovascular risk factors (e.g., atherosclerosis, diabetes, obesity, hypertension, smoking, aging), precedes cognitive decline in Alzheimer's disease and contributes to its pathogenesis. These findings indicate that preservation of healthy cerebrovascular endothelium can be an important therapeutic target. Versatile small-molecule drug(s) targeting multiple pathways of Alzheimer's disease pathogenesis are known. By incorporating such drug(s) into the targeted "lipid-coated microbubble/nanoparticle-derived" (LCM/ND) lipid nanoemulsion type, one obtains a multitasking combination therapeutic for translational medicine. This multitasking therapeutic targets certain cell-surface scavenger receptors, mainly class B type I (i.e., SR-BI), making it possible for various Alzheimer's-related cell types to be simultaneously searched out for localized drug treatment in vivo. Besides targeting cell-surface SR-BI, the proposed LCM/ND-nanoemulsion combination therapeutic(s) include a characteristic lipid-coated microbubble (LCM) subpopulation (i.e., a stable LCM suspension); such LCM would facilitate accomplishing transcranial sonoporation (if additionally, desired for the Alzheimer's patient) and assist in advancing sonoporation to the clinic.

Introduction

The fundamental involvement of the cerebrovasculature in the pathogenesis of common dementias, widely reported in the biomedical literature, has recently been reviewed (e.g. [1,2]). In fact, vascular brain lesions are very common in people over 70 years old, and a large proportion of dementia cases may be attributable to cerebrovascular disease. Small-vessel disease is commonly found in patients who have other brain pathologies, such as the plaques and tangles associated with neurodegenerative disease; small-vessel disease also increases the risk of Alzheimer's disease. 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 [3-9]. On a worldwide basis, 36 million people had dementia in 2010; of these dementia patients, 60%–80% have Alzheimer's disease [4,10,11].

Central role of endothelial dysfunction

It has been reported that nanocomplexes can be readily transported into brain capillary *endothelial* cells (bovine and porcine) via SR-BI receptor-mediated endocytosis [12-15]. Accordingly, *endothelial* modulation and repair become feasible by pharmacological targeting [16-26] via SR-BI receptors (cf. [25]). As the detailed review by Mahringer et al. [27] points out, the blood-brain barrier (BBB) is equipped with several endocytic receptors at the luminal surface (i.e., the capillary endothelial membrane), including the type BI scavenger receptor (SR-BI). These authors explain that, after i.v. injection, surfactant/lipid-coated nanoparticles apparently bind to apolipoproteins (for example, apoA-I in blood plasma) and are subsequently recognized by the corresponding lipoprotein receptors, namely (in the presence of apoA-I), SR-BI type scavenger receptors at the BBB [1].

Furthermore, very recently published experimental work (in human-endothelial-cell monolayer cultures as well as in three-dimensional tissue-engineered human vessels) has demonstrated in detail [28] that HDL, acting via scavenger receptors (class B type I, i.e., SR-BI), blocks β -amyloid uptake into endothelial cells – in experimental monolayers as well as, the authors argue, in the human cerebrovascular endothelium [1,2]. These authors also point out that SR-BI is the principal HDL receptor on (human brain microvascular) endothelial cells and activates several HDL-signaling pathways (in addition to mediating selective cholesterol uptake) upon HDL docking. The authors observed that inhibiting SR-BI binding with a specific blocking antibody *abolished* the ability of HDL to suppress " β -amyloid-induced" monocyte adhesion to (human microvascular) endothelial cells [28]. It is worth noting that such blood-borne human monocytes (with their high expression of CLA-1 (the human SR-BI ortholog [29]) and/or SR-BI, as well as their ability to differentiate into macrophages to elicit an immune response locally) have recently been reported [30] (cf. [31]) to reduce Alzheimer's-like pathology and associated cognitive impairments in transgenic mice having Alzheimer's-like symptoms (refer [1] for a review).

Fung et al. [32] separately report that SR-BI mediates the uptake and transcytosis of HDL in brain microvascular endothelial cells (i.e., across the blood-brain barrier). These investigators further argue that manipulation of HDL transcytosis across the BBB to increase

Correspondence to: Joseph S. D'Arrigo, Cavitation-Control Technology Inc., Farmington, CT 06032, USA, E-mail: cavcon@ntplx.net

Key words: Alzheimer's disease; drug targeting; nanoemulsion; SR-BI; scavenger receptors; transcranial sonoporation

Received: January 2, 2018; **Accepted:** February 25, 2018; **Published:** February 28, 2018

delivery of plasma apolipoprotein A-I (apoA-I) may, in turn, facilitate increasing the transport of “HDL-like synthetic particles” containing therapeutic drug across the BBB to treat neurodegenerative disorders such as Alzheimer’s disease [32]. Therefore, the recently reviewed [1,2] “lipid-coated microbubble/nanoparticle-derived” (LCM/ND) nanoemulsion (refer below) can arguably serve as a targeted, apoA-I-based, (SR-BI mediated) therapeutic agent for Alzheimer’s disease and vascular dementia [28,33-35] (cf. [36-42]).

Targeted drug treatment for early dementia

This targeted-drug-delivery therapeutic 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 [43-53] and an apparent *endothelium*-dysfunction [33-41,49,54-60] in both Alzheimer’s disease and its major risk factors [53-72]. By incorporating drug candidates (such as Ederavone, DHA, or antibody therapeutics) into the LCM/ND lipid nanoemulsion type, known to be a successful drug carrier [73,74], one is likely to obtain a multitasking combination therapeutic for translational medicine. This therapeutic agent would target cell-surface SR-BI making it possible for various (above-described) cell types, all potentially implicated in Alzheimer’s disease (refer [1,2] for reviews; cf. [71,72]), to be simultaneously sought out and better reached for localized drug treatment of brain tissue *in vivo*. It is also possible that targeting multiple cellular sites, within the multiple-cell-type network underlying Alzheimer’s disease pathophysiology, may be successful even when each (SR-BI bearing) cell type targeted is affected in a relatively modest way; that is to say, the effects on the various cell types targeted may be additive, multiplicative, or otherwise synergistic [26].

With regard to receptor-mediated membrane transport across the BBB, brain microvascular endothelial cells are believed to control iron uptake and efflux, under the direct guidance of neighboring astrocytes [75,76]. Detailed evidence has been reported recently [75] showing that human brain microvascular endothelial cells, which constitute most of the blood-brain barrier, receive brain-iron status information via paracrine signals from ensheathing astrocytes. Lastly, aging, obesity, and smoking are significant determinants of brain iron accumulation in human subjects [77] and all have been long-associated with Alzheimer’s disease incidence [25,50-52,54,55,65,78-80].

Note that the above-mentioned (cf. preceding paragraph and Abstract) long association of specifically both obesity and diabetes with Alzheimer’s disease incidence has also renewed attention to the brain’s main facilitative glucose transporter protein, GLUT-1, involvement in and probable contribution to neurodegenerative diseases [81-83]. More than two decades ago it was already recognized that normal human-brain capillary endothelium has a high density of GLUT-1, whereas the cerebral microvessels in subjects with Alzheimer’s disease showed a markedly decreased GLUT-1 density when compared with age-matched controls [84,85]. More recently, Winkler et al. [86] demonstrated that GLUT-1 deficiency in cerebral endothelium (but not in astrocytes), in a mouse model of Alzheimer’s disease, initiates blood-brain barrier breakdown. These authors observed from their detailed experiments that reduced GLUT-1 expression (at the BBB) worsens Alzheimer’s disease cerebrovascular degeneration, neuropathology, and cognitive function – suggesting that (cerebral endothelial) GLUT-1 may represent a therapeutic target for Alzheimer’s disease vasculo-neuronal dysfunction and degeneration [86]. Further, other investigators [87] (cf. [88]) have recently provided evidence for brain glucose dysregulation as a critical event in Alzheimer’s disease pathogenesis that closely reflects both the severity of Alzheimer’s disease pathology and the expression

of symptoms. Moreover, abnormalities in brain glucose homeostasis may begin several years before the onset of clinical symptoms [87].

In summary, endothelial cells are the main component of the BBB, which is seriously disrupted in various neurological pathologies – including many neurodegenerative disorders [89-91]. An early BBB breakdown and/or dysfunction has been documented [92] in Alzheimer’s disease before dementia, neurodegeneration, and/or brain atrophy occur, and investigators have reported that targeting the BBB can influence the course of neurological disorder [92]. Hence, vascular-targeted therapies become plausible for the prevention and treatment of common dementias [4,36,89,93-95]. In respect to vascular tone, vasodilators (nitric oxide, acetylcholine) are repressed while vasoconstrictor (endothelin-1) is enhanced, thus contributing to endothelial dysfunction in Alzheimer’s disease [90,96]. Also, β -amyloid can induce apoptosis and/or necrosis of brain endothelial cells. Presence of β -amyloid, as well as tau protein oligomers, leads to accumulation of inflammatory molecules in microvessels – which further fosters endothelial dysfunction [90,97-99]. Other component cell types of the neurovascular unit are affected as well in Alzheimer’s disease [90]. For example, deposition and aggregation of β -amyloid within vascular smooth muscle cells leads to inflammation, oxidative stress, impaired vasorelaxation, and disruption of BBB integrity. At the same time, midlife vascular-risk factors such as hypertension, cardiovascular disease, diabetes, dyslipidemia, and obesity all increase the relative risk for Alzheimer’s disease [89,100-103]. These comorbidities are all characterized by low and/or dysfunctional HDL, which itself is an Alzheimer’s risk factor. Namely, (in addition to long-published lipid transport,) HDL regulates vascular health via modulating vasorelaxation, inflammation, and oxidative stress as well as promoting endothelial cell survival and integrity [36,102,104]. 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 earlier-described LCM/ND nanoemulsion [1,2], this multitasking lipid nanoemulsion can arguably serve as a targeted, apoA-I-based, (SR-BI mediated) therapeutic agent for common (late-onset) dementias (cf. [28,33,35,37-42]).

Promising developments regarding supplementary neurotherapy using targeted sonoporation

A completely separate and additional advantage of such LCM/ND (drug-delivery) nanoemulsion(s) stems from the characteristic lipid-coated microbubble (LCM) subpopulation existing in this nanoemulsion type [1,2]. This characteristic LCM subpopulation would now be available to substantially reduce the acoustic power levels needed for accomplishing endothelial sonoporation (refer [1] for a review), if additionally desired for further targeted (transcranial) neurotherapy (cf. [105-120]) of the Alzheimer’s patient. Over the past decade, neuroscientists have been exploring the use of ultrasound in combination with preformed (intravenous) microbubbles to temporarily open the BBB [1,2,121-126], allowing drugs or the immune system to target brain tumors or Alzheimer’s brain plaque *in vivo* effectively, repeatedly, and safely [127-133] in animals up to primates [127,134] and even in humans [134]. It is believed that (non-thermal focused) ultrasound pulses cause the (intravenously injected) preformed microbubbles to expand and contract (with acoustic pressure rarefaction and compression, respectively) against the BBB structure, thereby loosening the tight junctions [135,136] between endothelial cells which form the structural core of the BBB. Recently, this research approach was employed by Leinenga and Gotz [135] who utilized focused (transcranial) ultrasound coupled with intravenous

injection of lipid-encased microbubbles. These authors concluded that their findings suggest that microbubble-assisted ultrasound irradiation is useful for removing β -amyloid plaques in the mouse brain without causing observable damage, and should be explored further as a noninvasive method with potential as a (non-pharmacological) therapeutic approach for Alzheimer's disease [1,2,135,136].

It is worth noting that the above-proposed mechanism of plaque-burden reduction, by sonoporation (i.e., "loosening the tight junctions of the cells forming the BBB" [135,136]), might carry an additional effect. (Microbubble-assisted) sonoporation not only facilitates localized delivery of drugs and/or "activated" immune cells to target Alzheimer's brain plaque in vivo [135], but *also facilitates (passive-transport?) reduction of β -amyloid plaque burden from brain tissue in a mouse model of Alzheimer's disease [137]. Specifically, this same mechanism might also function to counteract characteristic decreased "brain clearance" of neurotoxic β -amyloid "monomer" [137]– which has been described as a central event in the pathogenesis of Alzheimer's disease (cf. [1,2,138]). Namely, the recent biomolecular study by Keaney et al. reports that controlled modulation of tight junction components at the BBB can enhance the clearance (into the plasma) of soluble human β -amyloid monomers from the brain in a murine model of Alzheimer's disease [137].*

The actual cellular and biophysical mechanism(s) of the reversible BBB "opening" process from sonoporation, when employing focused transcranial ultrasound coupled with injected preformed microbubbles, has been described further in other published studies over the last several years [1,139-145]. For example, the preformed microbubbles concentrate the ultrasound effects to the microvasculature, greatly reducing the ultrasound exposure levels needed to produce bioeffects; thus, with injected microbubbles one can apply focused ultrasound transcranially without significant skull heating [139,140]. Moreover, other investigators have recently pointed out [144,145] that microbubble-mediated sonoporation is also believed to actually enhance local drug uptake across the cell membrane itself (e.g., of endothelial cells). Hence, CNS-endothelial sonoporation offers a range of neurotherapeutic options that can include either: (1) inducing/facilitating endocytosis (and, in turn, transcytosis); (2) transient cellular-pore generation; and/or (3) widening of tight junctions between endothelial cells of the cerebral microvasculature. These varied neurotherapeutic options are important and useful, for both the researcher and the clinician, because the BBB disruption associated with various neurological disorders (e.g., Alzheimer's disease, vascular dementia) has not been characterized in full detail cellularly [1]. In the foreseeable future, taking full advantage of this ongoing, noninvasive, and targeted use of preformed (such as LCM/ND nanoemulsion-based) microbubbles with sonoporation, while optimizing drug-delivery efficiency (through judicious choice of acoustic parameters [129,133]) and minimizing side effects, may assist in advancing sonoporation to the clinic (cf. [1,144-150]).

In this neurotherapeutic approach to the clinic, both the researcher and the clinician are still faced with the challenge of translation from rodent to large animal or man – yet significant progress on minimizing potential side effects, in large-animal transcranial-ultrasound work, has already been reported in the literature (refer [1] for a review). For example, an earlier study by Xie et al. [140] in pigs has demonstrated that intravenous lipid-encapsulated microbubbles, combined with transtemporal-applied 1-MHz ultrasound, can transiently and reversibly increase BBB permeability in a large-animal model. These authors explain that their study achieved an alteration in BBB permeability with lower peak negative pressures and

lower doses of ultrasound contrast (i.e., intravenous, film-stabilized microbubbles) in a large-animal model and, thus, transient alterations in BBB permeability sufficient for enhanced drug delivery and without unwanted bioeffects (hemorrhage, necrosis, apoptosis) [140] in human subjects appear increasingly feasible (refer [1,2] for added discussion).

Conclusion

The proposed multitasking combination therapeutic may also display greater efficacy at different stages of Alzheimer's disease (cf. [72]); as a result, this multitasking (drug-delivery) therapeutic could represent a promising way to treat, delay, or even prevent the disease in the future [1,2]. In addition, preformed (lipid-stabilized) microbubbles, as contained within this combination therapeutic [1,73], are known to substantially reduce the acoustic power levels needed for accomplishing temporary noninvasive (transcranial) ultrasound treatment [1,105-109,111-113,130,151-156], or sonoporation [1,110,114-119,157-159], if additionally desired for the Alzheimer's patient.

Funding Sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. J.S.D. is an employee of Cav-Con Inc.

Conflicts of Interest

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

Acknowledgments

Many thanks are due to numerous past (basic-research and clinical) colleagues for cultivating important collaboration, over the past few decades, on some of the published investigations described in this review and/or their generous help with various experimental measurements.

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