



Targeting Renin–Angiotensin System Against Alzheimer’s Disease

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Renin Angiotensin System (RAS) is a hormonal system that regulates blood pressure and fluid balance through a coordinated action of renal, cardiovascular, and central nervous systems. In addition to its hemodynamic regulatory role, RAS involves in many brain activities, including memory acquisition and consolidation. This review has summarized the involvement of RAS in the pathology of Alzheimer’s disease (AD), and the outcomes of treatment with RAS inhibitors. We have discussed the effect of brain RAS in the amyloid plaque (A β) deposition, oxidative stress, neuroinflammation, and vascular pathology which are directly and indirectly associated with AD. Angiotensin II (AngII) via AT1 receptor is reported to increase brain A β level via different mechanisms including increasing amyloid precursor protein (APP) mRNA, β -secretase activity, and presenilin expression. Similarly, it was associated with tau phosphorylation, and reactive oxygen species generation. However, these effects are counterbalanced by Ang II mediated AT2 signaling. The protective effect observed with angiotensin receptor blockers (ARBs) and angiotensin converting enzyme inhibitors (ACEIs) could be as the result of inhibition of Ang II signaling. ARBs also offer additional benefit by shifting the effect of Ang II toward AT2 receptor. To conclude, targeting RAS in the brain may benefit patients with AD though it still requires further in depth understanding.

Keywords: RAS, ARB, ACEI, amyloid β , oxidative stress, vascular disease, inflammation, AD

INTRODUCTION

Renin Angiotensin System (RAS) is a hormonal system that regulates body fluid, electrolyte homostasis, and vascular tone (Yim and Yoo, 2008; Sparks et al., 2014). These classical functions of RAS are mediated by angiotensin effector peptides including Ang II, III and 1–7 (Atlas, 2007). Ang II, the primary effector peptide, is produced in the blood and exerts a number of effects on kidney, adrenal glands, sympathetic nervous system and baroreceptor reflexes (Reid, 1992; Dasgupta and Zhang, 2011). Studies have also shown the presence of local RAS in many different tissues including brain (Ganten et al., 1983; Wang et al., 1996; Vila-Porcile and Corvol, 1998; Grobe et al., 2010; Ferrão et al., 2014). In the central nervous system, angiotensinogen is synthesized by astrocytes and subsequently cleaved by renin, angiotensin converting enzyme (ACE) and aminopeptidases or ACE2 and Neprilysin (Bodiga and Bodiga, 2013). Despite some speculations, it is not clearly known where these RAS enzymes are locally synthesized in the brain (McKinley et al., 2003).

The angiotensin ligands interact with their receptors including angiotensin (AT) 1A, 1B, 2, 4 and Mas and controls various brain function (Guimond and Gallo-Payet, 2012; Premer et al., 2013). The receptors are differentially expressed in several parts of the brain (Kakar et al., 1992; Braga, 2011).

AT1A is expressed in areas mainly involved in regulation of blood pressure and electrolyte balance including subfornical organ, paraventricular nucleus of the hypothalamus, lateral septum, cerebral cortex, and hippocampus (Johren et al., 1995; MacGregor et al., 1995; Lenkei et al., 1997), brainstem baroreflex arc, olivocerebellary system, and preoptic region (Lenkei et al., 1997). While AT1B is expressed in structures which involve in higher brain function and memory including cerebral cortex and hippocampus (Johren et al., 1995).

Activation of AT1 receptors is associated with increase in oxidative stress (Prusty et al., 2017), anxiety and stress (Saavedra et al., 2005; Wincewicz and Braszko, 2014), ischemic brain damage (Panahpour et al., 2014), and cognitive impairment (Nakagawa et al., 2017).

AT2 receptor, on the other hand, is observed in parts of the brain which regulate learning and memory including hippocampus, cingulate cortex, superior colliculus, lateral septum, in thalamic nuclei, in the subthalamic nucleus, in the locus coeruleus, and in the inferior olive (Millan et al., 1991; Lenkei et al., 1996). AT2 receptor is also expressed in brain structures including red nucleus, pedunculopontine tegmental nucleus, bed nucleus of the supraoptic decussation, paragenual nucleus, motor hypoglossal nucleus, cerebellar nuclei (Song et al., 1991, 1992; Tsutsumi and Saavedra, 1991; Lenkei et al., 1996), substantia nigra (Garrido-Gil et al., 2013; Valenzuela et al., 2016), and ventral tegmental area (Garrido-Gil et al., 2013). However, the extent of the receptor expression is limited after the fetal period (AbdAlla et al., 2009). AT2 receptor signaling is suggested to play beneficial role in neurogenesis (Umschweif et al., 2014), cerebral blood flow (Iwai et al., 2004; Fuchtemeier et al., 2015), neuronal plasticity (Namsolleck et al., 2013), and learning and memory (Jing et al., 2012). Activation of the receptor is also reported to attenuate inflammation (Rompe et al., 2010), oxidative stress (Lu et al., 2015) and abnormal neuronal firing (Grammatopoulos et al., 2004; Matsuura et al., 2005) observed as the result of AT1 receptor stimulation (Guimond and Gallo-Payet, 2012).

In addition to AT1 and AT2 receptors, recent evidences show the presence of other receptors in CNS including AT4 and Mas (Singh and Karnik, 2016). AT4 receptor interacts with a different angiotensin ligand called angiotensin IV, and it is reported to regulate learning and memory in brain areas including the hippocampus, neocortex and motor nuclei (Wright et al., 1999; Chai et al., 2000). The receptor is also localized in claustrum, choroid plexus, pontine nucleus, thalamic nuclei, substantia nigra pars compacta and hypothalamus (Zhuo et al., 1998; Chai et al., 2000). It is also suggested for its neuroprotective effect against cerebral ischemia (Faure et al., 2006). Mas receptor also contributes for the diverse actions of RAS in the brain (Jackson et al., 2018). The receptor is mainly localized in the hippocampus, amygdala, anterodorsal thalamic nucleus, cortex, and hypoglossal nucleus (Bunnemann et al., 1990; Becker et al., 2007; Freund et al., 2012; Lazaroni et al., 2012). Activation of the receptor by angiotensin 1–7 was found to strengthen synapses in areas involved in memory (Bunnemann et al., 1990; Hellner et al., 2005; Uekawa et al., 2016).

Brain RAS generally involves in regulating central activities including learning, memory, anxiety, depression, cognition, and emotional stress (Gard, 2004; Paul et al., 2006; de Gasparo et al., 2013), but it also complements functions of the peripheral RAS (McKinley et al., 2003). Importantly, there are growing evidence indicating the contribution of brain RAS in development of neurodegenerative disorders including AD (Zhu et al., 2011; Tian et al., 2012; AbdAlla et al., 2013; Ana Flavia et al., 2017; Takane et al., 2017). However, it is not exactly known how RAS system influences the development and progression of AD. It is not also well understood how medications acting on RAS system affect AD though some studies have shown a link between RAS and accumulation of toxic A β peptides (Murphy and LeVine, 2010; Gouras et al., 2015), tau phosphorylation (Tian et al., 2012), oxidative stress (Chrissobolis et al., 2012), mitochondrial dysfunction (Nozoe et al., 2008), neuroinflammation (Vargas et al., 2012) and cholinergic dysfunction (Barnes et al., 1990).

AMYLOID AND ALZHEIMER'S DISEASE

A β ₄₂ and A β ₄₀ are the two-predominant A β -proteins that are highly susceptible for aggregation to form oligomers, protofibrils, and fibrils (Shin et al., 1997; Ahmed et al., 2010). Under normal physiological conditions, brain eliminates toxic peptides via enzymatic degradation, perivascular drainage and receptor-mediated efflux transport (Higuchi et al., 2005; Wang et al., 2011; Iliff et al., 2012; Provias and Jeynes, 2014; Baranello et al., 2015). Impairment of either of these clearance mechanisms may result in accumulation of A β peptide. The accumulation can cause neuronal membrane damage, an increase in oxidative stress, receptor-mediated alteration of signal transduction, alteration of membrane pore, increase in intracellular level of calcium ion and mitochondrial damage (Yankner, 1996; Carrillo-Mora et al., 2014). These changes also trigger persistent loss of cholinergic projections to the neocortex (Supnet and Bezprozvanny, 2010).

A β deposition facilitates the formation of pathological phosphorylated tau proteins (Busciglio et al., 1995; Zheng et al., 2002; Bloom, 2014). Accumulation of toxic tau protein could also occur independent of amyloid β (Katsuno et al., 2005). The abnormal aggregation and deposition of tau protein can result in formation of neurofibrillary tangles leading to a progressive loss of neurons (Buee et al., 2000; Hanger et al., 2009; Wolfe, 2012). Tau mediated neurodegeneration could be due to sequestration of tau protein and disturbance of microtubule function (Alonso et al., 2008; Iqbal et al., 2009). This results impairment of normal axon flow and subsequent loss of neurons and their connectivity (Iqbal et al., 2009; Baird and Bennett, 2013).

RENIN ANGIOTENSIN SYSTEM AND A β PEPTIDES: *IN VITRO* STUDIES

In vitro studies have shown the role of ACE in the degradation of A β peptides halting the development of amyloid plaque (Hu et al., 2001; Oba et al., 2005). The enzymatic action of ACE in the breakdown A β peptides have demonstrated by several

studies (Hemming and Selkoe, 2005; Sun et al., 2008; Zou et al., 2009). Whilst ACE inhibitors were reported to promote A β aggregation (Hu et al., 2001). ACE2, a homolog of ACE, was also reported to have a catalytic role in the cleavage of A β_{43} to A β_{40} and this was inhibited by specific ACE2 inhibitor called DX600 (Liu et al., 2014). N domain part of the enzyme was found responsible for hydrolysis A β peptides at N-terminal position. ACE hydrolyses the most neurotoxic peptides A β_{43} and A β_{42} (Welander et al., 2009; Brouillette et al., 2012), in to amyloid peptides that are less susceptibility to aggregate and form senile plaques. ACE also metabolizes the most abundant amyloid peptide, A β_{40} with the potential to reduce the A β_{42} oligomerization and deposition (Kim et al., 2007; Murray et al., 2009). ACE reduces amyloid β peptides the main risk factor for the development and progression of AD (Karran et al., 2011) (Table 1). These studies altogether indicate the metabolic action of RAS enzymes in reducing amyloid plaque deposition via degradation of the most toxic form amyloid peptides composed of 40-43 amino acid sequences.

RENIN ANGIOTENSIN SYSTEM AND ALZHEIMER'S DISEASE: ANIMAL STUDIES

In vitro studies have shown the role of ACE in degradation of A β peptides thereby reducing deposition and accumulation of amyloid plaque while inhibition of the enzyme is detrimental (Hemming and Selkoe, 2005; Sun et al., 2008; Zou et al., 2009; Liu et al., 2014). Ramipril (ACE inhibitor) also increased A β peptides in ACE10/10 mice with AD (Bernstein et al., 2014). Recent studies, however, does not support the idea that ACEIs increases accumulation of A β peptides in AD animal models (Eckman et al., 2006; Hemming et al., 2007; Ferrington et al., 2011, 2012). These studies challenge the notion that ACEIs inhibit degradation of A β peptides and favoring amyloid plaque formation. Some ACEIs even reduced A β peptide level in animal models of AD (AbdAlla et al., 2013). Moreover, ACEIs showed beneficial effect in reducing AD signs and symptoms (Dong et al., 2011; Tota et al., 2012; AbdAlla et al., 2015). Administration of perindopril (ACEI) has shown an instrumental effect in increasing density of normal neurons and improving learning and memory (Hou et al., 2008). A study on Tg2576 AD model demonstrated the positive role of captopril in preventing signs of

neurodegeneration (AbdAlla et al., 2013). These studies support the potential benefit of ACEIs in alleviating sign and symptom of AD; however, with contrasting reports. A study on Tg2576 mice showed increase in deposition of A β_{42} after treatment with captopril (Zou et al., 2007). In line with this study, treatment with ramipril elevated brain level of A β_{42} peptide in AD⁺ACE (10/10) mice. Most *in vivo* studies have shown a positive correlation between increased expression of ACE and signs of AD but ACE inhibitors have protective effect against AD (Table 2). The protective effect of ACE inhibitors could be explained partly via suppressing brain derived neurotrophic factor decline and TNF- α release. They were also found to ameliorate oxidonitrosative stress and nitrotyrosine production (Ali et al., 2016) with that in turn reduces amyloidogenesis and subsequent A β deposition (Goel et al., 2016). However, further investigations are required to see if the contradicting reports were intrinsic to the specific inherent nature of the drug or methodological issue.

A review by Kehoe indicated Ang II (as with ACE) increased accumulation and deposition A β peptides in AD animal models (Kehoe, 2009). Ang II increases A β level, promotes cerebrovascular dysfunction, and micro-vascular amyloid deposition which those in turn worsens AD outcome (Faraco et al., 2016). ARBs, e.g., telmisartan, have shown to prevent cognitive decline associated with A β_{40} injection (Mogi et al., 2008). Olmesartan was also associated with improved cognitive function and hippocampal synaptic plasticity (Takeda et al., 2009). Losartan was reported to prevent neuropathological and cognitive deficits observed in AD (Ongali et al., 2014). These studies showed the beneficial roles of ARBs in animal models of AD. The protective effect could be explained in part via suppressing AT1 receptor mediated APP mRNA up regulation, A β peptide production and phosphorylated tau induced neurotoxicity (Zhu et al., 2011). The protective effect of these drugs could also be attributed as a result of unopposed action of Ang II on AT2 receptor (Horiuchi et al., 2010; Gallo-Payet et al., 2011) and stimulation of AngIV/AT4R signaling as observed in losartan (Royea et al., 2017). AT2 receptor mediated signaling pathways are known to prevent degeneration of neurons (Li et al., 2005; McCarthy et al., 2009). In line with these reports, valsartan have shown to attenuate oligomerization of A β peptides into high molecular weight oligomeric peptides and reduces cognitive deterioration (Wang et al., 2007). However, other studies with the same model have shown that A β induces the formation of oligomers of AT2 receptor in the

TABLE 1 | The effect of ACE-Is on Amyloid- β level: *In vitro* study.

Cloned culture	Effects of ACE expression	Effects of ACE inhibition	Reference
Seminal plasma	Decrease A β_{40} level	Lisinopril promote A β_{40} production	Hu e/al., 2001
Neuroblastoma	Decrease A β_{40} and A β_{42} level	Captopril promote A β_{40} and A β_{42} level	Hemming and Selkoe, 2005
HEK293	Increase break down of A β_{43} to A β_{42}	DX600 inhibit breakdown A β_{43} to A β_{42}	Liu et al., 2014
COS7 cells	Increase breakdown of A β_{40}	–	Oba et al., 2005
CHO cells	Increase breakdown of m and h A β	–	Sun et al., 2008
COS7 cells	Increase breakdown of A β_{42} to A β_{40}	ACEIs inhibit conversion of A β_{42} to-A β_{40}	Zou et al., 2009

ACEIs, angiotensin converting enzyme inhibitors; CHO, Chinese hamster ovary; HEK, human embryonic kidney cells 293; A β , Amyloid- β ; m A β , murine Amyloid- β ; h A β , human amyloid- β .

TABLE 2 | The effect of ACEIs on Brain A level: Animal studies.

Animal model	Tested drug	Results	Reference
A β_{42} induced SDR	Perindopril	Decrease A β_{42}	Hou et al., 2008
Tg2576 mice	Captopril/Enalapril	Reduced A β plaque and ROS accumulation	AbdAlla et al., 2013
C57BL/6 \times DBA2 and 3xTg AD	Captopril	No effect on A β levels	Hemming et al., 2007
LPS induced Mice	Perindopril	Decrease A β level	Ali et al., 2016
LPS induced WRs	Perindopril	Decrease A β levels and improved CBF	Goel et al., 2016
A E10/10 mice	Ramipril	Increase A β levels	Bernstein et al., 2014

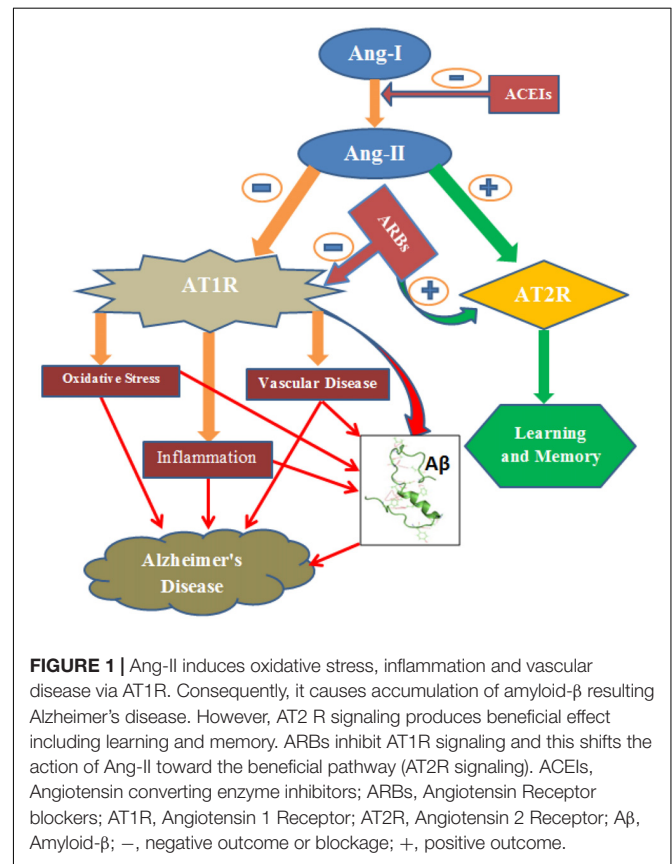
ACE, angiotensin converting enzyme; LPS, lipopolysaccharide; ROS, reactive oxygen species.

hippocampus that disrupts Ang II mediated signaling. The A β - induced AT2 receptor oligomerization was associated with enhanced neurodegeneration. Conversely, inhibition of cross-linked AT2 receptor delayed tau phosphorylation (AbdAlla et al., 2009).

In other studies, however, valsartan or eprosartan (ARBs), did not alter accumulation of A β oligomers and phosphorylated tau in triple transgenic mice (Ferrington et al., 2011). The contradiction could be reconciled by the difference in AD animal models used. Variability in the dose of drug, the age and strain of animal used in the experiment could also explain the discrepancy (Ferrington et al., 2012). Despite varying result of RAS on amyloidosis, the overall effects of this system seem to favor amyloidosis. More specifically, the Ang II favors production of A β peptides via the most widely expressed angiotensin receptor, AT1 (Hohle et al., 1995). In addition to reduction of A β deposition and its consequences, RAS inhibitors have also other beneficial roles including suppression of inflammation (Saavedra, 2012), oxidative stress (Prusty et al., 2017), vascular damage/ischemia (Takeda and Morishita, 2017), and increase in acetylcholine release (Barnes et al., 1990) and glutamate uptake (Ruginsk et al., 2015) (**Figure 1**).

Ang II enhances AT1 receptor mediated brain inflammation. Contrarily, ARBs attenuates the release of proinflammatory mediators (Lanz et al., 2010). Central infusion of Ang II increased hippocampal CD68- positive cells, indicating its hippocampal proinflammatory action (Takane et al., 2017). In contrarily, candesartan (ARB) decreased lipopolysaccharide (LPS) induced and AT1 receptor mediated release of proinflammatory mediators including TNF α , IL-1 β , I κ B α , iNOS, ICAM-1, and VCAM-1 in cerebral cortex (Benicky et al., 2009). In addition, candesartan attenuated brain level of NF- α , GFAP, COX-2, and NF- κ B in the same animal model. They have also demonstrated the advantage of unopposed action of Ang II on AT2 receptor in addition to AT1 receptor blockage mediated amelioration of proinflammatory mediators releasesuggesting the beneficial role of AT2 receptors in reducing neuroinflammation (Goel et al., 2018). Moreover, ARBs prevents impairment and preserves the integrity of blood brain barrier which in turn reduces infiltration of inflammatory mediators observed in many neurodegenerative disease including AD (de Vries et al., 1997; Panahpour et al., 2014; So et al., 2015).

AngII via AT1 receptor is also suggested as effector of oxidative stress (Nickenig and Harrison, 2002; Marchesi et al., 2008; Chan and Chan, 2013; Seifi et al., 2014; Prusty et al.,



2017). Ang II increased a reactive oxygen species called superoxide (Takane et al., 2017). On the other hand, telmisartan (ARB) was found to normalize diminished thioredoxin (Trx) system in addition to attenuating thioredoxin-interacting protein (TXNIP) expression. This reduces generation of endogenous reactive oxygen species (Erdi et al., 2016). Similarly, telmisartan reduced advanced glycation end products and 4-hydroxynonenal, which are the markers of oxidative stress and associated with Neurodegeneration (Safciuc et al., 2007; Barone et al., 2017). Candesartan also reduced brain level of free radicals by diminishing Malondialdehyde and increasing glutathione level (Tota et al., 2009). Thus partly alleviates the development and progression of AD (Gustaw-Rothenberg et al., 2010; Saharan and Mandal, 2014). Captopril (Bild et al., 2013) and losartan (Seifi et al., 2015) were also found to ameliorate oxidative stress.

TABLE 3 | The effect of ACEIs and ARBs on cognitive function: Human study.

Study design	Tested drug	Result	Reference
Cross sectional	ACE-Is and ARBs	Reduce cognitive decline	Ellul et al., 2007
Observational	ACEIs	Slow decline of memory and daily functions	Hajjar et al., 2008
Case Control	ACE-Is and ARBs	Decrease incidence of AD	Davies et al., 2011
Cohort	ARBs	Reduction in the incidence and progression of AD	Li et al., 2010
Cohort	ACE-Is	Slow cognitive decline	Soto et al., 2013
Observational	RAS-Ms	Slows cognitive decline	Wharton et al., 2015
Observational	CACE-Is	Reduce functional decline	O'Caomh et al., 2014
Cohort	ACEIs	Not effect on cognitive decline	Zhuang et al., 2016

ACEIs, angiotensin converting enzyme inhibitors; ARBs, angiotensin II Receptor Blockers; RAS-Ms, renin angiotensin system medications; CACE-I, centrally acting Angiotensin converting enzyme inhibitors.

Ang II is also implicated in neurovascular damage and cognitive impairment (Mogi et al., 2012; Bodiga and Bodiga, 2013; Bloch et al., 2015). Candesartan increased cerebral blood flow, reduced infarct size and improved cerebral ischemia (Ito et al., 2002; Engelhorn et al., 2004). Similarly, losartan prevented blood brain barrier disruption and restored blood flow after induction of hemorrhagic stroke. Moreover, telmisartan (Iwanami et al., 2010), valsartan (Takada et al., 2006), and olmesartan (Matsumoto et al., 2009) have shown a beneficial role in prevention of vascular damage via blockage of AT1 receptor. Suggested mechanism of ARBs on cerebral blood flow is in part explained via unblocked AT2 receptor activation (Iwai et al., 2004; Li et al., 2005; Jing et al., 2012). These studies generally show the benefit of ARBs in improving neurovascular network and cerebral blood flow after certain initial insult which in turn prevents onset and progressive neurodegeneration observed in AD (Bell and Zlokovic, 2009; Zlokovic, 2011). In addition to the above mechanisms described, Ang II is also speculated to inhibit acetylcholine release in which the deficiency is responsible for AD (Barnes et al., 1992; Tota et al., 2013). Conversely, pre-treatment with candesartan prevented Ang II induced reduction of acetylcholine level (Tota et al., 2009, 2013). This reduces cognitive impairment observed in AD (Burns, 2003; Herholz, 2008).

RENIN ANGIOTENSIN SYSTEM AND ALZHEIMER'S DISEASE: HUMAN STUDIES

Human studies have shown the involvement of RAS in the pathogenesis and progression of AD (Amouyel et al., 2000; Kolsch et al., 2005). Nevertheless, only few studies have shown a link between RAS and AD (Ellul et al., 2007; Davies et al., 2011). ACEIs and ARBs have shown a beneficial effect in slowing and reducing the cognitive impairment associated with AD (Li et al., 2012; Hsu et al., 2013; Saavedra, 2016). In a cross sectional study, patients taking ARBs and ACEIs had lower risk of cognitive deterioration (Jackson et al., 2018).

Central acting RAS inhibitors have shown a superior efficacy which imply brain RAS involvement in development and progression of AD (Hebert et al., 2013; Soto et al., 2013; Wharton

et al., 2015; Zhuang et al., 2016). A prospective multicentre cohort study showed slower rate of cognitive decline on older adults taking ACE-Is (Soto et al., 2013). ARBs and ACEIs were generally found to reduce the risk and progression of AD (Hajjar et al., 2008; Li et al., 2010; Davies et al., 2011). The central acting agent including perindopril was significantly associated with a slower rate of functional decline (Davies et al., 2011). Telmisartan reduced cognitive impairment in hypertensive patients with AD (Li et al., 2012). The drug reduced amyloid β , oxidative stress and neuroinflammation. The RAS also activates peroxisome proliferator activated receptor (PPAR) gamma which has a role in prevention of neurodegeneration (Inestrosa et al., 2005; Kume et al., 2012; Li et al., 2012). Other ARBs losartan (Moriwaki et al., 2004; Hong et al., 2010), and olmesartan (Matsumoto et al., 2010) have shown beneficial effect in AD patients. In contrast, in a 4-month of pilot clinical trial ramipril was not associated with reduction of CSF $A\beta_{1-42}$ level and cognitive impairment (Wharton et al., 2012). This limited effect of ramipril could be attributed to its limited blood brain barrier penetration (Sink et al., 2009). Most of these studies support the beneficial effect of RAS inhibitors in prevention and mitigation of cognitive impairments associated with AD (Table 3).

GENETIC STUDIES

Genetic studies have also reported for the associate of ACE with AD (Elkins et al., 2004). ACE protein is coded by several genes containing various variants, specifically the insertion/deletion variant (rs1799752) have been associated with AD. Some other variants, including single nucleotide polymorphisms rs4291A > T located 240 base pair from the initiation codon, and rs4343G > A encoding a silent mutation in exon 16 were also thought to be involved in AD (Helbecque et al., 2009; Gaiteri et al., 2016). AD patients with the haplotype of rs1800764 (CC): rs4291 (TT) responded better for ACEIs that can cross the blood brain barrier (captopril or perindopril). However, the response was not significant among independent carriers of rs1800764 or rs4291 (de Oliveira et al., 2014). Further stratification showed the benefit of ACEIs among ACE haplotypes (rs1800764 – T and rs4291 – A) and Apolipoprotein (APOE4) – carriers (rs1800764 – T or rs4291 – T). Nevertheless, APOE4+

carriers were non-responsive for ACEIs indicating the role of genetic variation and ACEIs response rate among AD patients (de Oliveira et al., 2018).

CONCLUSION

Understanding AD in terms of various pathophysiological pathways is worthwhile to unravel the complex nature of the disease process and identifying potential therapeutic targets. The brain RAS is reported to be involved in the development and progression of AD through AT1 receptor via increasing the production of amyloid- β , oxidative stress, inflammatory processes, and decreasing release of acetylcholine. However, RAS also is reported to have protective effect against AD. Through AT2 receptor activation that counterbalances the deleterious effects of AT1 receptor mediated RAS effects. With concept, beneficial effect of ARBs against AD is via the unopposed action of Ang II on AT2 receptors it as AT1

receptor is blocked these drugs increased Ang II concentration to act on AT2 receptor. ACE is reported to be involved in breakdown of amyloid β peptides, but most of the studies have contradicting result. This requires further understanding especially involvement of ACE in cleavage of amyloid β peptides *in vivo*. In summary, RAS through AT1 receptor is linked with AD pathology through its action on neurovascular change, oxidative stress, and inflammation as evidenced by the protective role of ARBs and ACEIs both in patients and animal models. However, the role of RAS in AD pathology is still not well established and need further in-depth understanding.

AUTHOR CONTRIBUTIONS

AG conducted the review and prepared the first draft while all authors contributed to substantial enhancement of the manuscript.

REFERENCES

- AbdAlla, S., El Hakim, A., Abdelbaset, A., Elfaramawy, Y., and Quitterer, U. (2015). Inhibition of ACE retards tau hyperphosphorylation and signs of neuronal degeneration in aged rats subjected to chronic mild stress. *Biomed Res. Int.* 2015:917156.
- AbdAlla, S., Langer, A., Fu, X., and Quitterer, U. (2013). ACE inhibition with captopril retards the development of signs of neurodegeneration in an animal model of Alzheimer's disease. *Int. J. Mol. Sci.* 14, 16917–16942. doi: 10.3390/ijms140816917
- AbdAlla, S., Lother, H., El Missiry, A., Langer, A., Sergeev, P., El Faramawy, Y., et al. (2009). Angiotensin II AT2 receptor oligomers mediate G-protein dysfunction in an animal model of Alzheimer disease. *J. Biol. Chem.* 284, 6554–6565. doi: 10.1074/jbc.M807746200
- Ahmed, M., Davis, J., Aucoin, D., Sato, T., Ahuja, S., Aimoto, S., et al. (2010). Structural conversion of neurotoxic amyloid-beta(1-42) oligomers to fibrils. *Nat. Struct. Mol. Biol.* 17, 561–567. doi: 10.1038/nsmb.1799
- Ali, M. R., Abo-Youssef, A. M., Messiha, B. A., and Khattab, M. M. (2016). Tempol and perindopril protect against lipopolysaccharide-induced cognition impairment and amyloidogenesis by modulating brain-derived neurotrophic factor, neuroinflammation and oxido-nitrosative stress. *Naunyn Schmiedebergs Arch. Pharmacol.* 389, 637–656. doi: 10.1007/s00210-016-1234-6
- Alonso, A. C., Li, B., Grundke-Iqbal, I., and Iqbal, K. (2008). Mechanism of tau-induced neurodegeneration in Alzheimer disease and related tauopathies. *Curr. Alzheimer Res.* 5, 375–384. doi: 10.2174/156720508785132307
- Amouyel, P., Richard, F., Berr, C., David-Fromentin, I., and Helbecque, N. (2000). The renin angiotensin system and Alzheimer's disease. *Ann. N. Y. Acad. Sci.* 903, 437–441. doi: 10.1111/j.1749-6632.2000.tb06395.x
- Ana Flavia, A.-S., Lucas, M. K., and Maria Jose, C.-S. (2017). The renin-angiotensin system and the neurodegenerative diseases: a brief review. *Protein Pept. Lett.* 24, 841–853.
- Atlas, S. A. (2007). The renin-angiotensin aldosterone system: pathophysiological role and pharmacologic inhibition. *J. Manag. Care Pharm.* 13(8 Suppl B), 9–20. doi: 10.18553/jmcp.2007.13.s8-b.9
- Baird, F. J., and Bennett, C. L. (2013). Microtubule defects & neurodegeneration. *J. Genet. Syndr. Gene Ther.* 4:203. doi: 10.4172/2157-7412.1000203
- Baranello, R. J., Bharani, K. L., Padmaraju, V., Chopra, N., Lahiri, D. K., Greig, N. H., et al. (2015). Amyloid-beta protein clearance and degradation (ABCD) pathways and their role in Alzheimer's disease. *Curr. Alzheimer Res.* 12, 32–46. doi: 10.2174/1567205012666141218140953
- Barnes, J. M., Barnes, N. M., Costall, B., Coughlan, J., Kelly, M. E., Naylor, R. J., et al. (1992). Angiotensin-converting enzyme inhibition, angiotensin, and cognition. *J. Cardiovasc. Pharmacol.* 19(Suppl. 6), S63–S71. doi: 10.1097/00005344-199219006-00011
- Barnes, J. M., Barnes, N. M., Costall, B., Horovitz, Z. P., Ironside, J. W., Naylor, R. J., et al. (1990). Angiotensin II inhibits acetylcholine release from human temporal cortex: implications for cognition. *Brain Res.* 507, 341–343. doi: 10.1016/0006-8993(90)90294-L
- Barone, E., Head, E., Butterfield, D. A., and Perluigi, M. (2017). HNE-modified proteins in down syndrome: Involvement in development of Alzheimer disease neuropathology. *Free Radic. Biol. Med.* 111, 262–269. doi: 10.1016/j.freeradbiomed.2016.10.508
- Becker, L. K., Etelvino, G. M., Walther, T., Santos, R. A., and Campagnole-Santos, M. J. (2007). Immunofluorescence localization of the receptor Mas in cardiovascular-related areas of the rat brain. *Am. J. Physiol. Heart Circ. Physiol.* 293, H1416–H1424. doi: 10.1152/ajpheart.00141.2007
- Bell, R. D., and Zlokovic, B. V. (2009). Neurovascular mechanisms and blood-brain barrier disorder in Alzheimer's disease. *Acta Neuropathol.* 118, 103–113. doi: 10.1007/s00401-009-0522-3
- Benicky, J., Sánchez-Lemus, E., Pavel, J., and Saavedra, J. M. (2009). Anti-inflammatory effects of angiotensin receptor blockers in the brain and the periphery. *Cell. Mol. Neurobiol.* 29, 781–792. doi: 10.1007/s10571-009-9368-4
- Bernstein, K. E., Koronyo, Y., Salumbides, B. C., Sheyn, J., Pelissier, L., Lopes, D. H., et al. (2014). Angiotensin-converting enzyme overexpression in myelomonocytes prevents Alzheimer's-like cognitive decline. *J. Clin. Invest.* 124, 1000–1012. doi: 10.1172/JCI66541
- Bild, W., Hritcu, L., Stefanescu, C., and Ciobica, A. (2013). Inhibition of central angiotensin II enhances memory function and reduces oxidative stress status in rat hippocampus. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 43, 79–88. doi: 10.1016/j.pnpbp.2012.12.009
- Bloch, S., Obari, D., and Girouard, H. (2015). Angiotensin and neurovascular coupling: beyond hypertension. *Microcirculation* 22, 159–167. doi: 10.1111/micc.12193
- Bloom, G. S. (2014). Amyloid-beta and tau: the trigger and bullet in Alzheimer disease pathogenesis. *JAMA Neurol.* 71, 505–508. doi: 10.1001/jamaneurol.2013.5847
- Bodiga, V. L., and Bodiga, S. (2013). Renin angiotensin system in cognitive function and dementia. *Asian J. Neurosci.* 2013:102602. doi: 10.1155/2013/102602
- Braga, V. A. (2011). Differential brain angiotensin-II type I receptor expression in hypertensive rats. *J. Vet. Sci.* 12, 291–293. doi: 10.4142/jvs.2011.12.3.291
- Brouillette, J., Caillierez, R., Zommer, N., Alves-Pires, C., Benilova, I., Blum, D., et al. (2012). Neurotoxicity and memory deficits induced by soluble low-molecular-weight amyloid-beta1-42 oligomers are revealed in vivo by using a novel animal model. *J. Neurosci.* 32, 7852–7861. doi: 10.1523/JNEUROSCI.5901-11.2012
- Buee, L., Bussiere, T., Buee-Scherrer, V., Delacourte, A., and Hof, P. R. (2000). Tau protein isoforms, phosphorylation and role in neurodegenerative disorders. *Brain Res. Brain Res. Rev.* 33, 95–130. doi: 10.1016/S0165-0173(00)00019-9

- Bunemann, B., Fuxe, K., Metzger, R., Mullins, J., Jackson, T. R., Hanley, M. R., et al. (1990). Autoradiographic localization of mas proto-oncogene mRNA in adult rat brain using in situ hybridization. *Neurosci. Lett.* 114, 147–153. doi: 10.1016/0304-3940(90)90063-F
- Burns, A. (2003). Treatment of cognitive impairment in Alzheimer's disease. *Dialogues Clin. Neurosci.* 5, 35–43.
- Busciglio, J., Lorenzo, A., Yeh, J., and Yankner, B. A. (1995). beta-amyloid fibrils induce tau phosphorylation and loss of microtubule binding. *Neuron* 14, 879–888. doi: 10.1016/0896-6273(95)90232-5
- Carrillo-Mora, P., Luna, R., and Colin-Baranque, L. (2014). Amyloid beta: multiple mechanisms of toxicity and only some protective effects? *Oxid. Med. Cell. Longev.* 2014:795375. doi: 10.1155/2014/795375
- Chai, S. Y., Bastias, M. A., Clune, E. F., Matsacos, D. J., Mustafa, T., Lee, J. H., et al. (2000). Distribution of angiotensin IV binding sites (AT4 receptor) in the human forebrain, midbrain and pons as visualised by in vitro receptor autoradiography. *J. Chem. Neuroanat.* 20, 339–348. doi: 10.1016/S0891-0618(00)00112-5
- Chan, S. H., and Chan, J. Y. (2013). Angiotensin-generated reactive oxygen species in brain and pathogenesis of cardiovascular diseases. *Antioxid. Redox Signal.* 19, 1074–1084. doi: 10.1089/ars.2012.4585
- Chrissobolis, S., Banfi, B., Sobey, C. G., and Faraci, F. M. (2012). Role of Nox isoforms in angiotensin II-induced oxidative stress and endothelial dysfunction in brain. *J. Appl. Physiol.* 113, 184–191. doi: 10.1152/jappphysiol.00455.2012
- Dasgupta, C., and Zhang, L. (2011). Angiotensin II receptors and drug discovery in cardiovascular disease. *Drug Discov. Today* 16, 22–34. doi: 10.1016/j.drudis.2010.11.016
- Davies, N. M., Kehoe, P. G., Ben-Shlomo, Y., and Martin, R. M. (2011). Associations of anti-hypertensive treatments with Alzheimer's disease, vascular dementia, and other dementias. *J. Alzheimers Dis.* 26, 699–708.
- de Gasparo, M., Speth, R. C., Baltatu, O. C., and Vanderheyden, P. (2013). Brain RAS: hypertension and beyond. *Int. J. Hypertens.* 2013:157180. doi: 10.1155/2013/157180
- de Oliveira, F. F., Bertolucci, P. H., Chen, E. S., and Smith, M. C. (2014). Brain-penetrating angiotensin-converting enzyme inhibitors and cognitive change in patients with dementia due to Alzheimer's disease. *J. Alzheimers Dis.* 42(Suppl. 3), S321–S324.
- de Oliveira, F. F., Chen, E. S., Smith, M. C., and Bertolucci, P. H. F. (2018). Pharmacogenetics of angiotensin-converting enzyme inhibitors in patients with Alzheimer's disease dementia. *Curr. Alzheimer Res.* 15, 386–398. doi: 10.2174/1567205014666171016101816
- de Vries, H. E., Kuiper, J., De Boer, A. G., Van Berkel, T. J., and Breimer, D. D. (1997). The blood-brain barrier in neuroinflammatory diseases. *Pharmacol. Rev.* 49, 143–156.
- Dong, Y. F., Kataoka, K., Tokutomi, Y., Nako, H., Nakamura, T., Toyama, K., et al. (2011). Perindopril, a centrally active angiotensin-converting enzyme inhibitor, prevents cognitive impairment in mouse models of Alzheimer's disease. *FASEB J.* 25, 2911–2920. doi: 10.1096/fj.11-182873
- Eckman, E. A., Adams, S. K., Troendle, F. J., Stodola, B. A., Kahn, M. A., Fauq, A. H., et al. (2006). Regulation of steady-state beta-amyloid levels in the brain by neprilysin and endothelin-converting enzyme but not angiotensin-converting enzyme. *J. Biol. Chem.* 281, 30471–30478. doi: 10.1074/jbc.M605827200
- Elkins, J. S., Douglas, V. C., and Johnston, S. C. (2004). Alzheimer disease risk and genetic variation in ACE: a meta-analysis. *Neurology* 62, 363–368. doi: 10.1212/01.WNL.0000106823.72493.FF
- Ellul, J., Archer, N., Foy, C. M., Poppe, M., Boothby, H., Nicholas, H., et al. (2007). The effects of commonly prescribed drugs in patients with Alzheimer's disease on the rate of deterioration. *J. Neurol. Neurosurg. Psychiatry* 78, 233–239. doi: 10.1136/jnnp.2006.104034
- Engelhorn, T., Goerike, S., Doerfler, A., Okorn, C., Forsting, M., Heusch, G., et al. (2004). The angiotensin II type 1-receptor blocker candesartan increases cerebral blood flow, reduces infarct size, and improves neurologic outcome after transient cerebral ischemia in rats. *J. Cereb. Blood Flow Metab.* 24, 467–474. doi: 10.1097/00004647-200404000-00012
- Erdi, F., Keskin, F., Esen, H., Kaya, B., Feyzioglu, B., Kilinc, I., et al. (2016). Telmisartan ameliorates oxidative stress and subarachnoid haemorrhage-induced cerebral vasospasm. *Neurol. Res.* 38, 224–231. doi: 10.1080/01616412.2015.1105626
- Faraco, G., Park, L., Zhou, P., Luo, W., Paul, S. M., Anrather, J., et al. (2016). Hypertension enhances Abeta-induced neurovascular dysfunction, promotes beta-secretase activity, and leads to amyloidogenic processing of APP. *J. Cereb. Blood Flow Metab.* 36, 241–252. doi: 10.1038/jcbfm.2015.79
- Faure, S., Chapot, R., Tallet, D., Javellaud, J., Achar, J. M., and Oudart, N. (2006). Cerebroprotective effect of angiotensin IV in experimental ischemic stroke in the rat mediated by AT(4) receptors. *J. Physiol. Pharmacol.* 57, 329–342.
- Ferrão, F. M., Lara, L. S., and Lowe, J. (2014). Renin-angiotensin system in the kidney: What is new? *World J. Nephrol.* 3, 64–76. doi: 10.5527/wjn.v3.i3.64
- Ferrington, L., Miners, J. S., Palmer, L. E., Bond, S. M., Povey, J. E., Kelly, P. A., et al. (2011). Angiotensin II-inhibiting drugs have no effect on intraneuronal Abeta or oligomeric Abeta levels in a triple transgenic mouse model of Alzheimer's disease. *Am. J. Transl. Res.* 3, 197–208.
- Ferrington, L., Palmer, L. E., Love, S., Horsburgh, K. J., Kelly, P. A., and Kehoe, P. G. (2012). Angiotensin II-inhibition: effect on Alzheimer's pathology in the aged triple transgenic mouse. *Am. J. Transl. Res.* 4, 151–164.
- Freund, M., Walther, T., and Von Bohlen Und Halbach, O. (2012). Immunohistochemical localization of the angiotensin-(1-7) receptor Mas in the murine forebrain. *Cell Tissue Res.* 348, 29–35. doi: 10.1007/s00441-012-1354-3
- Fuchtemeier, M., Brinckmann, M. P., Foddiss, M., Kunz, A., Po, C., Curato, C., et al. (2015). Vascular change and opposing effects of the angiotensin type 2 receptor in a mouse model of vascular cognitive impairment. *J. Cereb. Blood Flow Metab.* 35, 476–484. doi: 10.1038/jcbfm.2014.221
- Gaiteri, C., Mostafavi, S., Honey, C. J., De Jager, P. L., and Bennett, D. A. (2016). Genetic variants in Alzheimer disease - molecular and brain network approaches. *Nat. Rev. Neurol.* 12, 413–427. doi: 10.1038/nrneurol.2016.84
- Gallo-Payet, N., Guimond, M. O., Bilodeau, L., Wallinder, C., Alterman, M., and Hallberg, A. (2011). Angiotensin II, a neuropeptide at the frontier between endocrinology and neuroscience: is there a link between the angiotensin ii type 2 receptor and Alzheimer's disease? *Front. Endocrinol.* 2:17. doi: 10.3389/fendo.2011.00017
- Ganten, D., Hermann, K., Unger, T., and Lang, R. E. (1983). The tissue renin-angiotensin systems: focus on brain angiotensin, adrenal gland and arterial wall. *Clin. Exp. Hypertens. A* 5, 1099–1118. doi: 10.3109/10641968309048844
- Gard, P. R. (2004). Angiotensin as a target for the treatment of Alzheimer's disease, anxiety and depression. *Expert Opin. Ther. Targets* 8, 7–14. doi: 10.1517/14728222.8.1.7
- Garrido-Gil, P., Valenzuela, R., Villar-Cheda, B., Lanciego, J. L., and Labandeira-Garcia, J. L. (2013). Expression of angiotensinogen and receptors for angiotensin and prorenin in the monkey and human substantia nigra: an intracellular renin-angiotensin system in the nigra. *Brain Struct. Funct.* 218, 373–388. doi: 10.1007/s00429-012-0402-9
- Goel, R., Bhat, S. A., Hanif, K., Nath, C., and Shukla, R. (2016). Perindopril attenuates lipopolysaccharide-induced amyloidogenesis and memory impairment by suppression of oxidative stress and RAGE activation. *ACS Chem. Neurosci.* 7, 206–217. doi: 10.1021/acschemneuro.5b00274
- Goel, R., Bhat, S. A., Hanif, K., Nath, C., and Shukla, R. (2018). Angiotensin II receptor blockers attenuate lipopolysaccharide-induced memory impairment by modulation of NF-kappaB-Mediated BDNF/CREB expression and apoptosis in spontaneously hypertensive rats. *Mol. Neurobiol.* 55, 1725–1739. doi: 10.1007/s12035-017-0450-5
- Gouras, G. K., Olsson, T. T., and Hansson, O. (2015). beta-Amyloid peptides and amyloid plaques in Alzheimer's disease. *Neurotherapeutics* 12, 3–11. doi: 10.1007/s13311-014-0313-y
- Grammatopoulos, T. N., Johnson, V., Moore, S. A., Andres, R., and Weyhenmeyer, J. A. (2004). Angiotensin type 2 receptor neuroprotection against chemical hypoxia is dependent on the delayed rectifier K⁺ channel, Na⁺/Ca²⁺ exchanger and Na⁺/K⁺ ATPase in primary cortical cultures. *Neurosci. Res.* 50, 299–306. doi: 10.1016/j.neures.2004.07.010
- Grobe, J. L., Grobe, C. L., Beltz, T. G., Westphal, S. G., Morgan, D. A., Xu, D., et al. (2010). The brain renin-angiotensin system controls divergent efferent mechanisms to regulate fluid and energy balance. *Cell Metab.* 12, 431–442. doi: 10.1016/j.cmet.2010.09.011
- Guimond, M.-O., and Gallo-Payet, N. (2012). The angiotensin II type 2 receptor in brain functions: an update. *Int. J. Hypertens.* 2012:351758 doi: 10.1155/2012/351758

- Gustaw-Rothenberg, K., Kowalczyk, K., and Stryjecka-Zimmer, M. (2010). Lipids' peroxidation markers in Alzheimer's disease and vascular dementia. *Geriatr. Gerontol. Int.* 10, 161–166.
- Hajjar, I. M., Keown, M., Lewis, P., and Almor, A. (2008). Angiotensin converting enzyme inhibitors and cognitive and functional decline in patients with Alzheimer's disease: an observational study. *Am. J. Alzheimers Dis. Other Demen.* 23, 77–83. doi: 10.1177/1533317507309803
- Hanger, D. P., Anderton, B. H., and Noble, W. (2009). Tau phosphorylation: the therapeutic challenge for neurodegenerative disease. *Trends Mol. Med.* 15, 112–119. doi: 10.1016/j.molmed.2009.01.003
- Hebert, P. L., Mcbean, A. M., O'Connor, H., Frank, B., Good, C., and Maciejewski, M. L. (2013). Time until incident dementia among Medicare beneficiaries using centrally acting or non-centrally acting ACE inhibitors. *Pharmacoepidemiol. Drug Saf.* 22, 641–648. doi: 10.1002/pds.3449
- Helbecque, N., Codron, V., Cottel, D., and Amouyel, P. (2009). An age effect on the association of common variants of ACE with Alzheimer's disease. *Neurosci. Lett.* 461, 181–184. doi: 10.1016/j.neulet.2009.06.006
- Hellner, K., Walther, T., Schubert, M., and Albrecht, D. (2005). Angiotensin-(1-7) enhances LTP in the hippocampus through the G-protein-coupled receptor Mas. *Mol. Cell. Neurosci.* 29, 427–435. doi: 10.1016/j.mcn.2005.03.012
- Hemming, M. L., and Selkoe, D. J. (2005). Amyloid beta-protein is degraded by cellular angiotensin-converting enzyme (ACE) and elevated by an ACE inhibitor. *J. Biol. Chem.* 280, 37644–37650. doi: 10.1074/jbc.M508460200
- Hemming, M. L., Selkoe, D. J., and Farris, W. (2007). Effects of prolonged angiotensin-converting enzyme inhibitor treatment on amyloid beta-protein metabolism in mouse models of Alzheimer disease. *Neurobiol. Dis.* 26, 273–281. doi: 10.1016/j.nbd.2007.01.004
- Herholz, K. (2008). Acetylcholine esterase activity in mild cognitive impairment and Alzheimer's disease. *Eur. J. Nucl. Med. Mol. Imaging* 35(Suppl. 1), S25–S29. doi: 10.1007/s00259-007-0699-4
- Higuchi, M., Iwata, N., and Saido, T. C. (2005). Understanding molecular mechanisms of proteolysis in Alzheimer's disease: progress toward therapeutic interventions. *Biochim. Biophys. Acta* 1751, 60–67. doi: 10.1016/j.bbapap.2005.02.013
- Hohle, S., Blume, A., Lebrun, C., Culman, J., and Unger, T. (1995). Angiotensin receptors in the brain. *Pharmacol. Toxicol.* 77, 306–315. doi: 10.1111/j.1600-0773.1995.tb01032.x
- Hong, K. S., Kang, D. W., Bae, H. J., Kim, Y. K., Han, M. K., Park, J. M., et al. (2010). Effect of cilnidipine vs losartan on cerebral blood flow in hypertensive patients with a history of ischemic stroke: a randomized controlled trial. *Acta Neurol. Scand.* 121, 51–57. doi: 10.1111/j.1600-0404.2009.01299.x
- Horiuchi, M., Mogi, M., and Iwai, M. (2010). The angiotensin II type 2 receptor in the brain. *J. Renin Angiotensin Aldosterone Syst.* 11, 1–6. doi: 10.1177/1470320309347793
- Hou, D. R., Wang, Y., Zhou, L., Chen, K., Tian, Y., Song, Z., et al. (2008). Altered angiotensin-converting enzyme and its effects on the brain in a rat model of Alzheimer disease. *Chin. Med. J.* 121, 2320–2323.
- Hsu, C. Y., Huang, C. C., Chan, W. L., Huang, P. H., Chiang, C. H., Chen, T. J., et al. (2013). Angiotensin-receptor blockers and risk of Alzheimer's disease in hypertension population—a nationwide cohort study. *Circ. J.* 77, 405–410. doi: 10.1253/circj.CJ-12-0658
- Hu, J., Igarashi, A., Kamata, M., and Nakagawa, H. (2001). Angiotensin-converting enzyme degrades Alzheimer amyloid beta-peptide (A β); retards A β aggregation, deposition, fibril formation; and inhibits cytotoxicity. *J. Biol. Chem.* 276, 47863–47868. doi: 10.1074/jbc.M104068200
- Iloff, J. J., Wang, M., Liao, Y., Plogg, B. A., Peng, W., Gundersen, G. A., et al. (2012). A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid β . *Sci. Transl. Med.* 4:147ra111. doi: 10.1126/scitranslmed.3003748
- Inestrosa, N. C., Godoy, J. A., Quintanilla, R. A., Koenig, C. S., and Bronfman, M. (2005). Peroxisome proliferator-activated receptor gamma is expressed in hippocampal neurons and its activation prevents beta-amyloid neurodegeneration: role of Wnt signaling. *Exp. Cell Res.* 304, 91–104. doi: 10.1016/j.yexcr.2004.09.032
- Iqbal, K., Liu, F., Gong, C. X., Alonso, A. C., and Grundke-Iqbal, I. (2009). Mechanisms of tau-induced neurodegeneration. *Acta Neuropathol.* 118, 53–69. doi: 10.1007/s00401-009-0486-3
- Ito, T., Yamakawa, H., Bregonzio, C., Terron, J. A., Falcon-Neri, A., and Saavedra, J. M. (2002). Protection against ischemia and improvement of cerebral blood flow in genetically hypertensive rats by chronic pretreatment with an angiotensin II AT1 antagonist. *Stroke* 33, 2297–2303. doi: 10.1161/01.STR.0000027274.03779.F3
- Iwai, M., Liu, H. W., Chen, R., Ide, A., Okamoto, S., Hata, R., et al. (2004). Possible inhibition of focal cerebral ischemia by angiotensin II type 2 receptor stimulation. *Circulation* 110, 843–848. doi: 10.1161/01.CIR.0000138848.58269.80
- Iwanami, J., Mogi, M., Tsukuda, K., Min, L. J., Sakata, A., Jing, F., et al. (2010). Low dose of telmisartan prevents ischemic brain damage with peroxisome proliferator-activated receptor-gamma activation in diabetic mice. *J. Hypertens.* 28, 1730–1737. doi: 10.1097/HJH.0b013e32833a551a
- Jackson, L., Eldahshan, W., Fagan, S. C., and Ergul, A. (2018). Within the brain: the renin angiotensin system. *Int. J. Mol. Sci.* 19:876. doi: 10.3390/ijms19030876
- Jing, F., Mogi, M., Sakata, A., Iwanami, J., Tsukuda, K., Ohshima, K., et al. (2012). Direct stimulation of angiotensin II type 2 receptor enhances spatial memory. *J. Cereb. Blood Flow Metab.* 32, 248–255. doi: 10.1038/jcbfm.2011.133
- Johren, O., Inagami, T., and Saavedra, J. M. (1995). AT1A, AT1B, and AT2 angiotensin II receptor subtype gene expression in rat brain. *Neuroreport* 6, 2549–2552. doi: 10.1097/00001756-199512150-00024
- Kakar, S. S., Riel, K. K., and Neill, J. D. (1992). Differential expression of angiotensin II receptor subtype mRNAs (AT-1A and AT-1B) in the brain. *Biochem. Biophys. Res. Commun.* 185, 688–692. doi: 10.1016/0006-291X(92)91680-O
- Karran, E., Mercken, M., and De Strooper, B. (2011). The amyloid cascade hypothesis for Alzheimer's disease: an appraisal for the development of therapeutics. *Nat. Rev. Drug Discov.* 10, 698–712. doi: 10.1038/nrd3505
- Katsuno, T., Morishima-Kawashima, M., Saito, Y., Yamanouchi, H., Ishiura, S., Murayama, S., et al. (2005). Independent accumulations of tau and amyloid β -protein in the human entorhinal cortex. *Neurology* 64, 687–692. doi: 10.1212/01.WNL.0000151958.79884.86
- Kehoe, P. G. (2009). Angiotensins and Alzheimer's disease: a bench to bedside overview. *Alzheimers Res. Ther.* 1:3. doi: 10.1186/alzrt3
- Kim, J., Onstead, L., Randle, S., Price, R., Smithson, L., Zwizinski, C., et al. (2007). Abeta40 inhibits amyloid deposition in vivo. *J. Neurosci.* 27, 627–633. doi: 10.1523/JNEUROSCI.4849-06.2007
- Kolsch, H., Jessen, F., Freymann, N., Kreis, M., Hentschel, F., Maier, W., et al. (2005). ACE I/D polymorphism is a risk factor of Alzheimer's disease but not of vascular dementia. *Neurosci. Lett.* 377, 37–39. doi: 10.1016/j.neulet.2004.11.062
- Kume, K., Hanyu, H., Sakurai, H., Takada, Y., Onuma, T., and Iwamoto, T. (2012). Effects of telmisartan on cognition and regional cerebral blood flow in hypertensive patients with Alzheimer's disease. *Geriatr. Gerontol. Int.* 12, 207–214. doi: 10.1111/j.1447-0594.2011.00746.x
- Lanz, T. V., Ding, Z., Ho, P. P., Luo, J., Agrawal, A. N., Srinagesh, H., et al. (2010). Angiotensin II sustains brain inflammation in mice via TGF-beta. *J. Clin. Invest.* 120, 2782–2794. doi: 10.1172/JCI41709
- Lazaroni, T. L., Raslan, A. C., Fontes, W. R., De Oliveira, M. L., Bader, M., Alenina, N., et al. (2012). Angiotensin-(1-7)/Mas axis integrity is required for the expression of object recognition memory. *Neurobiol. Learn. Mem.* 97, 113–123. doi: 10.1016/j.nlm.2011.10.003
- Lenkei, Z., Palkovits, M., Corvol, P., and Llorens-Cortes, C. (1996). Distribution of angiotensin II type-2 receptor (AT2) mRNA expression in the adult rat brain. *J. Comp. Neurol.* 373, 322–339. doi: 10.1002/(SICI)1096-9861(19960923)373:3<322::AID-CNE2>3.0.CO;2-4
- Lenkei, Z., Palkovits, M., Corvol, P., and Llorens-Cortes, C. (1997). Expression of angiotensin type-1 (AT1) and type-2 (AT2) receptor mRNAs in the adult rat brain: a functional neuroanatomical review. *Front. Neuroendocrinol.* 18, 383–439. doi: 10.1006/frne.1997.0155
- Li, J., Culman, J., Hortnagl, H., Zhao, Y., Gerova, N., Timm, M., et al. (2005). Angiotensin AT2 receptor protects against cerebral ischemia-induced neuronal injury. *FASEB J.* 19, 617–619. doi: 10.1096/fj.04-2960fje
- Li, N. C., Lee, A., Whitmer, R. A., Kivipelto, M., Lawler, E., Kazis, L. E., et al. (2010). Use of angiotensin receptor blockers and risk of dementia in a predominantly male population: prospective cohort analysis. *BMJ* 340:b5465. doi: 10.1136/bmj.b5465
- Li, W., Zhang, J. W., Lu, F., Ma, M. M., Wang, J. Q., Suo, A. Q., et al. (2012). [Effects of telmisartan on the level of Abeta1-42, interleukin-1beta, tumor necrosis

- factor alpha and cognition in hypertensive patients with Alzheimer's disease]. *Zhonghua Yi Xue Za Zhi* 92, 2743–2746.
- Liu, S., Liu, J., Miura, Y., Tanabe, C., Maeda, T., Terayama, Y., et al. (2014). Conversion of Abeta43 to Abeta40 by the successive action of angiotensin-converting enzyme 2 and angiotensin-converting enzyme. *J. Neurosci. Res.* 92, 1178–1186. doi: 10.1002/jnr.23404
- Lu, J., Wu, L., Jiang, T., Wang, Y., Zhao, H., Gao, Q., et al. (2015). Angiotensin AT2 receptor stimulation inhibits activation of NADPH oxidase and ameliorates oxidative stress in rotenone model of Parkinson's disease in CATH.a cells. *Neurotoxicol. Teratol.* 47, 16–24. doi: 10.1016/j.ntt.2014.11.004
- MacGregor, D. P., Murone, C., Song, K., Allen, A. M., Paxinos, G., and Mendelsohn, F. A. (1995). Angiotensin II receptor subtypes in the human central nervous system. *Brain Res.* 675, 231–240. doi: 10.1016/0006-8993(95)00076-3
- Marchesi, C., Paradis, P., and Schiffrin, E. L. (2008). Role of the renin-angiotensin system in vascular inflammation. *Trends Pharmacol. Sci.* 29, 367–374. doi: 10.1016/j.tips.2008.05.003
- Matsumoto, S., Shimodozono, M., Miyata, R., and Kawahira, K. (2009). Benefits of the angiotensin II receptor antagonist olmesartan in controlling hypertension and cerebral hemodynamics after stroke. *Hypertens. Res.* 32, 1015–1021. doi: 10.1038/hr.2009.143
- Matsumoto, S., Shimodozono, M., Miyata, R., and Kawahira, K. (2010). The angiotensin II type 1 receptor antagonist olmesartan preserves cerebral blood flow and cerebrovascular reserve capacity, and accelerates rehabilitative outcomes in hypertensive patients with a history of stroke. *Int. J. Neurosci.* 120, 372–380. doi: 10.3109/00207450903389362
- Matsuura, T., Kumagai, H., Onimaru, H., Kawai, A., Iigaya, K., Onami, T., et al. (2005). Electrophysiological properties of rostral ventrolateral medulla neurons in angiotensin II 1a receptor knockout mice. *Hypertension* 46, 349–354. doi: 10.1161/01.HYP.0000173421.97463.ac
- McCarthy, C. A., Vinh, A., Callaway, J. K., and Widdop, R. E. (2009). Angiotensin AT2 receptor stimulation causes neuroprotection in a conscious rat model of stroke. *Stroke* 40, 1482–1489. doi: 10.1161/STROKEAHA.108.531509
- McKinley, M. J., Albiston, A. L., Allen, A. M., Mathai, M. L., May, C. N., Mcallen, R. M., et al. (2003). The brain renin-angiotensin system: location and physiological roles. *Int. J. Biochem. Cell Biol.* 35, 901–918. doi: 10.1016/S1357-2725(02)00306-0
- Millan, M. A., Jacobowitz, D. M., Aguilera, G., and Catt, K. J. (1991). Differential distribution of AT1 and AT2 angiotensin II receptor subtypes in the rat brain during development. *Proc. Natl. Acad. Sci. U.S.A.* 88, 11440–11444. doi: 10.1073/pnas.88.24.11440
- Mogi, M., Iwanami, J., and Horiuchi, M. (2012). Roles of brain angiotensin II in cognitive function and dementia. *Int. J. Hypertens.* 2012:169649. doi: 10.1155/2012/169649
- Mogi, M., Li, J. M., Tsukuda, K., Iwanami, J., Min, L. J., Sakata, A., et al. (2008). Telmisartan prevented cognitive decline partly due to PPAR-gamma activation. *Biochem. Biophys. Res. Commun.* 375, 446–449. doi: 10.1016/j.bbrc.2008.08.032
- Moriwaki, H., Uno, H., Nagakane, Y., Hayashida, K., Miyashita, K., and Naritomi, H. (2004). Losartan, an angiotensin II (AT1) receptor antagonist, preserves cerebral blood flow in hypertensive patients with a history of stroke. *J. Hum. Hypertens.* 18, 693–699. doi: 10.1038/sj.jhh.1001735
- Murphy, M. P., and LeVine, H. (2010). Alzheimer's disease and the β -Amyloid peptide. *J. Alzheimers Dis.* 19, 311–323. doi: 10.3233/JAD-2010-1221
- Murray, M. M., Bernstein, S. L., Nyugen, V., Condron, M. M., Teplow, D. B., and Bowers, M. T. (2009). Amyloid β -protein: A β 40 Inhibits A β 42 Oligomerization. *J. Am. Chem. Soc.* 131, 6316–6317. doi: 10.1021/ja8092604
- Nakagawa, T., Hasegawa, Y., Uekawa, K., Senju, S., Nakagata, N., Matsui, K., et al. (2017). Transient mild cerebral ischemia significantly deteriorated cognitive impairment in a mouse model of Alzheimer's disease via angiotensin AT1 receptor. *Am. J. Hypertens.* 30, 141–150. doi: 10.1093/ajh/hpw099
- Namsolleck, P., Boato, F., Schwengel, K., Paulis, L., Matho, K. S., Geurts, N., et al. (2013). AT2-receptor stimulation enhances axonal plasticity after spinal cord injury by upregulating BDNF expression. *Neurobiol. Dis.* 51, 177–191. doi: 10.1016/j.nbd.2012.11.008
- Nickenig, G., and Harrison, D. G. (2002). The AT1-type angiotensin receptor in oxidative stress and atherogenesis: part I: oxidative stress and atherogenesis. *Circulation* 105, 393–396. doi: 10.1161/hc0302.102618
- Nozoe, M., Hirooka, Y., Koga, Y., Araki, S., Konno, S., Kishi, T., et al. (2008). Mitochondria-derived reactive oxygen species mediate sympathoexcitation induced by angiotensin II in the rostral ventrolateral medulla. *J. Hypertens.* 26, 2176–2184. doi: 10.1097/HJH.0b013e32830dd5d3
- Oba, R., Igarashi, A., Kamata, M., Nagata, K., Takano, S., and Nakagawa, H. (2005). The N-terminal active centre of human angiotensin-converting enzyme degrades Alzheimer amyloid beta-peptide. *Eur. J. Neurosci.* 21, 733–740. doi: 10.1111/j.1460-9568.2005.03912.x
- O'Caomh, R., Healy, L., Gao, Y., Svendrovski, A., Kerins, D. M., Eustace, J., et al. (2014). Effects of centrally acting angiotensin converting enzyme inhibitors on functional decline in patients with Alzheimer's disease. *J. Alzheimers Dis.* 40, 595–603.
- Onjali, B., Nicolakakis, N., Tong, X. K., Aboukassim, T., Papadopoulos, P., Rosa-Neto, P., et al. (2014). Angiotensin II type 1 receptor blocker losartan prevents and rescues cerebrovascular, neuropathological and cognitive deficits in an Alzheimer's disease model. *Neurobiol. Dis.* 68, 126–136. doi: 10.1016/j.nbd.2014.04.018
- Panahpour, H., Nekooeian, A. A., and Dehghani, G. A. (2014). Candesartan attenuates ischemic brain edema and protects the blood-brain barrier integrity from ischemia/reperfusion injury in rats. *Iran. Biomed. J.* 18, 232–238.
- Paul, M., Poyan Mehr, A., and Kreutz, R. (2006). Physiology of local renin-angiotensin systems. *Physiol. Rev.* 86, 747–803. doi: 10.1152/physrev.00036.2005
- Premer, C., Lamondin, C., Mitzey, A., Speth, R. C., and Brownfield, M. S. (2013). Immunohistochemical localization of, and angiotensin II receptor subtypes in the rat adrenal, pituitary, and brain with a perspective commentary. *Int. J. Hypertens.* 2013:175428. doi: 10.1155/2013/175428
- Provias, J., and Jaynes, B. (2014). The role of the blood-brain barrier in the pathogenesis of senile plaques in Alzheimer's disease. *Int. J. Alzheimers Dis.* 2014:191863. doi: 10.1155/2014/191863
- Prusty, S. K., Sahu, P. K., and Subudhi, B. B. (2017). Angiotensin mediated oxidative stress and neuroprotective potential of antioxidants and AT1 receptor blockers. *Mini Rev. Med. Chem.* 17, 518–528. doi: 10.2174/1389557516666161025094539
- Reid, I. A. (1992). Interactions between ANG II, sympathetic nervous system, and baroreceptor reflexes in regulation of blood pressure. *Am. J. Physiol.* 262, E763–E778. doi: 10.1152/ajpendo.1992.262.6.E763
- Rompe, F., Artuc, M., Hallberg, A., Alterman, M., Stroder, K., Thone-Reineke, C., et al. (2010). Direct angiotensin II type 2 receptor stimulation acts anti-inflammatory through epoxyeicosatrienoic acid and inhibition of nuclear factor kappaB. *Hypertension* 55, 924–931. doi: 10.1161/HYPERTENSIONAHA.109.147843
- Royea, J., Zhang, L., Tong, X. K., and Hamel, E. (2017). Angiotensin IV receptors mediate the cognitive and cerebrovascular benefits of losartan in a mouse model of Alzheimer's disease. *J. Neurosci.* 37, 5562–5573. doi: 10.1523/JNEUROSCI.0329-17.2017
- Ruginsk, S., Vechiato, F., Elias, L., Antunes-Rodrigues, J., and Cruz, J. (2015). Angiotensin II reduces mRNA expression for glutamate transporters and glutamine synthetase in cultured hypothalamic astrocytes. *FASEB J.* 29, 968.919.
- Saavedra, J. M. (2012). Angiotensin II AT1 receptor blockers as treatments for inflammatory brain disorders. *Clin. Sci.* 123, 567–590. doi: 10.1042/CS20120078
- Saavedra, J. M. (2016). Evidence to consider angiotensin II receptor blockers for the treatment of early Alzheimer's disease. *Cell. Mol. Neurobiol.* 36, 259–279. doi: 10.1007/s10571-015-0327-y
- Saavedra, J. M., Ando, H., Armando, I., Baiardi, G., Bregonzio, C., Juorio, A., et al. (2005). Anti-stress and anti-anxiety effects of centrally acting angiotensin II AT1 receptor antagonists. *Regul. Pept.* 128, 227–238. doi: 10.1016/j.regpep.2004.12.015
- Safciuc, F., Constantin, A., Manea, A., Nicolae, M., Popov, D., Raicu, M., et al. (2007). Advanced glycation end products, oxidative stress and metalloproteinases are altered in the cerebral microvasculature during aging. *Curr. Neurovasc. Res.* 4, 228–234. doi: 10.2174/156720207782446351
- Saharan, S., and Mandal, P. K. (2014). The emerging role of glutathione in Alzheimer's disease. *J. Alzheimers Dis.* 40, 519–529.
- Seifi, B., Kadkhodae, M., Bakhshi, E., Ranjbaran, M., Ahghari, P., and Rastegar, T. (2014). Enhancement of renal oxidative stress by injection of angiotensin II into the paraventricular nucleus in renal ischemia-reperfusion injury. *Can. J. Physiol. Pharmacol.* 92, 752–757. doi: 10.1139/cjpp-2014-0108

- Seifi, B., Kadkhodae, M., Bakhshi, E., Ranjbaran, M., Zahmatkesh, M., Sedaghat, Z., et al. (2015). Angiotensin II in paraventricular nucleus contributes to sympathoexcitation in renal ischemia-reperfusion injury by AT1 receptor and oxidative stress. *J. Surg. Res.* 193, 361–367. doi: 10.1016/j.jss.2014.06.042
- Shin, R. W., Ogino, K., Kondo, A., Saido, T. C., Trojanowski, J. Q., Kitamoto, T., et al. (1997). Amyloid beta-protein (Abeta) 1-40 but not Abeta1-42 contributes to the experimental formation of Alzheimer disease amyloid fibrils in rat brain. *J. Neurosci.* 17, 8187–8193. doi: 10.1523/JNEUROSCI.17-21-08187.1997
- Singh, K. D., and Karnik, S. S. (2016). Angiotensin receptors: structure, function, signaling and clinical applications. *J. Cell Signal.* 1:111
- Sink, K. M., Leng, X., Williamson, J., Kritchevsky, S. B., Yaffe, K., Kuller, L., et al. (2009). Angiotensin converting enzyme inhibitors and cognitive decline in older adults with hypertension: results from the cardiovascular health study. *Arch. Intern. Med.* 169, 1195–1202. doi: 10.1001/archinternmed.2009.175
- So, G., Nakagawa, S., Morofuji, Y., Hiu, T., Hayashi, K., Tanaka, K., et al. (2015). Candesartan improves ischemia-induced impairment of the blood-brain barrier in vitro. *Cell. Mol. Neurobiol.* 35, 563–572. doi: 10.1007/s10571-014-0152-8
- Song, K., Allen, A. M., Paxinos, G., and Mendelsohn, F. A. (1991). Angiotensin II receptor subtypes in rat brain. *Clin. Exp. Pharmacol. Physiol.* 18, 93–96. doi: 10.1111/j.1440-1681.1991.tb01414.x
- Song, K., Allen, A. M., Paxinos, G., and Mendelsohn, F. A. (1992). Mapping of angiotensin II receptor subtype heterogeneity in rat brain. *J. Comp. Neurol.* 316, 467–484. doi: 10.1002/cne.903160407
- Soto, M. E., Van Kan, G. A., Nourhashemi, F., Gillette-Guyonnet, S., Cesari, M., Cantet, C., et al. (2013). Angiotensin-converting enzyme inhibitors and Alzheimer's disease progression in older adults: results from the Réseau sur la Maladie d'Alzheimer Français cohort. *J. Am. Geriatr. Soc.* 61, 1482–1488. doi: 10.1111/jgs.12415
- Sparks, M. A., Crowley, S. D., Gurley, S. B., Mirosou, M., and Coffman, T. M. (2014). Classical renin-angiotensin system in kidney physiology. *Compr. Physiol.* 4, 1201–1228. doi: 10.1002/cphy.c130040
- Sun, X., Becker, M., Pankow, K., Krause, E., Ringling, M., Beyermann, M., et al. (2008). Catabolic attacks of membrane-bound angiotensin-converting enzyme on the N-terminal part of species-specific amyloid-beta peptides. *Eur. J. Pharmacol.* 588, 18–25. doi: 10.1016/j.ejphar.2008.03.058
- Supnet, C., and Bezprozvany, I. (2010). The dysregulation of intracellular calcium in Alzheimer disease. *Cell Calcium* 47, 183–189. doi: 10.1016/j.ceca.2009.12.014
- Takada, J., Ibayashi, S., Ooboshi, H., Ago, T., Ishikawa, E., Kamouchi, M., et al. (2006). Valsartan improves the lower limit of cerebral autoregulation in rats. *Hypertens. Res.* 29, 621–626. doi: 10.1291/hypres.29.621
- Takane, K., Hasegawa, Y., Lin, B., Koibuchi, N., Cao, C., Yokoo, T., et al. (2017). Detrimental effects of centrally administered angiotensin II are enhanced in a mouse model of Alzheimer disease independently of blood pressure. *J. Am. Heart Assoc.* 6:e004897. doi: 10.1161/JAHA.116.004897
- Takeda, S., and Morishita, R. (2017). Angiotensin receptor blocker protects Alzheimer's disease brain from ischemic insult. *Am. J. Hypertens.* 30, 110–111. doi: 10.1093/ajh/hpw158
- Takeda, S., Sato, N., Takeuchi, D., Kurinami, H., Shinohara, M., Niisato, K., et al. (2009). Angiotensin receptor blocker prevented beta-amyloid-induced cognitive impairment associated with recovery of neurovascular coupling. *Hypertension* 54, 1345–1352. doi: 10.1161/HYPERTENSIONAHA.109.138586
- Tian, M., Zhu, D., Xie, W., and Shi, J. (2012). Central angiotensin II-induced Alzheimer-like tau phosphorylation in normal rat brains. *FEBS Lett.* 586, 3737–3745. doi: 10.1016/j.febslet.2012.09.004
- Tota, S., Goel, R., Pachauri, S. D., Rajasekar, N., Najmi, A. K., Hanif, K., et al. (2013). Effect of angiotensin II on spatial memory, cerebral blood flow, cholinergic neurotransmission, and brain derived neurotrophic factor in rats. *Psychopharmacology* 226, 357–369. doi: 10.1007/s00213-012-2913-8
- Tota, S., Kamat, P. K., Awasthi, H., Singh, N., Raghubir, R., Nath, C., et al. (2009). Candesartan improves memory decline in mice: involvement of AT1 receptors in memory deficit induced by intracerebral streptozotocin. *Behav. Brain Res.* 199, 235–240. doi: 10.1016/j.bbr.2008.11.044
- Tota, S., Kamat, P. K., Saxena, G., Hanif, K., Najmi, A. K., and Nath, C. (2012). Central angiotensin converting enzyme facilitates memory impairment in intracerebroventricular streptozotocin treated rats. *Behav. Brain Res.* 226, 317–330. doi: 10.1016/j.bbr.2011.07.047
- Tsutsumi, K., and Saavedra, J. M. (1991). Characterization and development of angiotensin II receptor subtypes (AT1 and AT2) in rat brain. *Am. J. Physiol.* 261, R209–R216. doi: 10.1152/ajpregu.1991.261.1.R209
- Uekawa, K., Hasegawa, Y., Senju, S., Nakagata, N., Ma, M., Nakagawa, T., et al. (2016). Intracerebroventricular infusion of angiotensin-(1-7) ameliorates cognitive impairment and memory dysfunction in a mouse model of Alzheimer's disease. *J. Alzheimers Dis.* 53, 127–133. doi: 10.3233/JAD-150642
- Umschweif, G., Liraz-Zaltsman, S., Shabashov, D., Alexandrovich, A., Trembovler, V., Horowitz, M., et al. (2014). Angiotensin receptor type 2 activation induces neuroprotection and neurogenesis after traumatic brain injury. *Neurotherapeutics* 11, 665–678. doi: 10.1007/s13311-014-0286-x
- Valenzuela, R., Costa-Besada, M. A., Iglesias-Gonzalez, J., Perez-Costas, E., Villar-Cheda, B., Garrido-Gil, P., et al. (2016). Mitochondrial angiotensin receptors in dopaminergic neurons. Role in cell protection and aging-related vulnerability to neurodegeneration. *Cell Death Dis.* 7:e2427. doi: 10.1038/cddis.2016.327
- Vargas, R., Rincon, J., Pedreanez, A., Viera, N., Hernandez-Fonseca, J. P., Pena, C., et al. (2012). Role of angiotensin II in the brain inflammatory events during experimental diabetes in rats. *Brain Res.* 1453, 64–76. doi: 10.1016/j.brainres.2012.03.021
- Vila-Porcielle, E., and Corvol, P. (1998). Angiotensinogen, prorenin, and renin are Co-localized in the secretory granules of all glandular cells of the rat anterior pituitary: an immunoultrastructural study. *J. Histochem. Cytochem.* 46, 301–311. doi: 10.1177/002215549804600303
- Wang, B. R., Shi, J. Q., Zhang, Y. D., Zhu, D. L., and Shi, J. P. (2011). Angiotensin II does not directly affect Abeta secretion or beta-/gamma-secretase activity via activation of angiotensin II type 1 receptor. *Neurosci. Lett.* 500, 103–107. doi: 10.1016/j.neulet.2011.06.014
- Wang, J., Ho, L., Chen, L., Zhao, Z., Zhao, W., Qian, X., et al. (2007). Valsartan lowers brain beta-amyloid protein levels and improves spatial learning in a mouse model of Alzheimer disease. *J. Clin. Invest.* 117, 3393–3402. doi: 10.1172/JCI31547
- Wang, J. M., Slembrouck, D., and Potter, W. D. (1996). Expression of angiotensinogen mRNA and localization of angiotensin II and renin in peripheral adrenergic neurons in primary culture. *Biochem. Biophys. Res. Commun.* 229, 876–881. doi: 10.1006/bbrc.1996.1895
- Welander, H., Franberg, J., Graff, C., Sundstrom, E., Winblad, B., and Tjernberg, L. O. (2009). Abeta43 is more frequent than Abeta40 in amyloid plaque cores from Alzheimer disease brains. *J. Neurochem.* 110, 697–706. doi: 10.1111/j.1471-4159.2009.06170.x
- Wharton, W., Goldstein, F. C., Zhao, L., Steenland, K., Levey, A. I., and Hajjar, I. (2015). Renin-angiotensin-system modulation may slow the conversion from mild cognitive impairment to Alzheimer's disease. *J. Am. Geriatr. Soc.* 63, 1749–1756. doi: 10.1111/jgs.13627
- Wharton, W., Stein, J. H., Korcarz, C., Sachs, J., Olson, S. R., Zetterberg, H., et al. (2012). The effects of ramipril in individuals at risk for Alzheimer's disease: results of a pilot clinical trial. *J. Alzheimers Dis.* 32, 147–156.
- Wincewicz, D., and Braszko, J. J. (2014). Telmisartan attenuates cognitive impairment caused by chronic stress in rats. *Pharmacol. Rep.* 66, 436–441. doi: 10.1016/j.pharep.2013.11.002
- Wolfe, M. S. (2012). The role of tau in neurodegenerative diseases and its potential as a therapeutic target. *Scientifica* 2012:796024. doi: 10.6064/2012/796024
- Wright, J. W., Stuble, L., Pederson, E. S., Kramar, E. A., Hanesworth, J. M., and Harding, J. W. (1999). Contributions of the brain angiotensin IV-AT4 receptor subtype system to spatial learning. *J. Neurosci.* 19, 3952–3961. doi: 10.1523/JNEUROSCI.19-10-03952.1999
- Yankner, B. A. (1996). Mechanisms of neuronal degeneration in Alzheimer's disease. *Neuron* 16, 921–932. doi: 10.1016/S0896-6273(00)80115-4
- Yim, H. E., and Yoo, K. H. (2008). Renin-angiotensin system - Considerations for hypertension and kidney. *Electrolyte Blood Press.* 6, 42–50. doi: 10.5049/EBP.2008.6.1.42
- Zheng, W. H., Bastianetto, S., Mennicken, F., Ma, W., and Kar, S. (2002). Amyloid beta peptide induces tau phosphorylation and loss of cholinergic neurons in rat primary septal cultures. *Neuroscience* 115, 201–211. doi: 10.1016/S0306-4522(02)00404-9
- Zhu, D., Shi, J., Zhang, Y., Wang, B., Liu, W., Chen, Z., et al. (2011). Central angiotensin II stimulation promotes beta amyloid production

- in sprague dawley rats. *PLoS One* 6:e16037. doi: 10.1371/journal.pone.0016037
- Zhuang, S., Wang, H. F., Wang, X., Li, J., and Xing, C. M. (2016). The association of renin-angiotensin system blockade use with the risks of cognitive impairment of aging and Alzheimer's disease: a meta-analysis. *J. Clin. Neurosci.* 33, 32–38. doi: 10.1016/j.jocn.2016.02.036
- Zhuo, J., Moeller, I., Jenkins, T., Chai, S. Y., Allen, A. M., Ohishi, M., et al. (1998). Mapping tissue angiotensin-converting enzyme and angiotensin AT1, AT2 and AT4 receptors. *J. Hypertens.* 16, 2027–2037. doi: 10.1097/00004872-199816121-00026
- Zlokovic, B. V. (2011). Neurovascular pathways to neurodegeneration in Alzheimer's disease and other disorders. *Nat. Rev. Neurosci.* 12, 723–738. doi: 10.1038/nrn3114
- Zou, K., Maeda, T., Watanabe, A., Liu, J., Liu, S., Oba, R., et al. (2009). A β 42-to-A β 40- and angiotensin-converting activities in different domains of angiotensin-converting enzyme. *J. Biol. Chem.* 284, 31914–31920. doi: 10.1074/jbc.M109.011437
- Zou, K., Yamaguchi, H., Akatsu, H., Sakamoto, T., Ko, M., Mizoguchi, K., et al. (2007). Angiotensin-converting enzyme converts amyloid beta-protein 1-42 (Abeta(1-42)) to Abeta(1-40), and its inhibition enhances brain Abeta deposition. *J. Neurosci.* 27, 8628–8635. doi: 10.1523/JNEUROSCI.1549-07.2007

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