Abstract

Purpose of Review There is an established association between hypertension and increased risk of poor cognitive performance and dementia including Alzheimer’s disease; however, associations between antihypertensive medications (AHM) and dementia risk are less clear. An increased interest in AHM has resulted in expanding publications; however, none of the recent reviews provide comprehensive review. Our extensive review includes 24 mechanistic animal and human studies published over the last 5 years assessing relationship between AHM and cognitive function.

Recent Findings All classes of AHM showed similar result patterns in animal studies. The mechanism by which AHM exert their effect was extensively studied by evaluating well-established pathways of AD disease process, including amyloid beta (Aβ), vascular, oxidative stress and inflammation pathways, but only few studies evaluated the blood pressure lowering effect on the AD disease process.

Summary Methodological limitations of the studies prevent comprehensive conclusions prior to further work evaluating AHM in animals and larger human observational studies, and selecting those with promising results for future RCTs.

Keywords Antihypertensive medication - Cognitive decline - Dementia - Alzheimer’s disease

Introduction

Alzheimer’s disease (AD), the most common cause of dementia [1], is characterized by extracellular amyloid beta (Aβ) deposition in the form of neuritic plaques, intracellular deposition of hyperphosphorylated microtubule-associated tau protein which culminates in synaptic loss, neuronal cell death, Aβ angiopathy, oxidative stress, and inflammatory processes resulting in cognitive impairment [2]. However, the exact mechanisms are still unclear.

There is a long established association between hypertension and increased risk of cognitive decline and AD in humans [3], but the potential association between antihypertensive treatment and reduced risk of AD has been harder to determine. Attempts to understand possible mechanisms have shifted attention toward the potential pleiotropic effects of the different classes of antihypertensive medication (AHM) and their potential impact on cognitive function [4, 5]. As a result, there are an increasing number of animal studies evaluating AHM, such as AHM acting through renin angiotensin system or altering calcium homeostasis.

This review aims to provide such an update in two parts. Part 1 provides an overview of the recent human observational and clinical trial literature, and part 2 reviews the recent physiological and animal work.
Methods

Search Strategy

The databases Embase, PsycINFO®, Medline, Medline in process, and other nonindexed citations and PubMed were searched from 2010 to February 2016 using the search terms: dementia or cognit* or mild cognitive impairment, and antihypertensives, or antihypertensive agents, or diuretics or diuretics that may be of significance in the development of dementia or mild cognitive impairment. Commercially available ACE-I was used as an antihypertensive medication alone [17, 19, 21, 29, 30].

Inclusion and Exclusion Criteria

Included animal or mechanistic studies required exposure to one of the antihypertensive classes of interest, calcium channel blockers (CCB), ARB, angiotensin converting enzyme inhibitors (ACE-I), beta blocker (BB), and diuretics, and to have a control or comparator group; however, a specific outcome measure was not required.

Article Selection

Abstracts were double read by SY and MS. Discrepancies were resolved by discussion. Full text articles were double read by the same team and data extracted into standard tables, collated by antihypertensive class.

Results

Animal and Human Mechanism Studies

Searches retrieved 138 PubMed records and 522 records from Medline, PsycINFO® and Embase. Of these, seven were review articles [6–12], 19 articles presented results from animal studies exploring mechanisms [13–31], and there were five human studies of which one was an autopsy study [32], two human cerebrospinal fluid (CSF) studies [33, 34], one small RCT [35], and one in vivo human cell study [36].

The methodology of the 19 animal studies varied widely in the selection of animals and drugs used, length of treatment times, and outcomes. Animal models ranged from mouse models using wild-type mice [13, 23], aged Swiss mice [31], wild-type mice treated with icv amyloid beta 25–35 to be used as an AD mouse model [27], and transgenic (Tg) AD mice alone [17, 19, 21, 29, 30], to rat models such as Wistar [18, 20], Sprague-Dawley [16, 22], or spontaneously hypertensive rats (SHR) [14, 15, 24, 26, 28]. Regarding AHM used, 17 of the 19 studies used CCB, ACE-I, or ARB alone or in combination. Commercially available ACE-I was used as captopril [17, 18, 29], enalapril [27], imidapril [27], lisinopril [14], perindopril [26, 27], and trandolapril [19]. ARBs used included losartan [18, 19, 25], olmesartan [24], telmisartan [15, 22, 28], and valsartan [14]. The renin inhibitor aliskiren was used in one study [13]. CCBs used included azelnidipine [24], isradipine [20, 30], lercanidipine [14], nicardipine [14, 16, 19, 20, 30], nifedipine [30], nimmopidine [16, 20, 22, 30], and a nonselective CCB flunarizine [31]. Other antihypertensives included BBs such as carvedilol and propranolol [19], diuretics such as amiloride and furosemide [19], and hydralazine [14, 19]. Experimental drugs such as angiotensin II [18], PD-123177 (angiotensin 2 receptor blocker) [20], and ICI 11,551 (a selective beta 2 receptor antagonist) [21] were also used. One study did not use antihypertensive medication [23]. One of the five identified human studies reported use of telmisartan and amloidipine [35], while four studies compared ARB users with other AHMs [32–34, 36]. Comparators used differed, as did the length of treatment times, which varied between 4 days and 15 months.

Outcome measures ranged from cognitive tests to biomarkers. Cognitive measures included water maze [15, 16, 19–21, 25, 26, 31], Y maze [13, 18], object recognition [21, 27], passive avoidance [18], open field [15, 22], and spontaneous alternation [27] tests. Locomotor function was assessed in five studies [22, 24, 26, 27, 31]. Numerous studies used serum, cerebrospinal fluid, or histopathological measures of amyloid beta and/or tau levels as their outcome [17, 19, 21, 23, 25, 29, 30]. Additional histopathological measures included pyramidal neurons in hippocampus [14], hippocampus morphology [16], and vascular pathology [24, 25]. Alteration in markers of oxidative stress [13, 18, 22, 24–26, 31], inflammation [13, 16, 22, 24, 26], apoptosis [20, 26], brain-derived neurotrophic factor (BDNF), and alpha tubulin levels [15] were also frequently used alone or in conjunction with cognitive measures. Some studies included measurement of various proteins of the renin angiotensin system (RAS) in the brain as their outcomes [13, 23, 25–27, 30]. Outcomes included infarct size [24, 31] and cerebral blood flow [13, 16, 24, 25] in studies evaluating the effect of antihypertensive medication in cerebral ischemia models. Surprisingly, only seven studies included blood pressure measurements as their outcome [13–15, 19, 24, 26, 28]. Human study outcomes also varied and included AD and vascular pathology in one autopsy study [32], amyloid and tau levels in cerebrospinal fluid (CSF) [33, 34], cognitive measures [36], and, in the small RCT, blood pressure measurements and cognitive outcomes [35].
CCB

One human study reporting on the effect of CCB use found that of the 167 AHM users, only nifedipine users had significantly lower Aβ levels when compared to 107 matched AHM never users [36] (Table 1).

Eight animal studies reported results of treatment with CCB alone [14, 16, 19, 20, 30, 31] or in combination with ARB [22, 23]. Azelnidipine decreased blood pressure, infarct size, and also reduced markers of oxidative stress and inflammation [24]. The nonselective CCB flunarizine reversed impairment in learning, memory, and motor function after cerebral ischemia and reversed cerebral ischemia-associated decrease in anti-oxidative stress markers [31]. Isradipine increased angiogenesis [30] and improved memory acquisition [20]. Lercanidipine decreased blood pressure and protected against neuronal death [14]. Nicardipine reduced Aβ1–42 and Aβ1–40 in the brain [19] and increased angiogenesis [30], but did not improve cognition [19]. Nifedipine increased angiogenesis [30]. Nimodipine improved regional cerebral blood flow and protected hippocampal morphology [16], reduced inflammatory markers [16], increased angiogenesis [30], improved memory acquisition [20], and prevented learning impairment in animals with cerebral ischemia [16] (Table 1).

ACE-I

The most extensively studied ACE-I was captopril, which was associated with genetic upregulation of proteins associated with neuronal function and membranes [17], reduced Aβ burden in the brain [17], decreased conversion of Aβ1–43 to Aβ1–42 [28], increased anti-oxidative stress markers [18], decreased oxidative stress markers [17], and better performance on learning and memory tasks [18]. Captopril treatment also inhibited ACE activity and decreased angiotensin II levels [17, 29]. Lisinopril did not protect against neuronal death even with significant blood pressure reduction [14]. Perindopril and enalapril inhibited plasma ACE activity by 90 % but only perindopril inhibited brain ACE activity by 50 % [27]. Perindopril decreased blood angiotensin II levels [26] and also levels of oxidative stress markers [26]. Perindopril improved memory function [26]. Trandolapril treatment reduced Aβ burden in the brain [19] (Table 2).

ARB

Losartan decreased angiotensin 1 and 4 receptor levels in the brain [25] and improved cerebral blood flow [25]. In one study, it decreased Aβ1–42 [19], while in another, it did not alter Aβ1–42 in the brain [25]. Treatment with losartan also resulted in better performance on learning and memory tasks [18, 25]. Telmisartan improved cerebral blood flow in humans [35], reduced neurologic deficits and improved locomotor function after cerebral ischemia [22, 35], reduced inflammatory and oxidative stress markers [22], reduced low-density receptors and apolipoprotein E expression in the brain [28], and increased BDNF levels in the hippocampus [15]. Treatment with telmisartan resulted in better performance on learning and memory tasks in animals [15]; however, there was no improvement in memory in people [35]. Olmisartan did not reduce blood pressure but reduced infarct size in cerebral ischemia and inflammatory markers [24]. Valsartan reduced blood pressure but did not protect against neuronal death [14] (Table 2).

ARBs were studied as a class in human studies. One brain autopsy study showed that ARB use was associated with significantly lower AD pathology, while no alteration of vascular pathology was observed when compared to other or no antihypertensive medication users [32]. Additionally, it was found that ARB use in people with normal cognition or mild cognitive impairment (MCI) was associated with lower levels of tau and phosphorylated tau [32, 34] and higher levels of Aβ1–42 in cerebrospinal fluid [34], and with decreased risk of dementia [34] when compared to other antihypertensive medication users (Table 2).

Diuretics

Only one animal study evaluated a diuretic, furosemide, and found that it reduced brain Aβ1–42 without affecting blood pressure [19].

BBs

Two animal studies reported on the effect of BB use (Table 3). Treatment with nonselective beta adrenergic receptor blockers, carvedilol and propranolol, resulted in decreased brain Aβ1–40 and Aβ1–42 levels; however, this did not translate into improved cognition [19]. Carvedilol reduced Aβ1–42 in the brain without affecting blood pressure [19]. In contrast, treatment with a selective beta 2 adrenergic receptor (β2AR) antagonist resulted in significantly worse working memory and increased amyloid plaque burden, Aβ1–42 levels, tau phosphorylation, and accumulation in the hippocampus, suggesting involvement of β2ARs in the amyloid pathway and in cognitive function [21].

Discussion

The importance of dementia as a clinical and public health issue is rapidly increasing as the population ages [37]. Thus, identifying new and effective approaches to prevention or treatment is critical. Due to the lengthy process of developing new medications, there has been a recent surge in interest
Table 1  Extraction table for mechanism studies: calcium channel blockers (CCB)

| Author            | Method: subjects | Method: groups | Method: treatment | Method: treatment route | Method: treatment time | Method: outcome                                                                 | Method: statistic       | Result                                                                 |
|-------------------|------------------|----------------|-------------------|------------------------|------------------------|-------------------------------------------------------------------------------|-------------------------|------------------------------------------------------------------------|
| Daschil et al.    | -Tg (APP-SD1) mice -WT (C57BL/6N) mice | -Four groups   | -Nicardipine      | -Nifedipine            | -Nimodipine            | -4 weeks                                                                     | -Aβ plaques in cortex   | Fisher t test -Aβ plaques were detected in cortex of TgAPP mice, while none in WT mice |
|                   |                  |                |                   |                        |                        | -L-type calcium channel subunit expression in plaques                          |                         | -L-type calcium channel subunit expression seen was in plaques, but not around |
|                   |                  |                |                   |                        |                        | -Angiogenesis in cortex slices after treating with L-type calcium channel blockers |                         | -L-type calcium channel inhibition with isradipine or nicardipine or nifedipine or nimodipine produced angiogenesis |
|                   |                  |                |                   |                        |                        |                                                                                |                         | -Aβ pretreated rats had delayed acquisition in memory tasks and this effect was reversed by higher dosages of isradipine, nimodipine |
|                   |                  |                |                   |                        |                        |                                                                                |                         | -Calpain 2, Caspase 12 and 3 were increased in Aβ pretreated rats which was reversed isradipine, nimodipine |
|                   |                  |                |                   |                        |                        |                                                                                |                         | -Stroke was associated with increased calcium and AchE activity and decreased GSH, which was reversed by flunarizine and donepezil |
| Gholamipour-Badie et al. | -Wistar rats | - Two groups | -Control           | -Aβ1–42                | -Aβ1–42 + isradipine    | -6 days                                                                      | -Morris water maze test | ANOVA -Lower and higher dose of flunarizine, and donepezil decreased impairment of learning, memory, motor function, and infarct size |
|                   |                  |                |                   |                        | -Aβ1–42 + nimodipine    |                                                                                |                         | -Stroke was associated with increased calcium and AchE activity and decreased GSH, which was reversed by flunarizine and donepezil |
| Gulati et al.  | -Aged Swiss mice | -N= 6         | -Control           | -Sham surgery (no carotid occlusion) -Bilateral carotid occlusion and reperfusion -20 mg flunarizine 1 h before carotid occlusion and reperfusion -40 mg flunarizine 1 h before carotid occlusion and reperfusion -5 mg donepezil 1 h before carotid occlusion and reperfusion | -Flunarizine (nonselective CCB) -Donepezil (acetylcholinesterase inhibitor (AchE-I)) | -Morris water maze test | -Motor-in-coordination -Cerebral infarct size -Glutathione (GSH), total calcium and AchE activity in brain tissue | ANOVA                   | -Flunarizine pretreatment resulted in less neurologic deficit and locomotor function |
| Justin et al. | -Sprague Dawley rats | -N= 5         | -Sham surgery (no carotid occlusion) -Bilateral carotid occlusion and reperfusion + carboxymethyl cellulose (CMC) -Bilateral carotid occlusion and reperfusion + telmisartan 5 mg/kg -Bilateral carotid occlusion and reperfusion + telmisartan 10 mg/kg | -Telmisartan -Telmisartan + nimodipine | -9 days | -Day 2 neurological assessment -Day 7 behavioral assessment -Day 9 histopathological studies -Day 9 oxidative stress and inflammation markers | Logistic regression model | -Telmisartan pretreatment resulted in less neurologic deficit and locomotor function |
|                  |                  |                |                   |                        |                        |                                                                                |                         | -Telmisartan increased glutamate, aspartate, and ATP levels in brain and decreased glutathione, nitric oxide levels |
|                  |                  |                |                   |                        |                        |                                                                                |                         | -Telmisartan decreased the pro-inflammatory cytokine (IL-1β, IL-6, TNF-α), lipid peroxide and nitric oxide levels; and increased anti-inflammatory cytokine IL-10 level |
| Author | Method: subjects | Methods: groups | Method: treatment | Methods: treatment route | Method: treatment time | Method: outcome | Method: statistic | Result |
|--------|-----------------|----------------|------------------|------------------------|----------------------|----------------|-----------------|--------|
| Lovell et al. [36] | Humans (case control study, \(N=1100\), >60 years old, mild dementia) | \(N=274\) | telmisartan 5 mg/kg + nimodipine 5 mg/kg | \(N=32\) CCB users with \(N=31\) matched nonusers | -Progression to dementia | Regression model | -CCB users had less decline than nonusers, and it decreased effect of ApoE presence | -Best results in all was when telmisartan was given in combination with nimodipine |
| Omote et al. [24] | Spontaneously hypertensive rats (SHR) | \(N=6\) | -Control was treated with carboxymethyl cellulose (CMC) | po | -14 days | Blood pressure (BP) | ANOVA | -BP, pulse, decreased while body weight, rCBF remained stable in all treatment groups compared to control group |
| Sakurai-Yamashita et al. [14] | Spontaneously hypertensive rats (SHR) | \(N=6\) | -Control with carotid occlusion | -Lercanidipine and nicardipine po in diet | -14 days | Delayed neuronal death of pyramidal neurons in hippocampus | ANOVA | -Blood pressure was reduced in all treatment groups but only lercanidipine protected against neuronal death, while other treatments did not provide protection |
| Wang et al. [19] | Tg2576 mice | -1600 FDA approved drugs were screened for A\(\beta\) regulating effect 184 drugs lowered A\(\beta\) by >30% and 26 drugs increased A\(\beta\) levels by >30% | -Drinking water | -1 month | -Blood pressure measurement | ANOVA | -Short-term use: propranolol, losartan significantly reduced blood pressure by 20%; propranolol, nicardipine, carvedilol reduced significantly A\(\beta\) 1–42 and 1–40 by 40% in the brain and plasma, losartan reduced A\(\beta\) 1–42 but not 1–40 |

Table 1 (continued)
| Author          | Method: subjects | Methods: groups | Method: treatment | Method: treatment route | Methods: treatment time | Method: outcome | Method: statistic | Result                                                                 |
|-----------------|------------------|----------------|------------------|-------------------------|-------------------------|----------------|----------------|---------------------------------------------------------------|
| Zhang et al.    | Sprague-Dawley rats | N = 4          | -Sham surgery    | -Via gastric perfusion  | -4 days                 | -Morris water maze test | ANOVA       | -long term treatment with propranolol and nicardipine did not improve cognition, but decreased Aβ in brain but not plasma |
|                 |                   |                | -Focal cerebral ischemia |                         |                         | -Brain MRI PWI       |              | -Vascular dementia group pretreated with nimodipine performed better on learning, had better regional cerebral blood flow, and had lower levels of NF-kB, TNF-α, IL-1β; hippocampus cell morphology was almost normal in this group similar to normal control and focal ischemia group |
|                 |                   |                | -Vascular dementia (bilateral carotid artery occlusion and reperfusion) |                         |                         | -Hippocampal levels of nuclear factor kB (NF-kB), tumor necrosis factor α (TNF-α), interleukin 1β (IL-1β) |              | |
|                 |                   |                | -Vascular dementia (bilateral carotid artery occlusion and reperfusion) pretreated with nimodipine 20 mg/kg |                         |                         | -Hippocampus nerve cell morphology |              | |
|                 |                   |                |                   |                         |                         |                   |              | |
|                 |                   |                |                   |                         |                         |                   |              | |
|                 |                   |                |                   |                         |                         |                   |              | |

Table 1 (continued)
Table 2  Extraction table for mechanism studies: angiotensin receptor blocker (ARB), angiotensin converting enzyme inhibitor (ACE-I), and diuretic

| Author       | Method: subjects | Methods: groups | Method: treatment | Method: treatment route | Method: treatment time | Method: outcome | Method: statistic | Result                                                                                                                                                                                                                                                                 |
|--------------|------------------|-----------------|-------------------|------------------------|------------------------|-------------------|------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| AbdAlla et al. [17] | Aged Tg2576 mice | -N= 2           | -Control          | -Captopril             | -6 months              | A\(\beta\) plaque load in hippocampus | ANOVA            | -Captopril treated Tg mice had significantly lower A\(\beta\), upregulated genes associated with neuronal membrane and neuronal process, reduced oxidative stress markers, reduced amyloidogenic process of APP, and decreased ACE and angiotensin II levels. This effect is most likely direct effect of the centrally acting captopril (not observed in enalapril which only acts peripherally) |
| Bild et al. [18] | Wistar rats      | -N= 5           | -Control (saline) | -Angiotensin II        | -i.c. v.                | -Y-maze task      | ANOVA            | -On Y maze task angiotensin II-treated animals preformed worse and captopril, losartan and PD 123177 treated animals did significantly better when compared to control group. In avoidance task angiotensin II-treated animals performed worse and losartantreated animals performed better when compared to control group. SOD, GPX, and MDA activity was decreased in angiotensin II-treated rats and increased in captopril-treated rats, when compared to control group |
| Dong et al. [13] | WT mice (C57BL/6 J) | -N= 3           | -Sham surgery     | -Bilateral carotid occlusion and reperfusion + vehicle | -Mini pump              | -Blood pressure   | ANOVA            | -Aliskerin did not alter blood pressure or cerebral blood flow |
| Goel et al. [26] | Wistar rats      | -N= 8           | -Wistar rats treated with vehicle | -i.c. v. LPS perindo- | -15 days              | Blood pressure    | ANOVA            | -LPS caused impaired memory in SHR and in normal rats which was reversed by perindopril. In SHR ACE activity and gene expression, angiotensin II level, oxidative stress, and inflammatory markers were increased. LPS caused further increase in ACE activity and gene expression, angiotensin II level, oxidative stress, |
| Author                  | Method: subjects | Methods: groups | Method: treatment | Method: treatment route | Method: treatment time | Method: outcome | Method: statistic | Result                                                                 |
|------------------------|------------------|-----------------|-------------------|------------------------|------------------------|-----------------|------------------|------------------------------------------------------------------------|
| Hajjar et al. [32]     | N = 890 participants with hypertension and autopsy available | N = 3           | Wistar rats treated with LPS 50 μg + perindopril 0.1 mg/kg | -po                    | -3 days                | AD pathology (CERAD, ADRDA/Khachaturian, Pathologic diagnosis) | Logistic regression analysis | -ARB users when compared to other and no antihypertensive medication users had significantly less AD pathology (50% reduction) |
| Hajjar and Levey 2015 [33]| N = 319 participants with CSF available | N = 2           | Wistar rats treated with perindopril 0.1 mg/kg | -po                    | -3 years               | Vascular pathology (large artery infarcts, microinfarcts, hemorrhage, atherosclerosis, arteriosclerosis) | Mixed model | -ARB use was associated with higher vascular pathology |
| Justin et al. [22]     | Sprague Dawley rats | N = 5           | SHR treated with LPS 25 µg + perindopril 0.1 mg/kg | -po                    | -9 days                | Day 2 neurological assessment | Logistic regression model | -Telmisartan pretreatment resulted in less neurologic deficit and locomotor function |
| Kishi et al. [15]      | Spontaneously hypertensive rats (SHR) | N = 5           | SHR treated with perindopril 0.1 mg/kg | -po                    | -4 weeks               | Blood pressure and heart rate | ANOVA            | -Telmisartan decreased the pro-inflammatory cytokine (IL-1β, IL-6, TNF-α), lipid peroxide and nitric oxide levels; and increased anti-inflammatory cytokine IL-10 level |

and inflammatory markers, which was decreased by perindopril
| Author          | Method: subjects | Methods: groups | Method: treatment | Method: outcome | Method: statistic | Result                                                                 |
|-----------------|------------------|-----------------|-------------------|----------------|------------------|-------------------------------------------------------------------------|
| Kume et al.     | 20 patients with hypertension and AD | $N = 2$ | $N = 10$ Telmisartan 40-80 mg daily | $N = 10$ Amlodipine 5-10 mg daily | -6 months | Blood pressure, Heart rate, Cognitive test (MMSE, ADAS-Cog, logical memory), Regional cerebral blood flow (rCBF) measured by SPECT, ACE2 (which transforms angiotensin 1–10 to angiotensin 1–9 activity (mice), Aβ levels (Aβ43, Aβ42, Aβ40), Angiotensin II levels (humans) | ANCOVA - Systolic blood pressure was better in both groups - rCBF improved significantly in areas of frontal, parietal, occipital lobe in telmisartan users - no improvement in cognition - ACE2 converted Aβ43 to Aβ42 - ACE converted Aβ43 to Aβ40 - ACE2 activity was decreased in human serum - Serum angiotensin levels were similar in people with AD and normal controls - Older people had lower CSF Aβ1–42 - ARB users had higher levels of CSF Aβ1–42 and lower levels of CSF p-tau than the other groups - ARB users were less likely to progress to dementia |
| Liu et al.      | Wild mice (C57BL/6J) Humans with AD and normal controls | $N = 9$ | | | Mann-Whitney U test | -ACE2 converted Aβ43 to Aβ42 - ACE converted Aβ43 to Aβ40 - ACE2 activity was decreased in human serum - Serum angiotensin levels were similar in people with AD and normal controls - Older people had lower CSF Aβ1–42 - ARB users had higher levels of CSF Aβ1–42 and lower levels of CSF p-tau than the other groups - ARB users were less likely to progress to dementia |
| Nation et al.   | 871 stroke and dementia free people with available CSF | $N = 3$ | $N = 90$ have used ARB | $N = 90$ have used other antihypertensive medication | -24 months | CSF Aβ1–42, p-tau levels | ANCOVA - Older people had lower CSF Aβ1–42 - ARB users had higher levels of CSF Aβ1–42 and lower levels of CSF p-tau than the other groups - ARB users were less likely to progress to dementia |
| Omote et al.    | Spontaneously hypertensive rats (SHR) | $N = 6$ | | | | -BP and pulse decreased while body weight and rCBF remained stable in all treatment groups compared to control group - Infarct volume decreased in olmesartan and azelnidipine-treated group, and it was more effective than low-dose monotherapy; however, high-dose azelnidipine (better BP reduction) was more effective than high-dose olmesartan - All treatments reduced oxidative markers, inflammatory markers, and preserved neurovascular unit in a dose-response manner - In old TgAPP mice losartan did not improve learning but improved memory acquisition and recall - In old TgAPP SOD, ANG1R, and ANG4R levels were increased which was reduced with Losartan |
| Ongali et al.   | TgAPP mice        | $N = 4$ | | | | -In old TgAPP mice losartan did not improve learning but improved memory acquisition and recall - In old TgAPP SOD, ANG1R, and ANG4R levels were increased which was reduced with Losartan |

Table 2 (continued)
| Author | Method: subjects | Methods: groups | Method: treatment | Methods: treatment route | Method: outcome | Method: treatment time | Method: statistic | Result |
|--------|-----------------|----------------|------------------|-------------------------|----------------|----------------------|-----------------|--------|
| Wang et al. [19] | Tg2576 mice | -1600 FDA approved drugs were screened for Aβ regulating effect: 184 drugs lowered Aβ by >30% and 26 drugs increased Aβ levels by >30% | Drinking water | -1 month -Selected group for chronic treatment: 6months | -SOD levels in brain -Angiotensin 1 and 4 receptors (ANG1R, ANG4R) | -Blood pressure measurement -Total Aβ1–40 or Aβ1–42 in the brain and plasma after short-term treatment -Morris water maze test after long-term treatment | ANOVA | -Losartan increased CBF i cerebral glucose uptake, and cerebrovascular responsiveness in old TgAPP mice -Losartan did not decrease AD pathology (Aβ1–42) -Short-term use: propranolol, losartan significantly reduced blood pressure by 20%; propranolol, nicardipine, carvedilol reduced significantly Aβ1–42 and 1–40 by 40% in brain and plasma, losartan reduced Aβ1–42 but not 1–40 -Furosemide and trandolapril significantly reduced Aβ without affecting BP -Long-term treatment with propranolol and nicardipine did not improve cognition but decreased Aβ in brain but not plasma |
| Yamada et al. [27] | Wild-type mouse treated i.c.v Aβ25–35 (AD mouse model) | -Perindopril (0.1, 0.3, 1.0 mg/kg) -Imidapril (0.3, 1.0, 3.0 mg/kg) -Enalapril (1.0, 3.0, 10 mg/kg) | po | -5 days | -Spontaneous alteration test (SAT) -Object recognition test -Spontaneous locomotor activities -Anxiety-related behavior in elevated plus maze -ACE activity in brain and plasma | ANOVA | -Perindopril in all dosages improved working memory (measured by SAT), object recognition -Plasma ACE was inhibited perindopril 1 mg/kg, imidapril 3 mg/kg, 10 mg/kg enalapril by 90% -Brain SACE was inhibited by 50% by 1 mg/kg perindopril but was less in other ACE-Is |
| Zhai et al. [28] | Wistar rats -Spontaneously hypertensive rats (SHR) | -Wistar rats -SHR treated with Vehicle -SHR treated with Telmisartan 0.3 mg/kg SHR -SHR treated with Telmisartan 3 mg/kg SHR | po | -3, 9, and 15months | -Blood pressure -LDL receptor, ApoE expression in the cortex and hippocampus | ANOVA | -In the cortex and hippocampus of SHR ApoE expression and LDL receptors was increased at all ages but was significantly reduced in both doses of telmisartan -At low dose, blood pressure remained unchanged |
| Zou et al. [29] | Tg2576 mice | -Tg2576 mice treated with captoril 0.25 mg/kg -Tg2576 mice treated with vehicle -TgAPP J20 mice | po | -11 months | -Aβ levels in brain (Aβ1–40, Aβ1–42, Aβ1–43) -ACE activity in brain | Student's t test Spearman's rank test | -In TgAPP mouse Aβ1–43 occurs before Aβ1–40 and Aβ1–42 -ACE converted Aβ1–43 to Aβ1–40 -Captoril pretreatment decreased ACE activity by 26% and increased Aβ1–43 deposition -In people with AD serum, Aβ1–43 level is higher and CSF level is lower when compared to normal control |

Table 2 (continued)
toward re-purposing currently available medications for the treatment of AD, including AHM. In this paper, we provide an extensive review of 24 mechanistic animal and human studies published over the last 5 years assessing the relationship between AHM and cognitive function.

Previous studies have shown a possible protective effect of certain AHM against AD risk [1], and it has been suggested that this protective effect is independent of, or in addition to, the blood pressure lowering effect [4, 5]. It is therefore not surprising that the mechanistic studies have focused on evaluating effects of AHM on well-established pathways in the AD disease process, including Aβ, vascular, oxidative stress, and inflammation pathways [2].

Of the six CCBs, nimodipine has been the most widely studied, and it was associated with angiogenesis and neuroprotection in the hippocampus, reduced inflammation, and improved cognitive function, but not with improved cerebral blood flow. Flunarizine and isradipine also improved cognition and had some effect on some of the above mentioned pathways.

Of the five ACE-Is studied, most studies evaluated effects of captopril and perindopril. Captopril was associated with neuroprotection [17], reduced Aβ burden in the brain [17, 29], decreased oxidative stress [17, 18], and better cognitive performance [18]. This effect was mediated by alteration of ACE activity and angiotensin II levels in the brain [17, 29]. Perindopril was associated with decreased oxidative stress [26] and improved cognitive function [26] and was shown to inhibit ACE activity in both blood and the brain ACE [27]. These findings suggest the beneficial effect of ACEs when crossing the blood-brain barrier; however, a previous observational study by Sink et al. did not support this hypothesis [38].

Of the four ARBs studied, losartan and telmisartan were examined in detail. Losartan use was associated with improved cerebral blood flow [25]. Yet, its effect on Aβ1–42 was equivocal with one study showing decreased levels [19], while another unchanged levels of Aβ1–42 [25]. Treatment with losartan also resulted in better performance on learning and memory tasks [18, 25]. These findings suggest beneficial effect via vascular rather than amyloid pathways, which is supported by its angiotensin 1 and 4 receptor lowering effect in the brain [25]. The other medication evaluated in detail was telmisartan, which, similar to losartan, was associated with improved cerebral blood flow in humans [35], reduced inflammation, oxidative stress [22], and markers of brain lipid metabolism [28]. Telmisartan also improved cognitive performance in animals [15], however, not in humans [35]. This negative finding in humans was replicated in a large multinational double-blind randomized placebo controlled trial, TRANSCEND, comparing ARB (telmisartan) use to placebo [3].

Previous animal studies and also RCTs with AHM have shown that blood pressure reduction, particularly in close proximity to development of cognitive impairment, does not alter dementia risk. Additionally, it is possible that treatment comes too late to mitigate the injury related to chronic exposure, suggesting an earlier window of benefit after which neural damage is hard to remediate. Thus, other mechanisms involved in AD development should to be explored. Medications explored in mechanistic studies have been different agents to those used in RCTs.

Conclusions

Similar to human observational studies and RCTs, different classes of AHM show similar result patterns in animal studies. Inconsistencies in the sources of evidence from the use of different animal types, ages, treatment times, and outcome
measures limit the possibility of drawing firmer conclusions. Similar to observational studies, the relative lack of information on blood pressure levels is a major limitation. These limitations restrict our ability to draw wider ranging conclusions about use of specific antihypertensive classes, subclasses, or individual drugs. However, AHM that have had promising results in animals and larger human observational studies should be selected for future RCTs.

Compliance with Ethical standards

Conflict of Interest Dr. Peters reports grants from National Institute of Health Research and Imperial College, London. Drs. Schuchman, Jean Peters, Carlson, and Yasar declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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