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Review Article
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Targeting Hypertension to Manage Alzheimer's Disease: Rational and Promise

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Abstract

Epidemiological, clinical and experimental animal studies uncover the close and complex interaction between Alzheimer's disease and hypertension, a major risk factor for cardiovascular disease and stroke. Here we overview recent evidences on the impacts of both conditions on cerebral vasculature and discuss the ways in which hypertension may contribute to the onset and progression of Alzheimer's disease.

Keywords: Alzheimer's disease; Cognitive impairment; Hypertension; Nitric oxide; Small vessel disease; Angiogenesis; Vasoreactivity

Abbreviations: ACE: Angiotensin Converting Enzyme; Ach: Acetyl Choline; AD: Alzheimer's Disease; AngII: Angiotensin II; BBB: Brain Blood Barrier; BP: Blood Pressure; eNOS: endothelial Nitric Oxide Synthase; HT: Hypertension; mBFV: mean Blood Flow Velocity; mPFC: medial PreFrontal Cortex; MRI: Magnetic Resonance Imaging; MWM: Morris Water Maze; NFT: Neurofibrillary Tangles NO: Nitric Oxide; NOR: Novel Object Recognition test; RAGE: Receptor for Advanced Glycation End Products; ROS: Reactive Oxygen Species; RR: Risk Reduction; SP: Senile Plaques; TGFβ: Transforming Growth Factor β; VEGF: Vascular Endothelial Growth Factor; WT: Wild Type

Introduction

Alzheimer's disease (AD) is the most common form of dementia. Up to date AD cannot be prevented, slowed or cured. As a consequence, both industrial and developing countries are facing an epidemic crisis given that the number of cases would double every 20 years. By 2050, it is estimated that 115.4 million people will be affected by dementia [1]. For a century now, AD has been considered as a purely neurodegenerative disease even though a vascular component of the disease was put forward at its first description: AD was first described by Alois Alzheimer, an expert of vascular dementia [2], who thought AD to be caused partly by vascular malfunction [3,4]. The autopsy of Auguste D's [5] brain revealed what will become the hallmarks of the disease: the senile plaques (SPs) and the neurofibrillary tangles (NFT).

Scientific community held the SPs and the NFT responsible for what we know now as Alzheimer's disease leaving aside the vascular damages that are also present. Currently, it is increasingly recognized that vascular disease plays a major role in AD pathogenesis and that risk factors such as diabetes mellitus, hypercholesterolemia and atherosclerosis are linked to the onset and the progression of the disease [6]. Among these factors, hyper tension (HT) is becoming obviously the most common and most alarming one.

AD impacts on cerebral vasculature: Functional and structural changes

Cerebral amyloid angiopathy: The senile plaques are the aggregated proteinaceous extracellular deposits mainly composed of amyloid β (Aβ). Aβ is one of the products of proteo lytic cleavage of amyloid precursor protein (APP) by γ- and β-secretase, giving rise to 30-43 amino acid amyloid-β peptides, this sequence of events being known as the amyloidogenic pathway. The most abundant Aβ (1-40) and Aβ (1-42) peptides are known to be the most deleterious due to their facility to aggregate and form the senile plaques. When Aβ peptide accumulates in the adventitia and media of lepto meningeal and parenchymal arteries, it provokes a cerebral amyloid angiopathy (CAA). A patient may have CAA leading to lobar intra-cerebral hemorrhage and dementia, independently from AD; in turn all patients with AD have CAA to a greater or lesser extent.

The most common form associated to vessels is Aβ (1-40) [7], this form being more soluble than Aβ (1-42). The reason why this form accumulates in the vessels is still unknown but recent *in vitro* studies show that the mix of Aβ (1-40) and Aβ (1-42) is necessary to cause the vascular damage [8]. CAA initially induces a hyper-contractile phenotype [9] that may alter the cerebral blood flow, causing brain ischemia and hypoxia. In arterioles, Aβ is highly toxic to smooth muscle cells, inducing the loss of their adhesion properties and their degeneration [10]. Aβ peptide can either cause the capillary occlusion or the disruption of the blood brain barrier (BBB), provoking micro bleeds and allowing the passage of neurotoxic components.

When there is cerebral vascular failure, two main events occur: first, the blood supply decreases inducing a decrease in the availability of oxygen and glucose. Second, draining the brain solutes, including Aβ, is unsuccessful. These two scenarios are likely present in the brain of AD patients.

Underlying small vessel disease: Gaetano Perusini, an Italian physician that collaborated with Alois Alzheimer, noted "some regressive alterations of the arterial wall of large brain vessels" [5] and arteriosclerosis of the small vessels [5] in the report of Auguste D's autopsy. Currently, it appears that the small vessel structural changes represent a third hallmark of AD.

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Now, it is well established that all the vessel components including the extracellular matrix, are affected in AD. In AD patients, there is an increase of 50% in collagen IV as well a loss of proteoglycans in the vessels of the affected brain regions [11]. Pericytes are perivascular cells that contribute to the maintenance of BBB, the architecture of the vessel, the clearance of solutes from the brain parenchyma and the vascular reactivity [12]. A reduction in the coverage of capillaries by pericytes as well as BBB disruption has also been evidenced [13]. To assess the role of pericytes in AD, mice overexpressing human APP with Swedish mutation ($APPs^{w/0}$) were crossed with mice whose pericytes were deficient in platelet-derived growth factor receptor-β ($Pdgfr\beta^{+/-}$). This model has shown that the loss of pericytes contributed to a default of Aβ clearance, NFT formation in the cortex and hippocampus, neuronal loss and of course, to vascular damage [12].

Arterioles in AD show an increase of fibrous tissue, stiffness and tortuosity and capillaries present a thickening of the basement membrane, suggesting that the molecule exchanges are more difficult, thus impairing the brain homeostasis [14] and disturbing brain perfusion.

Interestingly, there is a hierarchical sequence in which the different regions of the brain exhibit CAA and arteriosclerosis Thal et al. [15] correlated positively the cognitive impairment with the sequential spread of Aβ deposition in different regions of the brain along with the vessel modifications, namely arteriosclerosis / lipo hyalinosis and CAA. Initially CAA begins in the lepto meningeal arteries and ends up in the basal ganglia, whereas arteriosclerosis and lipo hyalinosis begins at the basal ganglia spreading through the white matter, then the cortex, cerebellum, thalamus and finally the brainstem.

Angiogenesis that occurs in response to hypoxia has been suggested, considering the findings on the increased collagen IV immune staining, and overexpression of several pro-angiogenic mediators, including vascular endothelial factor (VEGF), nitric oxide (NO), transforming growth factor-β and thrombin [16]. Whether this angiogenesis leads to the formation of mature and functional vessels remains controversial.

Functional impairment

The structural abnormalities of the brain microvasculature occurring in AD interfere with basic laws of fluid dynamics, haemorheological compromise will result in cerebral capillary resistance, high blood viscosity, abnormal flow patterns, and changes in shear stress and shear rate in vessel walls. The net effect is chronic 'disturbed' blood flow to the brain that impairs the delivery of essential nutrients, particularly oxygen and glucose, to cerebral neurons.

Hemodynamic parameters in AD patients have been measured using various techniques. Using transcranial Doppler, Stefani et al. have shown that middle cerebral artery mean flow velocity (MFV) was decreased at rest [17] in AD. Moreover, the cerebrovascular reactivity of these AD patients, assessed by calculating the breath hold index (BHI, the MVF increase, while the patient holds his breath, indicating vasodilation), was reduced compared to healthy aged-matched subjects. Furthermore, the pulsatile index (PI, calculated as (systolic velocity-diastolic velocity) / mean velocity), an index of vessel resistance, is significantly increased in AD, compared to non-AD patients [17]. Regarding brains' activity, functional MRI using the blood oxygen level-dependent (BOLD) signal has shown a decrease in the hippocampal neuronal activity and an increase in the prefrontal cortical neuronal activity in AD subjects, interpreted as a compensatory mechanism to the hippocampal hypo function [18].

Neuronal hypo metabolism has been assessed in AD using FDG PETScan. In the late-onset sporadic forms of AD, the parieto-temporal association area, posterior cingulate cortices and precuneus are the mainly affected brain areas [19]. Hypometabolism can be explained by a decrease of synaptic activity, reduction in GLUT transporters on brains' microvasculature, endothelial mitochondrial dysfunction but also by vascular structural damage [20].

Hypoxia in AD brain autopsies has been studied, using indirect measurements. In 20 AD brains, an increase in VEGF levels and a reduction in myelin associated glycoprotein to proteo lipid protein 1 (MAG:PLP1) ratio in the frontal cortex and parahippo campus, was evidenced, both indexes reflecting low oxygen levels in the tissue [21]. Furthermore, VEGF concentration measured by ELISA was significantly increased in the brains classified as level V-VI, in the Braak tangle stages, compared to those classified as level 0-II. This result suggests that there is a positive correlation between VEGF brain's concentration and the Braak stage [21].

Hypertension and its impact on the brain vasculature

Hypertension, defined as BP above 140/90 mmHg, is the most important cardiovascular risk factor worldwide [22]. Hypertension is also the major risk factor for cerebrovascular diseases, leading to hemorrhagic and ischemic stroke [23]. Hypertension is also responsible for cerebral small vessel disease, which is an important contributor to lacunar infarction, leukoaraiosis, micro bleeds [24], and cognitive decline in the elderly [25]. Small vessel disease can be visualized on cerebral MRI as white matter hyper intensity also known as leuko araiosis [26], lacunar infarcts and generalized brain atrophy, all together associated with the increasing risk of dementia [25]. With increasing age and long-standing high BP, changes in the structure and in the function appear. HT reduces the number of arterioles and capillaries in the cerebral vasculature, a phenomenon called micro vascular rarefaction and BP dependent, whereas the number of pial arteries does not seem to be affected [23]. Hypertensive arteriolar remodeling is characterized by a reduced lumen diameter and an increased cross sectional area [27]. Moreover, the mechanism of auto regulation, consisting in maintaining constant levels of brain perfusion within a range of mean arterial BP between 60 and 150 mmHg, is altered [28]. Within this range, arterioles constrict as BP increases by activation of the local myogenic tone; when cerebral arterioles lose this ability to constrict, downstream smaller vessels and especially capillaries are exposed to higher pressures increasing the probability of edema and cerebral hemorrhage. Moreover, the cerebral vasomotor tone is regulated through endothelium derived NO whose activity is impaired in HT [29]. As a consequence, BBB leakiness is increased leading to edema [30]. This can be attenuated by antihypertensive drugs [31].

Hypertension and cognitive decline

Epidemiological studies: The Atherosclerosis Risk in Communities study (ARIC) [32], studied twice, 6 years apart, the weight of cardiovascular risk factors in cognitive decline in 10,963 relatively young individuals (47 to 70 years old). Using multivariate analyses, they demonstrated that diabetes mellitus and hypertension were positively associated with cognitive decline but not hyperlipidemia, smoking status or carotid intima-media wall thickness at baseline. This study suggested that dementia could develop independently of arteriosclerosis.

The Framingham study [33] showed, 20 years after first biennial BP measurements in poorly untreated hypertensive patients, an inverse relationship between BP level and cognitive impairment, which was measured as a composite neuropsychological score. The composite score declined every 10 mmHg BP increment. In the same line, the Honolulu-Asian Aging Study [34] identified systolic BP as a predictor of reduced cognitive function in later life, as for every 10 mmHg increase in systolic BP, there was a 7% increased risk for intermediate cognitive dysfunction and a 9% increased risk for poor cognitive function, without association with midlife diastolic BP.

The severity of hypertension and its duration is also a matter of concern. The Epidemiology of vascular Aging study (EVA) [35] showed an association between high BP above 160/95 mmHg at baseline, and a cognitive decline at the 4-year assessment: the risk of cognitive decline was 4.3 (HR: 95%, CI: 2.1 to 8.8) in those without antihypertensive therapy and 1.9 (HR: 95%, CI: 0.8 to 4.4) in those being treated. The risk for the still untreated participants at the 2-year mid-course assessment was further increased to 6.0 (HR: 95%, CI: 2.4 to 15.0).

The Sweden Longitudinal Population Study [36] followed-up for 15 years 382 70-year-old patients and revealed that those who had a higher systolic BP (mean 178 VS 164 mmHg) and a higher diastolic BP (101 VS 92 mmHg) at age 70, were statistically more prompt to develop dementia ($p=0.034$ and $p=0.004$, respectively) compared to the normotensive patients. AD developed more likely for those with a higher diastolic BP at age 70 and vascular dementia at age 75, suggesting that AD would be more sensitive to HT than vascular dementia.

Thus, lowering mid-life systolic hypertension could be an effective strategy to prevent late-life dementia.

To slowdown cognitive decline with the use of antihypertensive drugs: Randomized clinical studies globally have shown an improvement in cognitive decline of the treated hypertensive patients. The SYST-EUR [37] study showed a 50% reduction in dementia incidence from 7.7 to 3.8 cases per 1000 patient-years after only 2 years administration of an antihypertensive strategy consisting of either one, or a combination of two or three treatments among a calcium channel blocker, an angiotensin converting enzyme (ACE) inhibitor and a thiazidic diuretic in patients with severe systolic hypertension. This therapeutic strategy pays off even in patients with prior cerebrovascular events.

The PROGRESS [38] study included subjects with prior stroke or transient ischemic attack and evaluated the potential of the combined use of ACE inhibitors and thiazidic diuretics to control BP and prevent post-stroke dementia. BP lowering treatment substantially reduced dementia but only when associated with recurrent stroke (RR: 34% [3-55]) and not dementia alone (RR: 12% [-8 ± 28]. Furthermore this study shows that BP lowering treatment also reduced cognitive decline but only when associated with recurrent stroke as well by 45% [21-61]. Those results suggest that even after an ischemic cerebral event, controlling BP levels may improve cognitive performance or dementia.

The SCOPE [39] trial experimented the efficiency of an angiotensin II (AngII) antagonist in reducing cognitive decline in hypertensive elderly (mean age 76 years old). The reduction of BP from 165/88 to 141/74 mmHg was associated with a significant reduction in attention and in episodic memory decline, a type of memory being highly impaired in AD. No significant changes were observed in speed of cognition, working memory or executive function. As a remark, the target BP was < 160/90 mmHg.

In a Cochrane review [40] assessing the effects of lowering BP to prevent cognitive decline and dementia, the authors selected three randomized, double-blind, placebo controlled trials and 12, 091 hypertensive patients. Antihypertensive treatment was administered for at least 6 months. They judged that there were no sufficient robust data to conclude, because of lost to follow-up, frequent switch of treatments and the great heterogeneity between trials.

Taken together, clinical studies suggest that HT has an important role in cognitive decline, and, for one of them, in AD (Sweden longitudinal study [36]). In order to assess a causal relationship and elucidate the underlying mechanism, appealing to animal models is of great support.

Hypertension in animal models: a window to AD onset

Insights into the mechanisms of AD-HT cross talk: The Giuseppe Lembo team [41] were pioneers in the field, who described the AD-like lesions in an HT mouse model induced by transverse aortic constriction. Hypertensive mice showed CAA and SP in the cortex and hippocampus. Based on their findings, the authors postulated that the origin of Aβ is vascular, and after circulating in the blood stream, it enters the brain to aggregate and form the SPs [41]. To further investigate this hypothesis they focused on RAGE, a receptor of AGEs (Advanced Glycation End products) of the immunoglobulin superfamily. The expression of RAGE is up-regulated in AD. Among many other ligands, RAGE is capable to bind Aβ and to transport circulating Aβ across the BBB towards the brain [42]. To determine whether RAGE was involved in HT and AD cross talk, they induced HT by transverse aortic coarctation in the RAGE knock-out (RO) mice [43] and found that SPs in RO mice were significantly reduced compared to SPs in WT hypertensive mice. Furthermore, they found that Aβ remained trapped in the vessels, causing oxidative stress and inflammation of vascular wall. They challenged the RO hypertensive mice to the following behavioral tests: the Barnes Maze test, which evaluates spatial memory and learning and is anatomically associated with the hippocampus [44] and the novel object recognition (NOR) test, which aims to assess the "episodic-like" memory [45], these type of cognitive processes being highly impaired in AD patients [46,47]. The RO hypertensive mice performed better than WT hypertensive mice in both tests. These results indicate that the absence of RAGE and accordingly the diminution of SPs accumulation would protect the brain [43].

Using a different model of HT induced by infusing a hypertensive dose of AngII in 3 and 24 month old C57Bl6 mice, Csiszar et al. [48] evidenced a hippocampal spatial memory impairment evaluated by the Y-maze test. At the NOR test, they showed that the age and HT have a synergistic negative effect resulting in an "episodic-like" memory deficit. Next, these authors focused on the expression of AD related gene in the hippocampus of hypertensive wild type mice. They reported that age combined with HT changes the expression of multiple genes related to APP pathway, tauopathy and apolipoprotein-E signaling, but does not change the expression of APP, γ and β-secretase directly [48]. The HT-mediated impairment of signaling pathways was proposed by these authors as a possible mechanism underlying the interaction of HT with AD onset.

Our team studied another model of dual pathology [49], using the transgenic APPPS1 mice infused with hypertensive dose of AngII. The APPPS1 mice were chosen because they do not present NFT and develop very modest CAA [50]. Our hypothesis was that HT, by inducing vascular lesions, would precipitate the development of AD. Four and a half month old hypertensive APPPS1 mice (the early stage of disease progression) were evaluated in the episodic-like memory test in which temporal and spatial components of this type of memory can be assessed [51]. Our study revealed a specific impairment of the spatial component of the memory in these mice, that can be anatomically associated with the medial prefrontal cortex (mPFC) [52]. This cognitive deficit was associated with an increase in the number of cortical amyloid plaques and in soluble amyloid levels in the brain and in plasma as well a 30% to 40% increase in CAA. Using a collagen IV immune staining, we found that micro vessels in the cortex of normotensive AD mice were significantly more abundant and less organized, this phenomena being reported also in AD patients and interpreted as angiogenesis. In contrast, hypertensive APPPS1 mice presented a 25% decrease in cerebral micro vessel density. In addition, we determined that brain levels of VEGF-A, nitric oxide synthase (NOS) 1 and 3 and the nitrite/nitrate were reduced in hypertensive APPPS1 mice. Our results suggest that HT impedes angiogenic process in the important brain regions such as mPFC and hippocampus, both regions being associated with memory and learning, and accelerates the development of AD-like alterations, partly through cerebral vasculature impairment.

Kruyer et al. [53] developed a dual pathology mouse model of HT and AD, using the transgenic TgSwDI$^{+/-}$ mice, in which HT was induced by administration of L-NAME, an inhibitor of NO synthesis. Regarding the amyloid burden quantified using Thioflavin S and immunochemistry, they found that HT in AD mice have a trend to increase in both Aβ (1-40) and Aβ (1-42) compared to AD normotensive mice. Moreover, AD hypertensive mice present a significant increase in the percentage of vessel length covered by SPs, indicating a significant increase of CAA. This study suggests that both forms, Aβ (1-40) and Aβ (1-42), contribute to CAA confirming results that were obtained *in vitro* by Qosa et al. [8]. Kruyer et al. [53] went a step further on the analysis of the vascular system. Electronic microscopy revealed a disruption of the BBB in AD hypertensive mice. To assess whether HT aggravated the BBB leakage these authors quantified the albumin concentration present in the brain parenchyma, which was significantly increased in AD hypertensive mice. They also found that AD hypertensive mice, compared to AD normotensive mice, show a more severe neuronal loss measured by NeuN immune staining, as well as pericyte loss measured by PDGFRβ immune staining [53]. This study is particularly relevant to our questioning because it provides the additional evidence that adding HT to an AD mouse model such as TgSwDI$^{+/-}$ accelerates the onset of the disease and aggravates the symptoms.

Hope for antihypertensive drug therapy

Treating HT can target different pathways, all aiming at normalization of BP: beta blockers, diurtetics, calcium blockers, ACE inhibitors and AngII receptor blockers (ARBs) are the main classes of anti-hypertensive drugs. As mentioned above, clinical trials suggest that some antihypertensive drugs may delay the cognitive impairment in AD [54]. The experimental studies using the animal AD models under hypertensive treatment provide useful mechanistic insights onto how the antihypertensive therapy contributes to improvement of cognition in AD.

Beta-adrenergic receptor blockers (β-blockers)

Wang et al. [55] tested the nebivolol molecule on Tg2576 mice, an AD mouse model which expresses the human APP695 isoform with the Swedish double mutation (APP695K670N, M671L; APPSwe) on a C57Bl6 genetic background. Apart from being an antihypertensive drug, nebivolol has estrogen-like neuro protective properties, interferes with Aβ processing, and works as an antioxidant reducing the ROS endothelial damage and increasing the NO production via the activation of endothelial NOS-3 [55]. Nebivolol was given to 7 month old mice for 6 weeks at a dose of 1 mg/kg/day or more chronically, to 10 month old mice for 5 months at a dose of 1 mg/kg/day. No significant BP change was observed although there was a tendency to decreased heart rate without being statically significant. Regarding the amyloid load, the short-term treatment decreased by 30% the concentration of Aβ (1-40) and Aβ (1-42) in the Tg2576 mice brain without altering the expression of the actors of amyloidogenic pathway, APP or BACE (β-secretase). Accordingly, it increased the level of Aβ (1-42) in the plasma of Tg2576 mice suggesting that this molecule reduces brain amyloid load by contributing to its clearance from the brain parenchyma [55]. Furthermore, the chronic treatment increases NOS-3 expression and reduces NOS-2 expression associated with inflammation. The team challenged the chronically treated Tg2576 mice to the NOR task with a short gap of 1 hour and a long gap of 24 hours between the acquisition and test trials. Nebivolol Tg2576 treated mice performed better than the non-treated mice only in the short gap NOR task. Mice were also tested in the Morris water maze (MWM) to assess learning and spatial memory, which as mentioned above, is anatomically associated with the hippocampus, but failed to rescue the spatial memory and learning deficit.

Central angiotensin-converting enzyme inhibitor: molecules passing the BBB

Yamada et al. [56] tested the perindopril molecule in C57Bl6 mice that received intra cerebro ventricular (i.c.v) administration of 3 nmol Aβ (25-35). The i.c.v administration of Aβ induces cognitive impairment, oxidative stress, inflammatory response and impairment of the cholinergic pathways, all being pathological hallmarks of AD [56]. The perindopril treatment started 1 day after the i.c.v administration of Aβ and lasted for 5 days at a dose of 1 mg/kg/day. This dose significantly decreased BP but had no effect on the heart rate [56]. The amyloid load was not quantified in this study. The group was particularly interested in the brains ACE activity because it increases the concentration of AngII, which is detrimental to memory processes [56]. They found that perindopril reduces by 50% the brain ACE activity. They hypothesize that this reduction may explain the perindopril mediated improvement of working memory deficits, assessed in the Y-maze, and long term memory deficit, assessed in the NOR task.

Complementary to the precedent study, Abd Alla et al. [57] tested the captopril molecule in the Tg2576 mouse model of AD. Captopril treatment at 20 mg/kg/day started at age of 12 months and lasted for 6 months. Regarding the amyloid load, captopril decreased the SPs by 58.4% ± 15.6% specifically in the hippocampus, reduced the Aβ vascular deposits and the γ-secretase and β-secretase enzymatic activity of Tg2576 treated mice compared to non-treated mice. Regarding neuronal regeneration [57], captopril up regulated several genes and proteins, markers of neuronal activity that are down-regulated in Tg2576 mice, including the genes such as Rab6b, Wasl, Rph3a, Veli1, Clasp2 and Kif5 and the proteins like Scn1, Kcnc1 and Epha4 (respectively a voltage operated sodium channel, a voltage operated potassium channel and Ephrin type-A receptor 4). Furthermore, captopril diminished the increase in ACE activity, the AngII and ROS production and protein oxidation that are common in AD. This study suggested therefore, that AngII, one of the principal actors in HT, is able to disrupt signaling pathways outside the vascular compartment, giving a new perspective to the therapeutic mechanism of antihypertensive drugs.

One limit of this study by Abd Alla et al. [57] is the lack of functional behavioral tests. This issue has been addressed in the study by Ferrington et al. [58]. They challenged 16 months old 3xTgAD mice treated with 5gr/l in drinking water of captopril during 6 moths to the MWM and the T-maze. They found that captopril did not rescue the cognitive impairment whatever it is (working memory or spatial memory and learning). One possible explanation for the poor performance on cognitive test under captopril treatment is that the dose of 5 gr/l decreases the mean BP in these 3xTgAD mice below the normal level. Hence, hypotension has also been associated with cognitive impairment [59].

AngII type 1 receptor Blocker AT1 (ARBs)

Ferrington et al. [60] tested valsartan (0.17g/l) as well as eprosartan (0.8g/l) in a triple transgenic 3xTgAD mouse model of AD (PS1m146vKI, Thy1.2-APPswe, Thy1.2- tauP301L). All mice were 3 to 4 months old and were treated for 2 months. There was no change in the mean BP, the amyloid load and the ACE brain activity whatever the treatment. The lack of effect of these two molecules might come from the short-lasting treatment in relatively young mice.

Ongali et al. [61] tested the losartan molecule in the human APP transgenic mice. The study consisted in a 3-month therapy at 10 mg/kg/day starting from15 months. Regarding amyloid load, losartan did not decrease the level of SPs or soluble Aβ in the brain. In contrast, it reduced the cortical glial response but did not rescue the cholinergic deficit observed in non-treated mice. Furthermore, losartan reduced the up-regulation of oxidative stress markers p67phox and SOD2. It also restored vascular function measured by the middle cerebral artery vasodilatory response to acetylcholine and calcitonin gene-related peptide (CGRP). Accordingly, losartan reversed the down-regulation of NO endothelial synthesis. Moreover, losartan reduced the up-regulation of AT1 receptor, associated with cognitive decline in humans and animal models [57]. Finally, mice treated for 3 months with losartan and challenged to MWM, showed an increase in memory retention, whereas prophylactic losartan regimen (1 mg/kg/day starting in 2 month old pups and lasting till they reach 8 months, then the dose being increased to 10 mg/kg/day for 4 months), totally reversed the learning and memory deficits of AD mice [61]. This study suggests that losartan protects from cognitive decline through the vascular protection, glial cell activation and oxidative stress or yet AT1 receptor signaling but not through the amyloidogenic pathway since the amyloid burden remained unchanged.

Hypertension and Alzheimer's disease, hand by hand

Returning early in the history of AD, vascular disorder was in the front row but quickly became unattended. Later on, research uncovered an early vascular impairment in AD patients that worsens with age and that can predict the progression of the pathology. AD is a mysterious complex condition which is not fully understood and which prevalence will be dramatically increased the next 50 years. The cause of the disease remains unknown, some clues have been unraveled with the discovery of mutations in several genes, but the truth is that these mutations induce the pathology in less than 2% of the AD patients. Why sporadic, AD have a higher incidence in the present days may be explained by the life style of modern society. In this paper we discuss the accumulating scientific evidence on the strong link between AD and HT. Whether hypertension could cause AD or aggravate it, and what are the mechanisms involved remains elusive.

The vascular issue in AD is complex. There might be three ways in which vessels interact with the pathology. The first one is CAA in which the vessels are directly damaged by Aβ peptide causing a variety of modifications of the vascular bed resulting in hypo perfusion and are responsible for hypoxia and neuroglial energetic crisis, which leads to neuronal death. If hypertension enters the equation and remains untreated, it can lead to BBB leakage allowing entrance of neuro-toxic substrates into the brain, and, later in the course of the disease, to micro-bleedings or stroke, aggravating the whole scenario [62]. Along these lines, the limits between vascular dementia, mixed dementia and Alzheimer disease become blur [63].

The second way in which hypertension may aggravate AD is disrupting angiogenesis. We hypothesize that through angiogenesis, a healthy brain counteracts the hypoper fusion and hypoxia caused by the Aβ dependent impairment of vascular function. Henceforth, our model of dual pathology AD and HT [49] shows a significantly decreased cerebral micro vessel density, suggesting that HT might interfere with the angiogenesis process precluding the reestablishment of adequate brain perfusion.

The third mechanism may be that the high BP impairs cellular pathways implicated in regulating both vascular function and neuronal activity. The NO pathway is an example of such a common pathway [64,65]. The fact that the experimental studies have demonstrated that some antihypertensive drugs rescue from cognitive impairment, but were incapable to reduce the brain amyloid burden, suggests that still unraveled pathways play a prominent role in the pathogenesis of AD. The further elucidation of cellular and molecular mechanisms underlying the beneficial effects of antihypertensive drugs on cognition in AD may help to identify these pathways and to develop new affective therapeutic approaches in AD.

To conclude, the real problem with the conception of AD as a solely neurodegenerative condition is that neurons do not exist alone in the brain but as a part of neurovascular units. Blood vessels in the brain fulfill their essential function of delivering glucose, oxygen and nutrients and cleaning off wastes and neurotoxic substances, including Aβ. Consequently, neuro protective strategies are hopeless if the neuron's environment lacks the vital elements. Therefore, efforts must not only focus on neuro protective strategies to face dementia but on vascular protective strategies as well. Epidemiological and clinical studies in addition to animal experimental studies, have pointed out specific anti-hypertensive drugs as good candidates because they rescue cognitive impairment even though they do not deplete the brain from Aβ. According to published clinical trials, ACE inhibitor perindopril and ARB losartan seem to suit the best. High BP can be regulated through multiple pathways opening a vast new domain for choosing the appropriate anti-hypertensive regimen to treat AD. In conclusion we suggest that a therapy duo, that would associate both vascular and neuronal protective strategies, holds the key to fight efficiently AD.

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