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Short Review

Arterial Elasticity: Linking of Cardiovascular Risks, Pulse Pressure, Dementia, Aging, and Drug Targeting

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Abstract

Cerebrovascular atherosclerosis, and several other cardiovascular (or "inflamm-aging" type) diseases, are more frequent and advanced in subjects with Alzheimer's disease compared with normal aging. In addition, the observed pathogenic link to dementia (and its associated cerebral microvascular damage) is readily explained by alterations of arterial elasticity. A therapeutic strategy to delay dementia could be based upon localized drug delivery, using lipid nanocarriers (i.e., biobased nanoemulsion technology), targeted toward a major serum amyloid A (SAA) receptor involved in certain proinflammatory, SAA-mediated, cell signaling events. Moreover, by incorporating drug molecules into such lipid nanocarriers, one can obtain a "combination therapeutic" capable of targeting simultaneously (via cell-surface scavenger receptors) a variety of cell types, each potentially implicated in Alzheimer's disease and/or dementia, for focused drug delivery in vivo.

Keywords

Cognitive decline; dementia; drug delivery; nanocarrier; nanoemulsion; neuroinflammation; receptor nanotargeting

1. Introduction

Increased arterial stiffness is known to be involved with the decline of cognitive function with aging [1-3], and has become an important risk marker for poor brain aging and dementia [4-6]. Arterial stiffness is an independent risk factor for cardiovascular disease as well as Alzheimer's disease [7], and several "inflamm-aging" disease processes may overlap and thereby contribute to the synergism between arterial stiffness and Alzheimer's disease. As discussed by Hendrickx et al. [7], increasing epidemiological studies have reported an independent convergence between cardiovascular disease and Alzheimer's disease, which these authors believe indicates a mechanistic overlap between the two pathologies. These authors further argue that chronic low-grade inflammation is the mechanistic convergence, between cardiovascular disease and Alzheimer's disease, given its major contribution in both pathologies [7]. Hence, the aim of this short review (cf. title) is to further expand upon the proposed link between arterial stiffness and several pathogenic processes (cardiovascular risks, pulse pressure, dementia, and aging) – as well as to mention implications for therapeutic drug targeting (cf. Sections 4 & 5 below).

2. Aortic Stiffness, and Excessive Pulsatile Load/Pulse Pressure to the Brain

Similar to the age-dependent stiffening of large conductance arteries [3, 8] (e.g., the carotids), aortic stiffness is closely linked with cardiovascular disease and it is also a risk factor for cognitive impairment and dementia [1, 9, 10]. As explained by Liu et al. [1], with advancing age in humans (and in animal models [8]) the elastic fibers in the aortic vessel wall are gradually reduced and replaced by collagen fibers, which causes aortic stiffness. This loss of elasticity and recoil in the aorta, in turn, transmits excessive and damaging pulsatile load to the body organs. As particularly concerns the brain, the increased blood flow and pressure pulsatility can lead to microvascular damage due to the high-flow, low-resistance nature of the cerebrovascular system [1]. Beyond midlife, aortic stiffness increases rapidly and the excessive pulsatile load causes both cerebral microvascular damage and remodeling of the brain. Cooper and Mitchell [10] have already indicated that such cerebral microvascular damage contributes to impaired memory function with advancing age – as well as the pathogenesis of dementia (including Alzheimer's disease). In addition, investigators in this field of research generally agree upon at least one basic belief; namely, increased aortic stiffness is associated with cognitive decline. Moreover, in Alzheimer's disease, the cerebrovasculature is the location where several pathogenic processes converge and contribute to cognitive impairment and (eventually) dementia [11]. Any interested reader is directed for further research details to the relevant work of Jefferson et al. [12] on how aortic stiffening affects both regional cerebral blood flow (regional CBF) and related cerebrovascular reactivity in older adults. Basically, their research work found that greater aortic stiffening is associated with lower regional CBF but a higher cerebrovascular reactivity in cognitively normal older adults, especially among subjects with increased genetic predisposition for Alzheimer's disease. Hence, central arterial stiffening may contribute to decreases in regional CBF, -- despite preserved cerebrovascular reserve capacity [12].

3. Arterial Amyloidosis with Age

Over a lifetime, the aorta bears the greatest burden of the pulsatile strain from cardiac ejection. Elastic fiber fragmentation is associated with gradual deposition of much stiffer collagen fibers within the vessel wall, ultimately stiffening the aorta [10]. At the same time, Wang et al. [13] have pointed out past studies which demonstrate that amyloid (dysfunctional protein) is found in the aortic walls of almost 100% of the human population above 50 years of age. These authors stress that vascular amyloidosis, hypertension and atherosclerosis can be accurately interpreted as accelerated aging, and it is clear (from various studies [13]) that vascular amyloidosis, hypertension and atherosclerosis are each closely interrelated with arterial aging as equal partners. As concerns specifically amyloidosis, (out of about 30 proteins known to form pathogenic amyloid structures in human tissues) there are only four kinds of amyloid proteins which are mainly associated with particularly vascular amyloidosis – two of which (viz. apolipoprotein A-I, or apoA-I, and medin) have been reported to be susceptible to deposit at the aorta [13].

4. Amyloid Types Deposited in Large Arteries, and Implications for Drug Delivery

Medin is the most common amyloid protein described in humans, and is found in blood vessels of the upper body in virtually all people over 50 years of age [14]. Degenhardt et al. have recently reported that aggregates of medin also develop in the aorta and brain vasculature of wild-type mice in an age-dependent manner. Importantly, mice that genetically lack medin display markedly less cerebrovascular dysfunction in the aged brain. These authors argue that given the prevalence of medin aggregates in the general population and its role in vascular dysfunction with aging, targeting medin may become a novel approach to sustain healthy aging [14]. Moreover, Migrino et al. [15] have recently investigated and reported on the relationship between human cerebrovascular medin and Alzheimer's disease and vascular dementia. Cerebral arteriole medin was quantified from 91 brain donors, which led these investigators to conclude that cerebral arteriole medin is associated with and could be a potential novel risk factor or biomarker for Alzheimer's disease and vascular dementia [15].

The second above-mentioned amyloid protein (susceptible to deposit at the aorta – cf. Sect. 3) is apoA-I, which represents another interesting target for drug delivery. ApoA-I holds the added advantage that it has already been employed in various past, published (in vivo) drug-delivery studies (see [16] for a recent review). Specifically, the targeting agent involved (i.e., a biobased lipid nanocarrier [see below]) has already been repeatedly descibed, in the peer-reviewed literature, to function as a targeted apoA-1-based, scavenger receptor class B type I (SR-BI) mediated, drug-delivery agent [16, 17]. As concerns this class of targeting vehicle used, cell-surface scavenger receptors (mainly SR-BI) emerged as the major receptor candidate facilitating enhanced endocytosis of certain lipid nanocarriers -- (i.e., "lipid-coated microbubble/nanoparticle-derived" (LCM/ND) nanoemulsions) into various target cells [17].

Earlier research (see [17] for a review) has already confirmed that SR-BI receptors (or their human ortholog CLA-1) additionally function as cell-surface receptors [16, 18-22] that mediate SAA-induced proinflammatory effects (cf. [21]). However, Baranova et al. further report that (in cell culture) various ligands for CLA-1/SR-BI "efficiently compete" with SAA for CLA-1/SR-BI binding

[20]. Now since: i) both apoA-I and SAA are ligands (i.e., substrates) for SR-BI, and ii) apoA-I is the major apolipoprotein for the high-density lipoprotein (HDL) particle, then one would expect that a similar benefit (of "competitive binding" to SR-BI receptors) may well accompany the clinical intravenous use of the ("HDL-like") LCM/ND lipid nanoemulsion vehicle (see below, and cf. [16]). Note also that the documented similarities in lipid composition, between HDL versus the biomimetic (LCM/ND-nanoemulsion) nanocarrier particles, can partially simulate or mimic the known heterogeneity of HDL particles. Accordingly, biomedical application of such colloidal drug-nanocarriers may be extendible to the treatment of complex medical disorders like dementia [17].

5. SAA Versus SR-BI Targeting, and Alzheimer's Disease

Since the apoA-I vascular (aortic) amyloidosis already cited above (in ref. [13]) has been discussed in more detail elsewhere by the original investigators involved [23], their analysis and interpretation of apoA-I amyloid formation is worth noting: During atherosclerosis, the acute phase reactant SAA (in blood) may displace apoA-I from HDL. This displacement leads to increased concentration of lipid-free apoA-I in the vessel intima (artery inner lining) as well as to conformational changes of apoA-I. These effects on apoA-I make it more fibrillogenic (and some forms of amyloid fibrils have been shown to be cytotoxic) [23]. Therefore, on the basis of the same logic (and also alluded to in Sect. 4 above), a similar benefit of "competitive binding" (i.e., SAA versus apoA-I) [16] may now potentially be employable for the inhibition of inflammatory cascades which may, in turn, attenuate amyloidogenic processes – such as Alzheimer's disease. Specifically, an effective preventive and therapeutic strategy could be based upon nanotargeting drug(s), using ("HDL-like") lipid nanocarriers. This type of lipid nanocarrier (cf. Sect. 4, 2nd and 3rd paragr.) is known to target toward a major SAA receptor (i.e., class B scavenger receptors) responsible for proinflammatory, SAA-mediated, cell signaling events ordinarily leading to cognitive decline. Accordingly, the new end result would be to delay/attenuate dementia [16]. In other words, this novel targeting strategy is based on the suggestion that treating vascular abnormalities/arterial stiffness might improve cognitive outcomes in cognitive disorders. Support for this proposed targeting strategy can be found in the peer-reviewed literature describing an ongoing debate that Alzheimer's disease is not caused by its associated amyloid-β protein (Aβ) plaques (alone) but rather is due to a decrease in CBF. For example, Korte et al. [24] describe biomarkers indicating that the earliest event in Alzheimer's disease is a decrease in CBF – at least locally. These authors review and/or cite the earlier work of numerous other investigators leading to the conclusion that the level of soluble Aβ oligomers, and of hyperphosphorylation of the cytoskeletal protein tau that is induced by Aβ, correlated better with cognitive decline than did Aβ plaque level. Therefore. CBF reduction may play a crucial role in driving cognitive decline, and Korte et al. further point out that CBF reduction reaches over 50% in some brain areas [24].

Lastly, receptor-mediated endocytosis/transcytosis via lipoprotein receptors, particularly scavenger receptors, remains a major route of drug delivery across the blood-brain barrier; namely, (blood-borne) nanocomplexes can be readily transported into brain capillary endothelial cells (bovine and porcine) via scavenger receptor-mediated endocytosis (see [16] for a review). Moreover, by incorporating drug molecules into the LCM/ND lipid nanoemulsion type, one is likely to obtain a multitasking "combination therapeutic" capable of targeting cell-surface SR-BI [16, 17, 25-29]. This proposed multitasking combination therapeutic appears likely to display greater

efficacy at different stages of Alzheimer's disease (cf. [30]). Note also that this multitasking drug-nanocarrier approach can serve to simultaneously reduce the size and/or extent of the "multidrug cocktail" [31] that the clinician would otherwise need to employ for adequate, or fully effective, treatment of the varied etiology of Alzheimer's-disease symptoms (i.e., the "multiple aging pathways" [31] or various pathogenic cascades involved).

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Competing Interests

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

References

1. Liu Q, Fang J, Cui C, Dong S, Gao L, Bao J, et al. Association of aortic stiffness and cognitive decline: A systematic review and meta-analysis. Front Aging Neurosci. 2021; 13: 680205.
2. Levin RA, Carnegie MH, Celermajer DS. Pulse pressure: An emerging therapeutic target for dementia. Front Neurosci. 2020; 14: 669.
3. de Montgolfier O, Thorin-Trescases N, Thorin E. Pathological continuum from the rise in pulse pressure to impaired neurovascular coupling and cognitive decline. Am J Hypertens. 2020; 33: 375-390.
4. Hughes TM, Craft S, Lopez OL. Review of the 'potential role of arterial stiffness in the pathogenesis of Alzheimer's disease'. Neurodegener Dis Manag. 2015; 5: 121-135.
5. Nowak KL, Rossman MJ, Chonchol M, Seals DR. Strategies for achieving healthy vascular aging. Hypertension. 2018; 71: 389-402.
6. Thorin-Trescases N, de Montgolfier O, Pincon A, Raignault A, Caland L, Labbe P, et al. Impact of pulse pressure on cerebrovascular events leading to age-related cognitive decline. Am J Physiol Heart Circ Physiol. 2018; 314: H1214-H1224.
7. Hendrickx JO, Martinet W, Van Dam D, De Meyer GRY. Inflammation, nitro-oxidative stress, impaired autophagy, and insulin resistance as a mechanistic convergence between arterial stiffnes and Alzheimer's disease. Front Mol Biosci. 2021; 8: 651215.
8. Winder NR, Reeve EH, Walker AE. Large artery stiffness and brain health: Insights from animal models. Am J Physiol Heart Circ Physiol. 2021; 320: H424-H431.
9. Suri S, Chiesa ST, Zsoldos E, Mackay CE, Filippini N, Griffanti L, et al. Associations between arterial stiffening and brain structure, perfusion, and cognition in the Whitehall II imaging sub-study: A retrospective cohort study. PloS Med. 2020; 17: e1003467.
10. Cooper LL, Mitchell GF. Aortic stiffness, cerebrovascular dysfunction, and memory. Pulse. 2016; 4: 69-77.

11. Klohs J. An integrated view on vascular dysfunction in Alzheimer's disease. Neurodegener Dis. 2020; 9: 109-127.
12. Jefferson AL, Cambronero FE, Liu D, Moore EE, Neal JE, Terry JG, et al. Higher aortic stiffness is related to lower cerebral blood flow and preserved cerebrovascular reactivity in older adults. Circulation. 2018; 138: 1951-1962.
13. Wang Y, Feng X, Shen B, Ma J, Zhao W. Is vascular amyloidosis intertwined with arterial aging, hypertension and atherosclerosis? Front Genet. 2017; 8: 126.
14. Degenhardt K, Wagner J, Skodras A, Candlish M, Koppelmann AJ, Wild K, et al. Medin aggregation causes cerebrovascular dysfunction in aging wild-type mice. Proc Natl Acad Sci U S A. 2020; 117: 23925-23931.
15. Migrino RQ, Karamanova N, Truran S, Serrano GE, Davies HA, Madine J, et al. Cerebrovascular medin is associated with Alzheimer's disease and vascular dementia. Alzheimers Dement. 2020; 12: e12072.
16. D'Arrigo JS. Nanotargeting of drug(s) for delaying dementia: Relevance of Covid-19 impact on dementia. Am J Alzheimers Dis Other Demen. 2020; 35: 1533317520976761.
17. D'Arrigo JS. Stable nanoemulsions: Self-assembly in Nature and Nanomedicine. Elsevier: Amsterdam; 2011. pp. 415. ISBN 978-0-444-53798-0.
18. D'Arrigo JS. Biobased nanoemulsion for blocking Covid-19 from accelerating Alzheimer's disease. Juvenis Sci. 2021; 7: 5-11.
19. D'Arrigo JS. Nanotargeting dementia etiology: Aiming drug nanocarriers toward receptors for vascular endothelium, serum amyloid A, inflammasomes, and oxidative stress. Nano Prog. 2020; 2: 25-30.
20. Baranova IN, Vishnyakova TG, Bocharov AV, Kurlander R, Chen Z, Kimelman ML, et al. Serum amyloid A binding to CLA-1 (CD36 and LIMPII analogous-1) mediates serum amyloid A protein-induced activation of ERK1/2 and p38 mitogen-activated protein kinases. J Biol Chem. 2005; 280: 8031-8040.
21. Mullan RH, McCormick J, Connolly M, Bresnihan B, Veale DJ, Fearon U, et al. A role for the high-density lipoprotein receptor SR-BI in synovial inflammation via serum amyloid-A. Am J Pathol. 2010; 176: 1999-2008.
22. Erickson MA, Jude J, Zhao H, Rhea EM, Salameh TS, Jester W, et al. Serum amyloid A: An ozone-induced circulating factor with potentially important functions in the lung-brain axis. FASEB J. 2017; 31: 3950-3965.
23. Mucchiano GI, Jonasson L, Haggqvist B, Einarsson E, Westermark P. Apolipoprotein A-I–derived amyloid in atherosclerosis: Its association with plasma levels of apolipoprotein A-I and cholesterol. Am J Clin Pathol. 2001; 115: 298-303.
24. Korte N, Nortley R, Attwell D. Cerebral blood flow decrease as an early pathological mechanism in Alzheimer's disease. Acta Neuropathol. 2020; 140: 793-810.
25. D'Arrigo JS. Alzheimer's disease, brain injury, and C.N.S. nanotherapy in humans: Sonoporation augmenting drug targeting. Med Sci. 2017; 5: 29.
26. D'Arrigo JS. Nanotherapy for Alzheimer's disease and vascular dementia: Targeting senile endothelium. Adv Colloid Interface Sci. 2018; 251: 44-54.
27. D'Arrigo JS. Treating dementia early: Limiting cellular damage in brain tissue. OBM Geriatr. 2019; 3: 19.

28. D'Arrigo JS. Delaying dementia: Targeted brain delivery using lipid cubic phases. OBM Neurobiol. 2019; 3: 13
29. D'Arrigo JS. Targeting early dementia: Using lipid cubic phase nanocarriers to cross the blood-brain barrier. Biomimetics. 2018; 3: 4.
30. Krstic D, Knuesel I. Deciphering the mechanism underlying late-onset Alzheimer disease. Nat Rev Neurol. 2013; 9: 25-34.
31. Ladiges WC. Time for an Alzheimer's disease cocktail. Aging Pathobiol Ther. 2020; 2: 14-15.