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Review Article

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Role of Extracellular Matrix Stiffness Inhibitors in Alzheimer's Disease

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Abstract

Alzheimer's disease is closely related with ageing and age-related extracellular matrix stiffness increase. The association between stiffness and NF-kB activation was demonstrated and link between tissue stiffness and inflammation was suggested. The inhibitors of extracellular matrix stiffening have been reviewed as potential drug components for Alzheimer's disease retardation, prevention and treatment.

Keywords

Ageing, Alzheimer's disease, Stiffness, Inhibitors, NF-κB, Nrf2, Curcumin, Chitosan oligosaccharides.

Introduction

Cardiovascular disease (CVD) and Alzheimer's disease (AD) are age-related deceases [1-3]. Mechanobiology of the brain in ageing and Alzheimer's disease have been recently reviewed [2].

Close association can be suggested between biological tissues stiffness and oxidative stress and inflammation. The objective of this brief review is to demonstrate that ageing is directly related with biological tissue stiffening and that tissue stiffness plays an important role in various age-related pathologies especially in AD.

In order to retard ageing and to prevent development of age-related diseases it is important to find destiffening methods and substances, especially natural without side effects.

Ageing, Stiffness and Cytoskeleton

Advanced glycation end products (AGEs) contribute to amyloidosis in Alzheimer disease. AGEs may act to promote accumulation of additional amyloid [4]. So AGE crosslink breakers, for example alagebrium (ALT-711), can retard AD development. Alagebrium also reduced carotid artery stiffness by 37% [5]. AGEs in cardiovascular disease, diabetic complications, and Alzheimer's disease must be taken into account. Alagebrium can decrease amyloidosis in AD, figure 1.

Ageing is associated with increased tissue stiffness and cytoskeleton actin polymerization.Related with ageingdecrease in bound water content leads to an increase in biological tissue stiffness, and increased tissue stiffness results in NF-kB activation and triggerers actin polymerization [6]. Cytoskeleton controls activation, proliferation and apoptosis of T cells. During aging there is a decline in activation of CD_4T cells [7]. T-cell activation depends on 3D mechanical microenvironment. Responsiveness of T cells to stimuli is higher on stiffer substrates [7]. T-cells are activated in AD patients [8]. So increased tissue stiffness with advanced age can be associated with AD and activated T cells.

Stiffness and Autophagy

It has been shown that rapamycin improves learning and memory and reduces Aβ and Tau pathologyby increasing autophagy [9]. The researchers at Free University of Berlin consider that influence and mechanism of ECM stiffness on autophagy in cancer cells still remains unclear. The increasing matrix stiffness results in elevated autophagy.Rho-ROCK-ERK signal pathway and actin cytoskeleton were essential for the regulation of autophagy by matrix stiffness [10]. The mechanobiology of autophagy has been recently reviewed [11]. Impaired autophagy could lead to Aβ accumulation.

Yes-associated protein (YAP) and the transcriptional co-activator with PDZ-binding Motif (TAZ) regulate gene expression depending on mechanical forces. YAP/TAZ cytosolic

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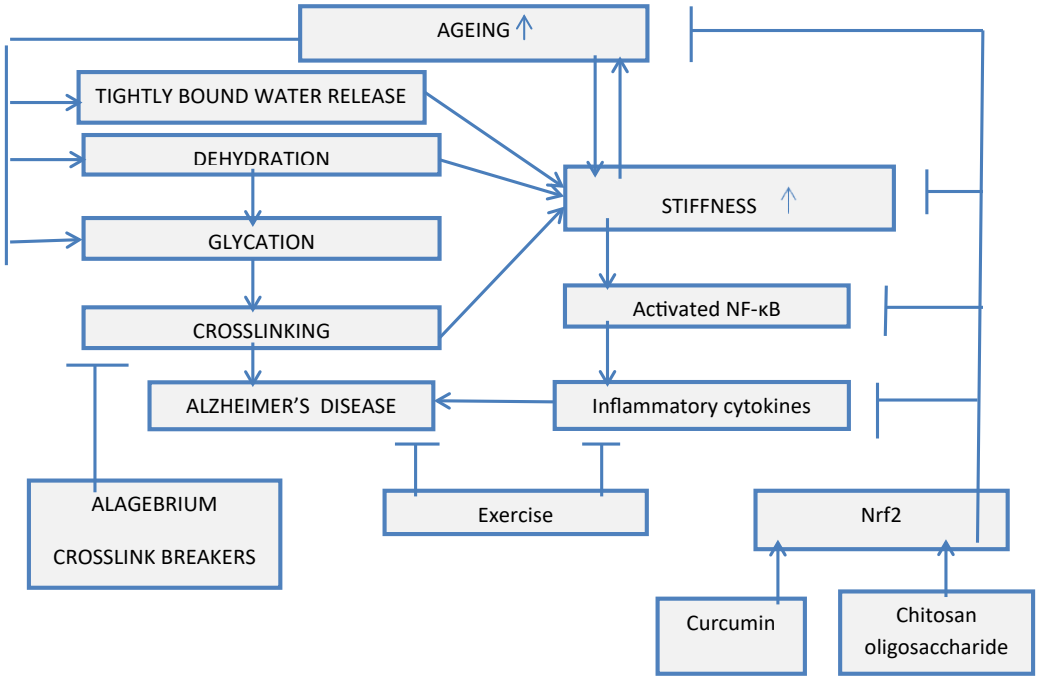

Figure 1: Association between tissue stiffness and alzheimer's disease.

Ageing increases extracellular matrix stiffness due to entropy driven transformation of tightly bound water molecules into loosely bound and free water, dehydration and crosslinking by glycation end products. All those processes lead to initiation and development of Alzheimer's disease. Crosslink breakers and exercise can retard Alzheimer's disease initiation. Increase of stiffness results in activation of NF-κB and expression of pro-inflammatory cytokines developing Alzheimer's disease. Alzheimer's disease inhibitors, such as curcumin and/or chitosan oligosaccharides can activate Nrf2 and prevent NF-κB activation.

localization and nuclear translocation depends on mechanical properties of microenvironment and mechanotransduction [12]. YAP activity depends on extracellular matrix stiffness. YAP and TAZ are active and localize in the nucleus of cells on a stiff matrix, where they promote the expression of several growth-related genes and induce cell proliferation.YAP/TAZ is inactive and localized in the cytoplasm on soft matrix.

Trehalose has been reported as autophagy activator and enhancer [13,14] and trehalose also prevents transformation of tightly bound water into loosely bound and free water. [14,15]. Trehalose also inhibits inflammatory cytokine production [16].

Stiffness and Ad

Extracellular to intracellular water ratio increases with advanced age and can be related with driven by entropy increase in transformation of tightly bound water into loosely bound water. This transformation increases matrix stiffness. Dehydration also leads to increase of stiffness due to crosslinking related with glycation processes. Water plays an important role in amyloid formation and hydration water mobility is increased around tau amyloid fibers [14,15,17] .

Arterial stiffness, as measured by pulse wave velocity, was related with the extent of Aβ deposition [18]. It has been recently concluded that carotid artery stiffening, may contribute to AD pathology in patients with amnestic mild cognitive impairment [19].

AD can be associated with Aβ accumulation in brain. Overproduction of Aβ leads to the formation of plaque and AD development. Exercise leads to inhibition of Aβ expression [20,21].

Stiffness Inhibitors

Life style modifications have been proposed to improve arterial stiffness. Long-term ω-3 fatty acids (fish oil) supplementation in diet was also recommended to decrease arterial stiffness in the population with hypertension. Renin-angiotensin-aldosterone system antagonists, metformin, and 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors, antibodies against TNF-α have been also suggested [22]. For weight loss-induced decreases in arterial stiffness in overweight and obese men positive correlation between changes in arterial stiffness and circulating interleukin-6 (IL-6) levels was reported [23].

It has been found that low-dose aspirin consumption during 2 weeks decreases aortic stiffness in hypertensive patients [24]. And reduced risk of AD among 2 or more years users of aspirin was reported [25]. Long duration regular use of aspirin was also associated with reduced risk of prostate cancer [26] and breast cancer [27]. So it can be suggested that decreased stiffness leads to reduced risk of Alzheimer's disease.

The effect of curcumin on Alzheimer's disease has been reviewed [28]. Epidemiological studies demonstrated that incidence of AD among adults aged 70-79 years in India, where the consumption of curry is higher than in western countries, is 4.4 times less than that of adults aged 70-79 years in the United States. Curcumin suppresses production of pro-

inflammatory cytokines IL-1, IL-6 and TNF-α [29]. So curcumin can show beneficial effects also in the treatment of COVID-19 by mitigating cytokine storm [30]. Curcumin inhibits cellular gene expression regulated by transcription factors NF-kB, AP-1, and Egr-1 [31]. Curcumin also suppresses Aβ and tau accumulation in animal models and improves mitochondria function [32].Curcumin blocks the aggregation and formation of fibrils *in vitro* and *in vivo* [33]. Curcumin upregulates Nrf2 nuclear translocation [34,35]. (–)-epigallocatechin-3-gallate (EGCG) is a flavonoid with the inhibition of Aβ fibrillogenesis [36].

Curcumin intake decreases arterial stiffness [37]. Decreased stiffness can be suggested as a main beneficial factor in the prevention and treatment of AD by curcumin. It was reported that ibuprofen inhibits plaque pathology in a mouse model for AD [38]. Increases in cell contractility, cell-cell junction size, and stiffness-dependent increases in permeability, can be decreased with simvastatin treatment [39].

The potential of chitosan oligosaccharides (COS) in AD prevention and treatment has been much less investigated, [40] but it was reported that chitosan astrocytoma cells were activated by amyloid β peptide and interleukin-1β [41]. COS with molecular weights (MW) from 5,000 Da to 14,000 Da induced AMP-activated protein kinase (AMPK) activation in intestinal epithelial cells and inhibited NF-κB transcriptional activity and NF-κB-mediated inflammatory response [42]. NF-κB suppression upregulates Nrf2 nuclear translocation [14,35] and similarly to effect of curcumin has potential to be beneficial for AD treatment. Chitosan oligosaccharides promote Nrf2 nuclear translocation, figure 1 [43,44].

COS decrease the release of pro-inflammatory cytokinesinterleukin-1β and tumor necrosis factor TNF-α inan amyloid-β1-42-induced rat model of Alzheimer's disease [45].

Chitosan oligosaccharide graft citronellol derivatives (COS-g-Cit1-3) reduced the expression levels of TNF-α and COS-g-Cit1-3 inactivated the NF-κB signaling pathway via inhibiting the phosphorylation of p65, IKBα and IKKβ [46].

The above mentioned cellular processes depend on ECM stiffness as presented in figure 1.

Concluding Remarks

The aged tissue has higher stiffness and is prone to various pathologies. High tissue stiffness initiates and drives age-related diseases. So it is very important to develop destiffening strategy and to find effective stiffness suppressors. Aspirin and non- steroidal anti-inflammatory drugs have demonstrated destiffening effect and reducing risk of Alzheimer's disease, prostate and breast cancers. Chitosan oligosaccharides reduced the expression levels of TNF-α and inactivated the NF-κB signaling. NF-κB suppression upregulates Nrf2 nuclear translocation and could be beneficial in AD prevention and treatment. Curcumin intake decreases arterial stiffness. Curcumin upregulates Nrf2 nuclear translocation, suppresses production of pro-inflammatory cytokines IL-1, IL-6 and TNF-α, inhibits cellular gene expression regulated by transcription factors NF-kB, and suppresses Aβ and tau accumulation in brain of AD animal models. Exercise leads to inhibition of Aβ expression.

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Conflicts of Interest

The author declares no conflict of interest.

Research in Context

Systematic review

There is an urgent need with world population aging and initiation and increase in a number of age-related diseases including Alzheimer's disease (AD) in order to better understand basic mechanisms leading to the pathologies developing with advanced age and to find the treatment strategies that are able to retard and prevent AD and related diseases. The goal was to identify biological changes associated with aging and to determine how these changes can be related with AD.

Interpretation

Cellular processes strongly depend on extracellular matrix mechanical stiffness that regulates through cytoskeleton such processes as transcription factors translocation from cytoplasm to nuclear and changes in gene expression. Dehydration driven by entrophy growth, transformation of tightly bound water into loosely bound and free water and glycation crosslinking reactions increase stiffness of extracellular microenvironment with aging. In context of clinical application this article provides a discussion on the future research directions.

Future Directions

The effective potential tissue stiffness inhibitors could be developed with the goal to retard aging and to prevent initiation of AD and other age related diseases. The links between inflammation, oxidative stress andtissue stiffness will be further investigated.

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