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New insights into repurposing of renin-angiotensin system inhibitors against Alzheimer's disease

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ABSTRACT

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by a complex and multidimensional pathology, including amyloid-β plaques, hyperphosphorylated tau, neurofibrillary tangles, neuroinflammation, and oxidative stress. The renin-angiotensin system (RAS) plays a multifaceted role in the brain, with elevated levels of Angiotensin II (Ang II) and the up-regulation of angiotensin-converting enzyme (ACE) and angiotensin-1 (AT1) receptors being potential contributors to AD. ACE inhibitors such as Captopril, Fosinopril, Lisinopril, Perindopril, Trandolapril, and Zofenopril, along with angiotensin receptor blockers (ARBs) such as Azilsartan, Candesartan, Telmisartan, and Valsartan, are capable of crossing the blood–brain barrier. Pre-clinical and clinical studies have demonstrated that these RAS inhibitors exhibit anti-Aβ plaque, anti-tauopathy, free radical scavenging, and anti-inflammatory activities, making them highly reliable and effective potential therapeutic approaches for AD.

INTRODUCTION

Alzheimer's disease (AD) is a progressive neuro-degenerative disease. It is the most common form of dementia. Generally, it affects older people above 65 years of age. However, it can occur at any age. Clinical symptoms of AD include progressive loss of memory, irritability, impairment in cognitive function, and a mess in thinking and decision-making ability [1]. AD is characterized by the deposition of neurofibrillary tangles (NFTs) resulting from the aggregation of hyperphosphorylated tau protein and amyloid-β ($A\beta_{1-42}$) peptides. In addition, hyperactivation of the acetylcholinesterase enzyme (AChE), upregulation of glutamate transmission, glial cell activation, oxidative stress, mitochondrial dysfunction, and neuro-inflammation also occur in the AD brain. There is neuronal death, loss of synaptic plasticity, and shrinkage in the hippocampal region [2]. Age, chronic diseases, cardiovascular diseases, hypertension, diabetes, genetic, and environmental changes are some triggering factors for AD [3,4,5].

Only four medications are approved by FDA for the treatment of AD. Based on the mechanism of action, they are anti-cholinesterase inhibitors (Galantamine, Donepezil, and Rivastigmine) and NMDA (N-methyl-D-aspartate) receptor antagonists (Memantine). These medications only address the symptoms rather than the disease progression [6]. So, there is a need for new therapeutic approaches for AD. Again, the blood–brain barrier (BBB) plays a key role in drug delivery. Not all active drug moieties can cross BBB. So, it is necessary to target BBB during drug development against neurodegenerative diseases including AD [7].

Enormous shreds of evidence show aging and raised blood pressure are important risk factors for AD progression. The renin-angiotensin system (RAS) is an endocrinal hormonal system that mediates several physiological and pathological functions by controlling salt and water retention, blood volume, and systemic vascular resistance. Hypertension arises due to an imbalance of the RAS. Hyperactivation of RAS in the brain is responsible for the induction of AD. It generates oxidative stress and neuronal inflammation. In the AD brain, there is an

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inadequate blood supply and insufficient clearance of metabolic waste products. So, inhibition of RAS in the brain can enhance cognition in AD patients [8,9]. The review aims to insight into the novel use of RAS inhibitors against AD. It describes all the preclinical and clinical studies using search engines such as Scopus, Google Scholar, Science Direct, and PubMed with the keywords AD, Angiotensin, ACE, and angiotensin receptor blockers (ARBs), mainly from 2015 to 2024.

ALZHEIMER'S DISEASE

There is no exact etiology of AD established to date. However, NFTs inside neurons and amyloid plaques between neurons are the hallmarks of AD [10]. NFTs are formed by the hyperphosphorylation of Tau protein (p-tau). Tau is an important protein for stabilizing microtubules [11]. Insoluble β-Amyloid ($A\beta_{1-42}$) is a neurotoxic substance produced by cleaving amyloid precursor proteins (APPs). Deposition of Aβ peptide causes the aggregation of soluble oligomers and the formation of senile plaque. In the AD brain, there is a decline in the clearance of oligomerized Aβ [12]. Aβ-oligomer is capable of producing reactive oxygen or nitrous species (ROS/RNS) by postponing scavenging activity. The presence of ROS/RNS activates the microglia cells leading to mitochondrial dysfunction and the generation of pro-inflammatory markers [13,14].

Another hypothesis is on the role of neurotransmitters in AD. Acetylcholine (ACh) is a major neurotransmitter in the hippocampal area. In AD, the amount of ACh declines due to over activity of the AChE. Less availability of ACh causes improper synaptic transmission through muscarinic and nicotinic receptors leading to cognitive impairment [15]. In a normal brain, glutamate acts as an NMDA receptor agonist and plays a role in maintaining synaptic plasticity. Excessive production and release of glutamate cause neuronal damage [16]. Genetically, AD is developing due to the mutations in Apo lipoprotein E4, presenilin-1, and presenilin-2 genes [17,18].

Brain Renin-angiotensin system and Alzheimer's diseaseThe brain also contains the peripheral RAS components. Conversion of angiotensinogen to Ang I is done by renin-mediated cleavage. Ang I is then converted to Ang II by ACE-I. Ang II activates the angiotensin type-1 (AT_1 R) receptor. RAS causes neurodegeneration through Ang II- AT1 receptor stimulation inside the brain. Ang II induces the production of neurotoxic oligomerized Aβ and hyperphosphorylated tau [19]. The activated brain RAS uplifts the production of ROS and RNS. ACE-I is associated with neuroinflammation, oxidative stress, glial cell activation, elevated γ-secretase activity, and brain atrophy [20,21]. Binding of Ang II with AT_1 R activates the mitogen-activated protein kinase (MAPK), NRF2 and the JNK signaling pathway prompts vascular resistance, inflammation, and oxidative stress [22,23]. Hence, excessive Ang II concentrations, and up-regulation of ACE and AT_1 receptors are the potential contributors (Fig. 1) to AD [9,24].

On the other hand, Ang II is inactivated by ACE II to produce angiotensin 1-7, which can activate the MAS1 receptor and exert vasodilator effects. Ang II also activates the AT2 receptor. AT_2 receptors mediate anti-inflammatory and anti-fibrotic effects. Mas receptors mediate anti-inflammatory effects. So, the components of the angiotensin system like ACE

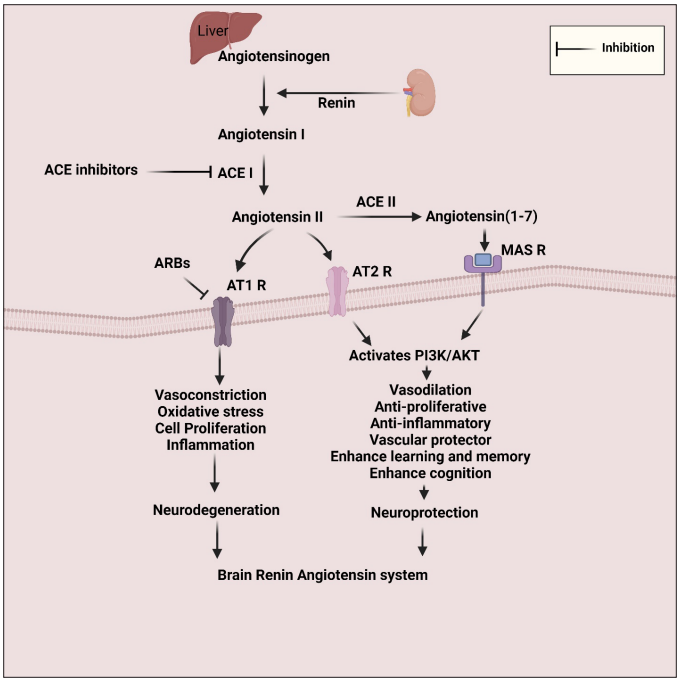

Figure 1. RAS in neurodegeneration and neuroprotection [The neuro-degenerative effects of Ang II are associated with ACE-I and AT1 receptors. The neuroprotective effects of Ang II are associated with the AT2 receptor and that of Ang 1-7 are associated with ACE-II and Mas receptor].

II, MAS1, and the AT2 receptor reverse the neurodegenerative effects of ACE and the AT1 receptor [9,25,26].

Stress, age, and chronic vascular disorders are major risk factors for up-regulating the brain RAS through the hypothalamic-pituitary-adrenocortical axis. Evidence of chronic unpredictable mild stress on a non-transgenic model found the hyperactivity of ACE protein, p-tau, and oligomerized Aβ in the hippocampal region [27]. From a meta-analysis, it is revealed that there is a synchronized correlation found between ACE 1 and *ApoE* ε4 allele [28]. The modified *ApoE* ε4 gene allele has a significant role in the development of sporadic AD due to the unbalancing lipid level in the brain [29]. An age-related cognitive impaired brain down-regulates the ACE II and AT2 receptors. Activation of AT_1 and nicotinamide oxidase (NOX) activate the nuclear factor kappa B (NF-kB), RhoA/Rho kinase pathway and inhibit PI3K/Akt signaling and glycogen synthase kinase- 3 beta (GSK-3β). Oxidative stress is mediated by nicotinamide adenine dinucleotide phosphate (NADPH) NOX which further stimulates superoxide production. Free radicals cause neuronal dysfunction, and neuronal death [30] and encourage neuronal inflammation by upregulating tumor necrosis factor α (TNFα), and proinflammatory cytokines like IL-1β and IL-6 [31]. Apoptosis cascade and neuronal inflammation induce neuronal death, reduction in ACh, and impaired G-protein signaling [32] (Fig. 2).

RAS INHIBITORS IN AD

A lot of RAS components are altered in the AD brain. Arterial hypertension is a major contributor to the development of AD. So, anti-hypertensive drugs inhibiting RAS are now

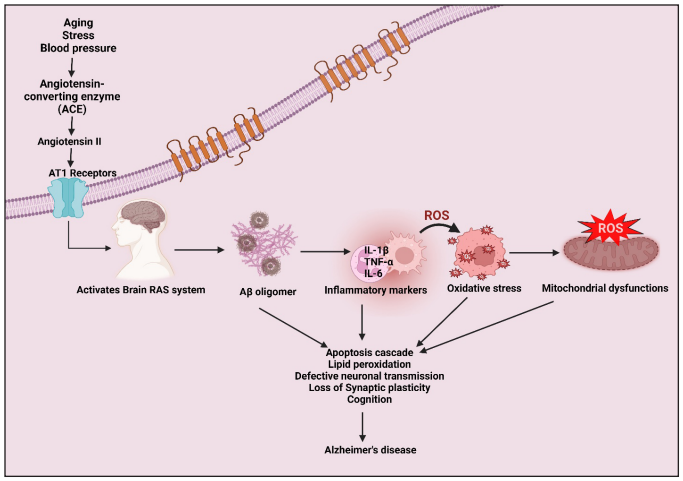

Figure 2. Angiotensin II (Ang II) in the pathogenesis of AD [Ang II oligomerizes Aβ, encourages the inflammatory, oxidative, and apoptosis pathways thereby resulting in loss of synaptic plasticity and integrity; impaired cognition and neuronal transmission].

repurposed for AD management. Notably, the AD patient's brain has a higher amount of ACE-I, which produces Ang II and aldosterone [33]. Targeting these two components can be useful in RAS-induced AD. Anti-hypertensive drugs like ACE inhibitors and Ang II receptor (AT1 receptor)ARBs are the first-line treatment options due to their indication and safety profile [34]. These two classes of drugs down-regulate the RAS. ACE inhibitors inhibit the ACE-I and ARBs block the AT_1R.

The ACE inhibitors such as Benazepril, Enalapril, Moexepril, Quinapril, and Ramipril cannot cross the BBB. In contrast, Captopril, Fosinopril, Lisinopril, Perindopril, Trandolapril, and Zofenopril are the drugs that penetrate BBB [35]. Similarly, ARBs such as Eprosartan, Irbesartan, Losartan, and Olmesartan do not cross BBB whereas the drugs such as Azilsartan, Candesartan, Telmisartan, and Valsartan can cross the BBB [36].

Preclinical studies

The *in-vitro* and *in-vivo* studies on ACE inhibitors and ARBs are given in Table 1.

ACE inhibitors

ACE inhibitors are structurally and chemically different. Based on the presence of different chemical groups they are classified into three groups such as sulfhydryl-containing ACE inhibitor (Captopril), dicarboxyl-containing ACE inhibitor (Enalapril), and phosphorus-containing ACE inhibitor (Fosinopril). Different ACE inhibitors have different pharmacokinetic properties and potency based on chemical structure. According to the drug bank data, lisinopril and captopril exhibit 30%–75% bioavailability, respectively. Other ACEIs are considered prodrugs due to their very low bioavailability ranging from 4% to 60%. All are orally absorbed but show different rates of crossing the BBB. Lipophilicity is denoted in log *p* value. This property strongly decides the BBB permeability of ACEIs. An increase in log *p* enhances the permeability. Fosinopril has the highest log *p* value (4.71) with the highest BBB permeability among ACEIs whereas Lisinopril has the lowest (−1.2) log *p* value [37,38].

In vitro studies

Both Perindopril and Captopril reduce NO production and activate the transregulation and translation of microglial cells. Both reduce bradykinin production, and neuronal inflammation and improve neurodegeneration [39,40]. Enalapril reduces Aβ-peptide formation, ROS production, and TNFα. It decreases the mortality of cells in human neuroblastoma cells. It declines apoptotic measurement, decreases nitrite concentration, and scavenges the activity of free radical and peroxy nitrate [41]. In an LPS-induced cell line model, Captopril attenuates NO production, reduces iNOS, decreases TNFα, and decreases amyloid plaque in the hippocampus and cortex region [39]. So, the anti-oxidant and neuroprotective effects of ACEIs may be useful in the treatment of AD and other neurodegenerative disorders.

In vivo studies

Captopril

Captopril delays neurodegeneration by reducing tau hyperphosphorylation (p-tau), and regulating the amyloidogenic process of APP [42,43]. In STZ induced cognitive impairment model, Captopril increases SOD (superoxide dismutase) and Catalase; reduces MDA (malonyl dialdehyde) and NOX [42]. It significantly suppresses the apoptotic marker Bax and the inflammatory markers such as NF-kB, IL-1 β, COX-1, and COX-2; and elevated anti-apoptotic Bcl-2 levels in H_2O_2-induced oxidative damage in C6 cells [44]. This shows that the anti-oxidant and anti-inflammatory actions of Captopril may be attributed to its efficacy in improving learning and memory.

It remarkably improves cognition, particularly in APoE4- carriers of specific ACE genotypes [45]. In scopolamine-induced memory deficits, Captopril improves spatial learning and memory at 25 mg/kg doses in Swiss mice [46]. It reduces Aβ levels, decreases amyloidogenesis, suppresses ROS, and shows neuroprotection against the $AlCl_3$-induced AD-like pathology [47]. It is also effective against STZ-induced AD in rats. It increases hippocampal P-ERK, inhibits GSK-3β, reduces oxidative stress, and has anti-inflammatory effects [48]. It significantly increases the hippocampal BDNF, IL-6, oxidative stress pointers, and nitric oxide in scopolamine-induced memory impairment in rats [49]. So, Captopril is also improving cholinergic function.

Ramipril

Ramipril is a potent lipid-soluble anti-hypertensive drug. It improves cognition by acting on central RAS via anti-inflammatory mechanisms [50]. It declines the over-expression of ACE in myelomonocytes. It improves the immunological response and decreases cognitive deterioration by reducing the Aβ content in the AD brain [51]. Ramipril improves spatial learning and memory in scopolamine-induced cognitive dysfunction in mice at a dose of 4 mg/kg for 8 days [46]. In another experiment following the whole brain irradiation

Table 1. *In vivo* and *In vitro* pre-clinical trial outcomes of some RAS inhibitors in the management of AD.

Name of the Drug	Preclinical study model	Actions	References
Captopril	LPS-induced cell line model	Attenuates NO production, reduces iNOS, decreases TNFα, and decreases amyloid plaque.	[39]
	BV2 microglial cell	Reduce NO production, and inflammatory markers, and activate the trans regulation and translation	[40]
	AlCl3-induced cognitive impairments	Improves spatial learning and memory, reduces Aβ levels, and ROS, and shows neuroprotection.	[46]
	STZ- induced AD	Increases hippocampal P-ERK, inhibits GSK-3β, reduces oxidative stress, and inflammatory effects.	[47]
Ramipril	Scopolamine-induced cognitive dysfunction in mice	Improves spatial learning and memory	[45]
Fosinopril	Scopolamine-induce cognitive impairments in rats	Enhances learning and memory by increasing Ach content	[63]
Lisinopril	i.c.v. STZ-induced dementia in mice	Improves memory, learning, and brain cholinergic activity, reduces inflammation and oxidative stress	[52]
	STZ-induced cognitive impairment in mice	Increases GSH and decreases Aβ content, AChE activity, and oxidative stress	[53]
Perindopril	LPS-induced cognitive dysfunction in mice	Decreases amyloidogenesis, p-tau, oxidative stress, and inflammatory markers; increases BDNF	[62]
	AlCl3-induced AD in male Swiss albino mice	Decreases AChE activity, increases SOD, decreases MDA, and suppresses microglial activation	[56]
	D-galactose-induced AD	Improves memory functions; decreases the $A\beta_{42}$, p-tau, AChE activity, and BACE1	[58]
	LPS-induced neuroinflammation	decreases TNFα and STAT3 and reduces the morphological change	[61]
Enalapril	Human neuroblastoma cells	Reduces Aβ-peptide formation, NO2 concentration, ROS production, and TNFα, declines apoptotic measurement	[41]
Telmisartan	BV2 microglial cells	Decreases IL1, increases IL_{10}, and inhibits NF-Kβ, NO, and iNOS	[71]
	C6 rat astrocytoma cells and BV2 microglial cells	Increases IL10 and AT_2R expression and decreases AT1R expression	[72]
	Cerebellar granular cells	Decreases LDH release, AKt dephosphorylation, and GSK3β dephosphorylation; activates PPARγ	[73]
	BV2 murine microglial cell	Decrease NO, TNFα, TGFβ1 and COX-2 expression, and increase Aβ-phagocytosis	[74]
	5XFAD mice	Reduces the amyloid burden, CD11b, and improves spatial learning and memory	[79]
	Ovariectomized rat	Improves spatial learning and memory by reducing the expression of BACE1. It also improves brain histology near the hippocampal CA1 and CA3 regions. It reduces oxidative stress, MDA production, and inflammatory markers	[80]
	AT1 knock-out mice	Improves spontaneous alternation; decreases the transfer latency, $A\beta_{1-42}$ production, Tau phosphorylation, and inflammatory markers	[73]
Valsartan	Primary hippocampal neuronal culture	Regulates NMDA and AMPA	[75]
	Cognitive impaired rats	Increases IL10, AT2R expression, cell proliferation, and survival; reduces Aβ peptide formation and inflammatory markers (IL1β, IL6, and TNFα)	[41]
	APP mice	Increases transfer latency, improves memory and reduces the inflammatory response	[91]
	transgenic AD mice	Attenuates the Aβ-oligomerization, and oxidative stress; improves the ACh activity, cognitive impairment, and insulin content	[97,98]
	STZ-induced AD-like pathology	Reduces transfer latency, MDA and improves and ACh synthesis, SOD enzymatic activity, memory, and learning	[41]
Candesartan	5XFAD mice	Improves cortical AT_4R expression, impairment of memory and learning; decreases amyloid burden, neuronal inflammation	[74]
	LPS-induced inflammation in rat models	decreases activation of microglial, oxidative stress, and inflammatory markers, restores the insulin and glucose metabolism, and enhances the ACh activity	[93]
	Glutamate-induced neuronal injury in genome transcriptome mode	Suppresses overexpression of glutamate, IL6, $IL_{1β}$, and TNFα thereby reducing inflammation	[70]
Olmesartan	5XFAD mice	Reduces neurovascular dysfunction, oxidative stress, and synaptic plasticity, controls the brain and hippocampal cell damage, and improves cognition	[100]
Azilsartan	AlCl3-induced AD-like pathology	Reverses cognitive dysfunction, improves antioxidant status, and decreases Aβ production	[102]

Table 2. Clinical trial status of some RAS inhibitors and their combinations with other antihypertensive drugs in the management of Alzheimer's disease.

Name of the drug	Current status	Duration and sponsorship	Clinical outcomes
Candesartan (ARBs)	Phase 2 (Completed) Interventional	June 30, 2016, to Aug 17, 2022 Emory university	Manages Mild cognitive impairment by changing the biomarker in CSF, the hippocampal region on amyloid PET imaging, improves executive function, and enhances brain connectivity [106].
Telmisartan (ARBs)	Phase 1 (Completed) Interventional	June 15, 2015, to June 28, 2022 Emory University	Modifies brain RAS components like angiotensinogen, renin, and ACE, changes in the concentration of CSF, $A\beta_{42}$, and p-Tau, enhances cerebral blood flow and reduces inflammatory markers [107].
Telmisartan versus Perindopril (ARBs versus ACE inhibitors)	Phase 2 Interventional	March 12,2014, to estimate to complete on sept, 2023 Sunnybrook Health Sciences Centre	Changes hippocampal volume and improves neuropsychiatric functions [108].
Angiotensin I (1-7) (RAS inhibitors)	Phase 1	April 20, 2022, estimated to complete on Dec 2023 University of Arizona	Improves verbal memory functions, and changes in p-Tau [109].
Losartan+ Amlodipine + Exercise (ARBs+Ca2+ channel blocker)	Phase 2 Phase 3 Completed Interventional	Feb 2,2017, to Nov 30, 2021 University of Texas Southwestern Medical Center	Changes in neurocognition, normalize brain volume and perfusion [110].
Losartan + Amlodipine (ARBs + Ca2+ blocker)	Phase 2 (Continuing) Interventional	April 10, 2018, to complete on July 31, 2023 University of Texas Southwestern Medical Center	Changes in intracranial pulsatility reduce Aβ and improve brain structure [111].
Losartan + Amlodipine (ARBs + Ca2+ blocker)	Phase 2 (Active) Interventional	Oct 25,2022 to complete June 1, 2027 Rong Zhang	Changes brain fibrillary Aβ, and tau, changes in cerebral blood flow, and improves cognition [112].
Ramipril (ACE inhibitors)	Phase 4 Completed interventional	April 9, 2009, to July 26, 2011 The University of Wisconsin, Madison	Changes in CSF, ACE, and $A\beta_{42}$, prevent memory loss [113].

procedure in Fischer rats; Ramipril decreases the activation of microglial cells and elevates the Ang (1-7) thereby showing neuroprotective actions [52].

Lisinopril

It reduces inflammation and oxidative stress in i.c.v. STZ-induced dementia in mice. It modulates the peroxisome proliferator-activated receptor gamma PPAR-γ and has the potential to cross the BBB. It can also address Aβ proteases including insulin-degrading enzymes [52]. It increases GSH and decreases Aβ content, AChE activity, and oxidative stress in STZ-induced cognitive impairment in mice at a dose of 10 and 15 mg/kg for 18 days [53]. It significantly improves the learning and memory dysfunction in a *Drosophila melanogaster* model of AD [54]. It and atorvastatin significantly reduce total tau and pTau in PS19 transgenic mice [55]. It improves memory, and learning by increasing brain cholinergic, anti-oxidant, and anti-inflammatory activity.

Perindopril

It improves cognition against $AlCl_3$ and D-galactose-induced AD in male Swiss albino mice by decreasing AChE activity, increasing SOD, decreasing MDA, and suppressing microglial activation [56,57,58]. Perindopril improves the reduced glutathione content as an anti-oxidant in the hippocampus of rats [59]. Perindopril improves cognition in a mouse model of AD by inhibiting brain ACE activity [60]. However, Perindopril is less effective than captopril in AlCl3-induced amyloidogenesis and AD-like pathology [47].

A dose of 0.5 mg/kg for 30 days, decreases the $A\beta_{42}$, p-tau, AChE activity, and BACE1 in D-galactose-induced AD in rats to improve learning, memory, and cognition [61]. At a dose of 0.5 and 1 mg/kg for 7 days, it decreases amyloidogenesis, p-tau, oxidative stress, and inflammatory markers in LPS-induced cognitive dysfunction in mice. It also increases neurotrophic factors like BDNF [62]. In another study, at a dose of 0.1 mg/kg for 5 days, it decreases TNFα and STAT3 and reduces the morphological change in LPS-induced neuroinflammation [61]. Hence, the memory-enhancing effect of Perindopril may be attributed to cholinergic, anti-oxidant, and anti-inflammatory activity.

Other ACEIsFosinopril has a high lipophilicity profile. It enhances learning and memory by increasing ACh content in scopolamine-induced cognitive impairments in rats [63]. Enalapril alone ameliorates cerebrovascular dysfunctions but has no effects on amyloidosis in a mouse model of AD [64]. Imidapril and Enalapril are less potent inhibitors of brain ACE. So, they have no beneficial effect on AD [60].

Angiotensin receptor blockers (ARBs)

ARBs are a key class of antihypertensive drugs. They are non-peptide compounds that exhibit different structures. Except for Irbesartan, all ARBs have a free carboxylic acid group. They may have a common tetrazole-biphenyl structure (Candesartan, Irbesartan, Valsartan, and Losartan) or a common benzimidazole group (Candesartan and Telmisartan). These different structures contribute to their different pharmacokinetic profiles and different affinity to the AT1R [65]. They are absorbed orally and their bioavailability ranges from 13% for Eprosartan to 60%–80% for Irbesartan. They have high protein binding properties and high polar surfaces. These properties limit the BBB permeability. Their partition coefficient (LogP) ranges from 2.98 (Olmesartan) to 6.66 (Telmisartan), with increasing permeability to the brain [37,38].

ARBs inhibit nuclear translocation of NF-kB, decrease NOX activation, reduce ROS production, decrease the activity of COX-2, and prostaglandins, halt iNOS activity, decrease pro-inflammatory cytokine production and increase neuroprotectors like IL-10 [66]. They act by blocking the AT_1 receptor. They promote the conversion of Ang II to Ang IV thereby increasing the activity of AT_2R or AT_4R and hence are neuroprotective [67].

In vitro studies

Candesartan restores the cell proliferation of neural stem cells and inhibits Aβ-oligomerization through PI3K activation [68]. It also shows an anti-inflammatory effect through the activation of AT2 receptor [69]. It prevents overexpression of glutamate, IL6, IL1β, and TNFα thereby reducing inflammation. It has also a protective effect on glutamate-induced neuronal injury in a genome transcriptome model [70].

In BV2 microglial cells Telmisartan decreases IL1, increases IL10, and inhibits NF-Kβ, NO, and iNOS [71]. In C6 rat astrocytoma cells and BV2 microglial cells, Telmisartan increases IL10 and AT2R expression and decreases AT1R expression [72]. In cerebellar granular cells, telmisartan decreases LDH release, AKt dephosphorylation, and GSK3β dephosphorylation; and activates PPARγ [73]. Candesartan and Telmisartan decrease NO, TNFα, TGFβ1, and COX-2 expression, and increase Aβ-phagocytosis in BV2 murine microglial cells [71,74].

Valsartan regulates NMDA and AMPA receptors in primary hippocampal neuronal culture [75]. Both Valsartan and Telmisartan restore the cholinergic function [76]. Losartan increases protective signaling through Ang IV/AT4R in mice [77]. Most of the sartans (Losartan, Candesartan, and Telmisartan) have neuroprotective effects by increasing BDNF and VEGF [78]. In addition, they increase cholinergic function and show anti-inflammatory effects which may contribute to their efficacy against cognitive impairment.

In-vivo studies

Telmisartan

Telmisartan reduces amyloid burden, CD11b, and improves spatial learning and memory in 5XFAD mice at a dose of 1 mg/kg (intranasal) for 2 months [79]. It improves spontaneous alternation; and decreases the transfer latency, $Aβ_{1-42}$ production, Tau phosphorylation, and inflammatory markers at a dose of 10 mg/kg p.o. [76]. It improves spatial learning and memory by reducing the expression of BACE1. It also improves brain histology near hippocampal CA_1 and CA_3 regions. It reduces oxidative stress, MDA production, and inflammatory markers in the ovariectomized rat model [80]. It shows neuroprotection in AT1 knock-out mice of both sexes [73].

It inhibits the neurotoxicity of microglial cells through NF-κB degradation in LPS-induced neuronal inflammation in C57BL/6 mice [81]. It reduces the expression of NF-κB as well as pro-inflammatory cytokines and upregulates the expression of nuclear factor erythroid 2-related factor 2 (Nrf2) and the levels of heme oxygenase-1 and NADPH quinone oxidoreductase 1 enzymes in cuprizone-induced demyelination and behavioral dysfunction at a dose of 5 mg/kg, p.o. in 6 weeks old male C57BL/6 mice [82]. It alters the AMPK–mTOR–autophagy pathway and microglial viability in LPS-induced neuronal inflammation in BV2 microglial cell lines [83].

It is an FDA-approved anti-hypertensive drug. It acts as a partial agonist of PPARγ. The preclinical studies revealed that activation of PPARγ declines cognitive impairment by crossing the BBB [84]. It also reduces the accumulation of cellular Aβ, phosphorylated-Tau protein, and neuro-inflammation [85]. It also shows neuro-protection, suppresses neuronal apoptosis, and reduces oxidative stress [86]. This contributes to its efficacy against neurodegenerative diseases, particularly AD.

Losartan

It is a prototype ARB that prevents Ang II conversion centrally in mice models [87]. It increases cerebral blood flow. It reduces neuropathology and neuronal damage [88,89]. It reduces AT1R expression and improves AT4R expression [77]. When losartan is conjugated with ascorbic acid, the brain availability of Losartan carboxylic acid, a metabolite of Losartan, increases. It has a neuroprotective effect [90]. Losartan increases IL10, AT2R expression, cell proliferation, and survival; reduces Aβ peptide formation and inflammatory markers (IL1β, IL6, and TNFα) at a dose of 0.24 mg/kg administered for 35 days [78,89]. It increases transfer latency, improves memory, and reduces inflammatory response at a dose of 10 mg/kg for 4 months in APP mice [91]. Because of its low BBB permeability, Losartan can be conjugated with small molecules to improve its brain permeability and efficacy against neurodegenerative diseases.

CandesartanCandesartan controls the NADPH oxidase expression, and lipid peroxidation [92]. It improves cortical AT4R expression, impairment of memory and learning; decreases amyloid burden, and neuronal inflammation at a dose of 1 mg/kg (intranasal) in 5XFAD mice [69,74]. It decreases activation of microglial, oxidative stress, and inflammatory markers, restores insulin and glucose metabolism, and enhances the ACh activity in LPS-induced inflammation in rat models at doses of 0.1 mg/kg and 2 mg/kg for 35 days [61,93]. It increases ACh production and neuroprotective factors like BDNF and VEGF in rats [70,94].

It decreases neuronal damage and improves memory impairments by reducing the brain MDA and increasing

the catalase and total thiol at a dose of 1 mg/kg, p.o. in d-galactose-induced cognitive dysfunction [95]. It inactivates the NLRP3 inflammasome, NF-kB Activation, and MAPK Phosphorylation in the mouse macrophage cell line model [96]. So, Captopril by reducing oxidative stress, neuronal inflammation, and microglial activation and improving cholinergic function has the potential to be used to improve memory functions in AD.

Valsartan

Valsartan attenuates the Aβ-oligomerization, and oxidative stress; and improves the ACh activity, cognitive impairment, and insulin content in transgenic AD mice at a dose of 10 and 40 mg/kg [97,98]. It reduces transfer latency, and MDA and improves ACh synthesis, and SOD enzymatic activity thereby improving memory, and learning in STZ-induced AD-like pathology at a dose of 30 mg/kg [41]. Like other ARBs, Valsartan also has the potential against cognitive impairment due to its cholinergic and antioxidant actions.

Olmesartan

Olmesartan is a neuroprotective agent. It prevents oligomerization of Aβ and neuronal senescence by down-regulating p16 and p21 [99]. It reduces neurovascular dysfunction, oxidative stress, and synaptic plasticity, controls brain and hippocampal cell damage, and improves cognition in 5XFAD mice [100].

Amyloid-β plaques, oxidative stress, and neuroinflammation are the pathological features of AD. RAS has a role in the pathology of AD. Memory is a cholinergic function [9,101].

Inhibitors of the RAS like ACEIs and ARBs improve the cholinergic function. They show antioxidant and anti-inflammatory actions. They reduce Aβ. So, ACEIs and ARBs have the potential to be repurposed against AD and other forms of dementia.

Clinical trials

After the successful outcomes from preclinical models, a lot of clinical trials were conducted on RAS inhibitors against AD. The growth of Aβ plaques and NFTs cannot be eliminated only by cholinesterase inhibitors or NMDAR antagonists. Targeting other approaches like neuronal inflammation, oxidative stress, and NMDAR activity through RAS inhibitors using anti-hypertensive drugs (ACE inhibitors and ARBs) are under clinical trial for the treatment of AD (Table 2). Retrospective cohort studies are conducted to evaluate the risk management of developing AD between RAS-acting drugs and non-RAS-acting drugs. RAS-acting drugs are more effective against AD than non-RAS-acting drugs. RAS-acting drugs can prevent AD pathology and improve cognition [103]. Phase II clinical trials are underway for several novel antihypertensive drug classes, including ACE inhibitors (Perindopril) and ARBs (Telmisartan and Candesartan) [104,105].

CONCLUSION

RAS inhibitors (ACE inhibitors and ARBs) present a promising strategy for developing effective treatments for AD. By leveraging their mechanisms of action and established safety profiles, RAS inhibitors offer a more direct route to clinical application, potentially bypassing lengthy development processes. Pre-clinical and clinical investigations have shown that RAS inhibitors possess anti-Aβ plaque, anti-tauopathy, free radical scavenging, and anti-inflammatory activities. Furthermore, ongoing research continues to reveal the complexities of Alzheimer's pathology, suggesting that innovative drugs could provide meaningful therapeutic options for managing this devastating neurodegenerative condition. Consequently, ACE inhibitors and ARBs are considered a highly reliable and effective future therapeutic approach against AD.

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AUTHOR CONTRIBUTION

All authors agreed to submit the article to the current journal, gave final approval of the version to be published, made significant contributions to conception and design, data collection, analysis, and interpretation, participated in its writing or critically revised it for important intellectual content, and agreed to be responsible for all aspects of the work. According to the requirements/guidelines of the International Committee of Medical Journal Editors (ICMJE), all of the writers are qualified to be authors.

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