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Short Review

Pathophysiological Linkage between Aging and Cognitive Decline: Implications for Dementia Treatment

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Abstract

The cardiovascular risk factors for dementia trigger widespread inflammation and oxidative stress. These two interacting processes lead to neurodegeneration, gradual cognitive/memory decline, and eventually (late-onset) dementia. In addition, there is supporting evidence pointing to elevated pulse pressure as a clear risk factor for cognitive decline. Accordingly, an effective therapeutic strategy to delay dementia could be based upon nanotargeting bioactive molecules, using lipid nanocarriers, toward cell-surface scavenger receptors. The resulting nanocarrier therapeutic is likely to be "multitasking", i.e., be capable of entering various target cells. Such targeting behavior of this proposed therapeutic appears likely to provide enhanced efficacy at different stages of dementia.

Keywords

Cognitive decline; dementia; lipid nanoparticles; nanocarrier; nanoemulsion; neuroinflammation; scavenger receptors; targeted delivery

1. Introduction

As concerns the brain, cerebrovascular risk factors for Alzheimer's disease precede cognitive decline, often by decades. Increasing evidence points towards: 1) risk factors for cardiovascular disease being very similar to risk factors for dementia. 2) At the same time, additional evidence indicates that various genetic factors may be shared factors for both dementia and cardiovascular disease. 3) Since chronic inflammation, in particular, is often associated with cardiovascular disease as well as the process of amyloid-beta (Aβ) deposition, the inhibition of inflammatory cascades may attenuate amyloidogenic processes – such as Alzheimer's disease. However, the associations between risk factors and dementia vary accordingg to when measurements are taken within the lifespan, which thereby often complicates the interpretation of research within this field [1-3].

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

As explained by various investigators earlier (e.g., [3-12]), aging is associated with stiffening of the aorta, which then reduces wave reflection and increases the transmission of pulsation into the peripheral circulation. Beyond midlife, aortic stiffness increases rapidly. This increase exposes the cerebral microcirculation to abnormally high pulsatile load (i.e., high pulse pressure). Importantly, the high pulse pressure results in alterations within the microvasculature of the brain. Such vascular etiologies (as well as several cardiovascular "inflamm-aging" disease processes [10]) are believed to contribute to memory impairment and the pathogenesis of dementia, including Alzheimer's disease ([8, 13, 14]; see also Sect. 3).

In addition, elevated pulse pressure promotes endothelial dysfunction. Increasing clinical data indicates that penetration of high pulse pressure to cerebral microvessels likely causes functional, structural, metabolic, and hemodynamic alterations. These changes could ultimately promote neuronal dysfunction and cognitive decline [8].

3. Pulse Pressure, Pulse-Wave Velocity Assessment, and Cognitive Decline

Although some of the mechanisms linking higher pulse pressure and cognitive impairment remain unclear, there is supporting evidence (from population studies involving thousands of people [4]) for the belief that elevated pulse pressure is a risk factor for cognitive decline [15, 16]. Moreover, Liu et al. [3] have recently conducted a systematic literature search for, and quantitative analysis of, 29 peer-reviewed studies (between 1986-2020) that reported an association between aortic pulse-wave velocity (PWV) and cognitive function, cognitive impairment, and/or dementia. These authors concluded that aortic stiffness, measured by aortic PWV (a surrogate marker of arterial stiffness and increased pulse pressure), could be an independent predictor for cognitive impairment -- especially for older individuals [3, 4, 15, 16].

In addition, elevated pulse pressure delivers initial and continuous insults to the BBB. The result is chronic inflammation and oxidative stress in the BBB, as well as upregulated secretion of amyloid-β (Aβ) from the BBB. The increased secretion of Aβ contributes to the loss of BBB integrity, and causes persistent oxidative stress within the brain, neuroinflammation, Aβ deposition, and resulting neurodegeneration [4].

4. Targeted Natural-Product/Nutrient Delivery for Treating Dementia

Wang et al. [17] have pointed out that vascular amyloidosis, hypertension and atherosclerosis are disorders that, in many aspects, can be accurately interpreted as accelerated aging. As relates to specifically amyloidosis, there are only two kinds of amyloid proteins mainly associated with particularly vascular amyloidosis (viz. apolipoprotein A-I, or apoA-I, as well as medin) and which also are susceptible to deposit at the aorta [17].

In particular, apoA-I represents an especially interesting research target for drug delivery. Namely, ApoA-I has already been utilized in numerous published (in vivo) drug-delivery studies (see [18] for a recent review). As relates to the class of targeting vehicle (i.e., a biobased lipid nanocarrier) used, cell-surface scavenger receptors (mainly SR-BI) emerged as the major receptor candidate. This major receptor can facilitate enhanced (i.e., apoA-1-assisted) endocytosis, of the "stable" colloidal-lipid nanocarrier particles into various target cells [2, 18-20].

By way of defining "stability" in colloid science (and particularly regarding nanoemulsions in general), notice that a colloidal dispersion represents a state of higher free energy than that corresponding to the material in bulk. (In addition, the term "colloidal" refers to a state of subdivision in which the particles, or droplets or bubbles dispersed in another phase, have at least one dimension between 1 and 1,000 nm.) If there is a substantial energy barrier preventing the elimination of the colloidal state, the colloidal system will be metastable and may remain in that state for a very long time. Accordingly, the whole question of the preparation and stability of colloidal systems is closely tied up with the factors that give rise to free-energy barriers of adequate height to prevent the breakdown of the colloidal state. (Hence, the term "metastable" means the colloidal system is in a state of equilibrium corresponding to a local minimum of free energy.) When the free-energy barrier is sufficiently high, compared with the random thermal motion (Brownian motion) of the nanoemulsion particles, the dispersion will remain indefinitely in a metastable state. This dispersion (nanoemulsion) is said to be "colloidally stable" [2]. To summarize, (lipid) nanoemulsions are thermodynamically unstable systems; however, in certain cases, they can display long kinetic stability. This long stability, small droplet size (as well as small liquid-crystal size), and availability of low-energy production methods render certain lipid nanoemulsions particularly well suited as colloidal drug-delivery vehicles for pharmaceutical applications.

Interestingly, the interface of natural products and nanomedicine has recently been reported [21] (in a 2021 review published in ACS Pharmacology & Translational Science) to be delivering promising results in treating dementia. In fact, various natural compounds have been suggested as antioxidant and/or anti-inflammatory therapeutics for Alzheimer's disease [21-24]. Among these compounds, resveratrol has aroused great interest [22] due to its neuroprotective characteristics. For example, Loureiro et al. provide evidence that grape extracts (which contain resveratrol) increase the inhibition effect on Aβ aggregation in incubation studies [22]. Furthermore, Pasinetti has very recently reported [24] that polyphenolic metabolites, derived from a grapeseed polyphenolic extract, have potent anti-inflammatory activity and can cross the BBB. By combining these polyphenolic metabolites with resveratrol, his research group was able to provide greater protection against cognitive impairment and amyloid aggregation (in an Alzheimer's-disease mouse model) than when employing the same components alone [24].

Similarly, Zhu et al. [23] have recently drawn attention to several reviews concerning the

efficacy of probiotic supplementation for neurological disorders, and/or Alzheimer's disease, that have been published. Zhu et al. include their own findings that identified a significant effect of probiotics on improving cognitive function in studies on persons with mild cognitive impairment [23]. Finally, related to all the findings described in this paragraph, a brief mention of synbiotics (i.e., the combination of probiotics and prebiotics) is appropriate. Very recently, Pasinetti [24] reported designing synbiotics to produce specific bioavailable metabolites that penetrate the BBB, and reduce neuropathologies associated with Alzheimer's disease.

5. Concluding Remarks

Incorporating bioactive molecules into specifically the "high density lipoprotein-like" ("HDL-like") lipid nanoemulsion type produces a multitasking "combination therapeutic". This nanocarrier therapeutic would be capable of targeting cell-surface SR-BI [2, 18-20, 25-29]. Accordingly, the resulting nanocarrier therapeutic is likely to be "multitasking", i.e., be capable of entering various target cells [2, 18-20]. Such targeting behavior of this proposed therapeutic appears likely to provide enhanced efficacy at different stages of dementia (cf. [30]).

Besides the earlier-mentioned probiotics and plant-based natural products (cf. Sect. 4), other bioactive-based therapeutics could be formulated [31-33] using this same versatile nanoemulsion-delivery system. For example, various studies [31, 32] have provided evidence that proteins regulating coagulation of blood, especially thrombin, are elevated in the brains of patients with Alzheimer's disease. Accumulating evidence indicates that a chronic procoagulant condition exists in Alzheimer's disease [31]. Moreover, in experiments where thrombin was inhibited (using Alzheimer's-disease mouse models), the investigators observed a preservation of cognition and endothelial function as well as a reduction of neuroinflammation. Accordingly, a thrombin-based therapeutic (i.e., which inhibits thrombin action) could target multiple points of Alzheimer's disease pathology – including neurodegeneration, vascular activation, and neuroinflammation [32]. At the same time, the anticipated utility of this proposed multitasking (biomimetic-nanocarrier) therapeutic approach accords well with findings from other clinical work in Alzheimer's disease [34, 35] (cf. Abstract and Sect. 1). Namely, patients in advancing stages of Alzheimer's disease are reported to exhibit accelerated brain aging (i.e., an observed increasing "gap" between estimated biological brain age versus chronological age) that foretells conversion from mild cognitive impairment to dementia [36].

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The author did all the research work of this study**.**

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Competing Interests

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

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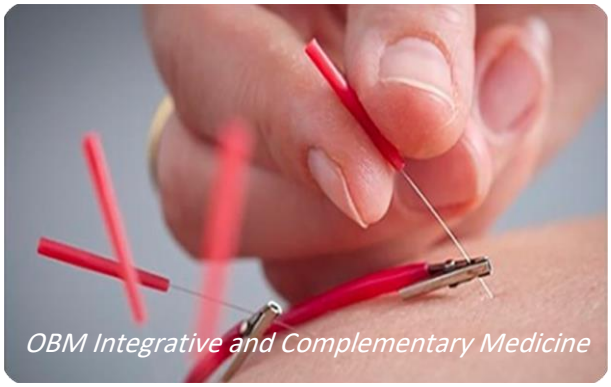

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