



The Protective Tributary Angiotensin Members of Renin-Angiotensin System Display Beneficial Effects in the Central Nervous System Disorders

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Abstract

The Renin-Angiotensin (Ang) System (RAS) is pleotropic machinery, contains members with different activities. New substrates, such as Ang-(1-7) and Ang-(3-7), of vascular and tissue source are being added to RAS. These new comers counter balance/oppose the effects of the traditional previously identified Ang I & II. Ang-(1-7) is identified as a biologically active member of RAS. Ang-(1-7) is synthesized from Ang II by the action of angiotensin converting enzyme ACE2, and acts on its G protein-coupled Mas receptors (MasR) and Mas-related G-protein-coupled receptor (Mrg-D) forming its own ACE2/Ang-(1-7)/Mas Axis (AAMA). This axis counteracts many of the Ang II-AT1 activities, especially vasoconstriction, inflammation and proliferation. A growing body of evidence supports AAMA presence in brain, and the role it plays in conditions other than the renal and cardiovascular diseases, such as Alzheimer's disease, Parkinson's disease, ageing, menopause etc. There are different and even conflicting results reported acceleratory or preventive effects of RAS components, angiotensin receptor antagonists (ARB) and ACE Inhibitors (ACEI) in AD. Moreover, there is also a difference between ARBs and ACEIs in this regard. Here, we review the importance of the AAMA axis and other protective arms of RAS with emphasis on the role of this axis in brain function, various neurodegenerative diseases and patients receiving ACEIs and ARBs.

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General-Synthetic Pathways of RAS Components

The Renin-Angiotensin System (RAS) is a potent regulator of blood pressure, body fluid and electrolyte homeostasis. RAS has long been considered as a linear system starts from a serpin family α 2-globulin, Angiotensinogen (AGT). Plasma AGT level is increased by plasma corticosteroid, estrogen, thyroid hormone, and angiotensin II. At least twelve products derived from AGT had already been detected, with several new comers are still expected. AGT is hepatically synthesized, cleaved by renin to angiotensin-(1-10) (Ang I) which is further processed to the biologically active peptides Ang-(1-8) (Ang II) by Angiotensin Converting Enzyme (ACE) and Ang-(1-7) by endopeptidases such as neprilysin, NEP (Figure 1). Moreover, AGT could also be directly converted to Ang I by a non-renin pathway (cathepsin, tonin, and tissue plasminogen). Ang I is cleaved to Ang II by ACE. Ang I is also converted to Ang II by a non-ACE pathway (chymase, cathepsin). Ang II undergoes further processing at the carboxyl terminus by ACE2 and Prolyl Carboxypeptidase (PCP) to yield Ang-(1-7). Low level PCP in the first 24 hour after stroke onset is associated with stroke severity and an unfavorable short-term stroke outcome [1]. Ang-(1-7) undergoes Decarboxylation (DC) of the aspartic acid residue to form Ala1-Ang-(1-7) (Ala1-Ang 7: alamandine). Ang I is also cleaved by Aminopeptidase A (APA) to Ang-(2-10) which acts on AT1R. Ang III/I could also be generated from Ang-(2-10) by ACE hydrolysis [2]. The dodecapeptide Ang-(1-12) is derived from the hydrolysis of the Tyr12-Tyr13 bond of angiotensinogen by an unknown (may be hydrolysis) enzymatic pathway. Ang-(1-12) could be cleaved to Ang-(1-7) by NEP, and it is a source for tissue Ang II (by ACE or chymase) formation. The divergency of Ang-(1-12) metabolic pathways might be highly tissue specific. The amino acid sequence of this novel peptide is similar to the sequence of Ang I plus -Leu11-Tyr12 (rodent) or Val11-Ile12 humans [3]. Ang-(1-12) at a concentration higher than that of Ang II acts directly on AT1 albeit [4]. Recent studies shed new light on renin production and release. The main source of renin is the Juxtaglomerular Cells (JGCs), which release renin from storage granules. JGCs originate *in situ* within the metanephric kidney from mesenchymal cells that are not related to smooth muscle lineages. The previous notion that JGCs stem from vascular

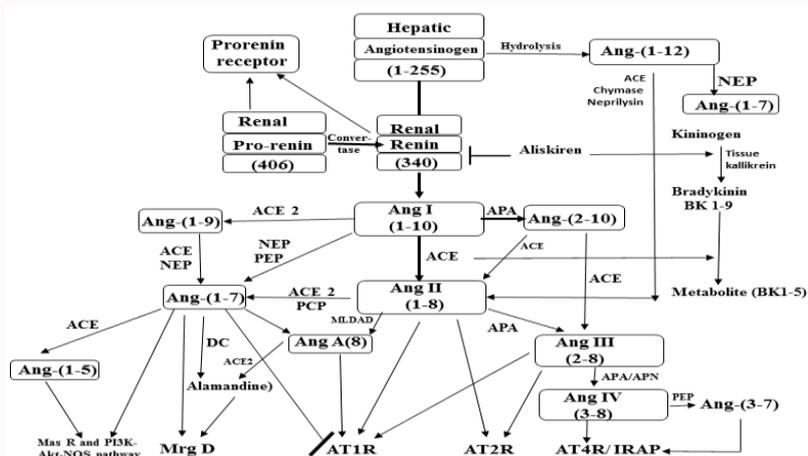


Figure 1: Synthetic cascade and metabolism of the deleterious and protective angiotensin peptides. ACE2: Angiotensin-Converting Enzyme type 2; APA/APN/ APN: Aminopeptidase A/M/N; AT1R, AT2R, AT3R, AT4R: angiotensin receptor type 1, 2, 3 and 4, respectively. DC: Decarboxylase; IRAP: Insulin-Regulated Aminopeptidase or AT4 receptor; MLDAD: Mononuclear Leukocyte-Derived Aspartate Decarboxylase; Mrg-D: Mas-related G-protein-coupled receptor, member D; NEP: Neprilysin; PCP: Prolyl-Carboxy-Peptidase (PCP); PEP: Prolyl-Endo-Peptidase. Prorenin is activated to renin by convertase. Ang-(1-7) and Ang II are also converted to Ang-(3-7).

smooth muscle cells may be explained by JGC differentiation: they acquire smooth muscle markers that are maintained throughout adulthood. It has become clear that AT1 receptors and increasing intracellular free $[Ca^{2+}]$ inhibits renin secretion in JGCs. In contrast, cAMP stimulates renin release [5]. The essential component of the RAS is depicted in (Figure 1).

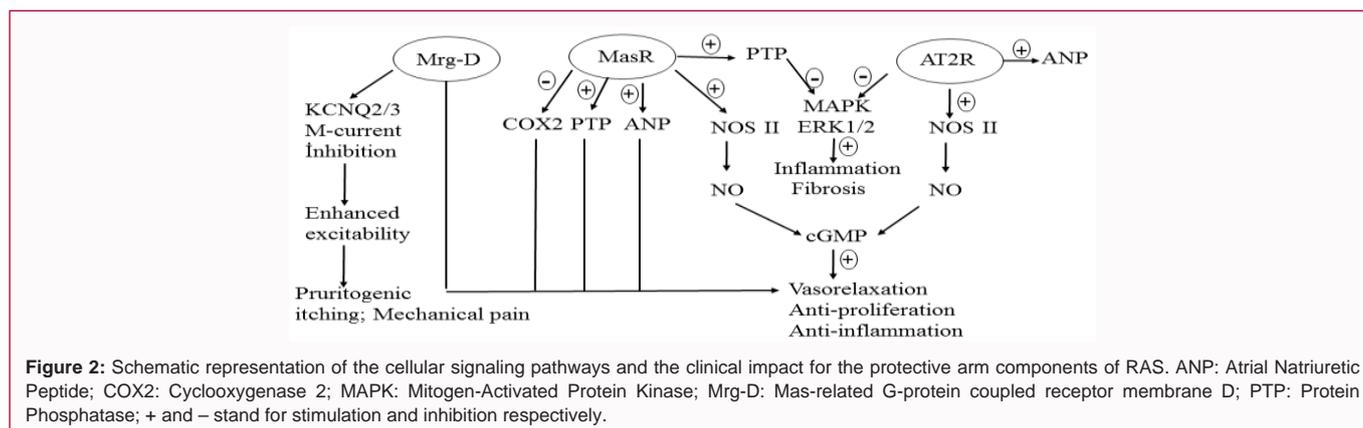
Ang II is converted to Ang A (1-8) under the effect of Mononuclear Leukocyte-Derived Aspartate Decarboxylase (MLDAD). The amino acid sequence of Ang A (A stands for alanine) (Ala-Arg-Val-Tyr-Ile-His-Pro-Phe) differs from Ang II only in one amino acid: Ala¹ instead of Asp. Ang A acts on AT1R. Ang A is converted to alamandine by hydrolysis and by ACE2. Alamandine can alternatively be formed by decarboxylation of the Asp residue of angiotensin-(1-7). It is physiologically found in human plasma at concentrations lower than 20% of normal Ang II concentrations. However, the Ang A/Ang II ratio is significantly increased in end-stage renal disease patients [6-8]. RAS interacts with various other systems with important clinical outcomes. Prostaglandin increases renin release and Ang II formation. There is a beneficial interaction between thromboxane synthesis inhibitors and ACE inhibitors due to reduction of renal vascular resistance by redirecting prostaglandin endoperoxide synthesis toward prostacyclin by the former, and prevention of Ang II synthesis by the latter (Figure 1) [9].

The other important interaction is that with endocrine system. RAS is involved in estrogen-vascular health maintenance. Although estrogen increases AGT and Ang I, it reduces hypertension. This activity could be attributed to reduction of ACE by estrogen with consequent elevation of AGT and Ang I, reduction of Ang II production, and shift towards Ang-(1-7). At the same time estrogen-inhibition of ACE reduces conversion of Ang-(1-7) to Ang-(1-5), and bradykinin metabolism. Because ACE reduction also leads to less degradation of bradykinin, another aspect of estrogens action would be enhanced vasodilation by both Ang-(1-7) and bradykinin, and reduced Ang II-vasoconstriction. This activity may provide the rationality for the use of estrogen to prevent cardiovascular disease in postmenopausal women who are at increased cardiovascular risk. Another interaction is that with oxytocin. An angiotensin IV and

oxytocin interaction has been shown to be involved in reversion or reduction of immobility time induced by oxytocin during the test for antidepressive property using forced swim test [10]. This study suggested that the proteolytic conversion of oxytocin into active metabolites, which possibly bind to receptors other than the oxytocin receptor, could be responsible for the reduced immobility time [11].

Angiotensin Converting Enzymes (ACEs)

ACE is type I integral membrane protein of M2 family zinc metallopeptidase. Its activity depends on chloride anion [12]. ACE can be inhibited by metal-chelating agents [13]. Under physiological conditions, the enzyme reaches about 60% of its maximal activity toward Ang I while it reaches its full activity toward bradykinin. ACE is located mainly in the capillaries of the lungs but can also be found in endothelial and renal epithelial cells. There are two isoforms of ACE in humans: somatic ACE (sACE) and germinal (testicular) ACE (gACE). Somatic ACE is found in many types of endothelial and epithelial cells. The gACE is present exclusively in germinal cells in the male testis. ACE can be released as a soluble enzyme into extracellular fluids, such as plasma and seminal and cerebrospinal fluids, following post-translational proteolytic cleavage by a membrane protein sheddase or secretase. ACE may be involved in the functioning of the brain and nervous system. ACE hydrolyzes neuropeptides such as enkephalin, substrate P, neurotensin and LH-RH. Several subtypes of ACE are involved in derivation of Ang subtypes from Ang I. It also degrades BK (1-9), a vasodilator, to its inactive metabolite [14,15]. ACE degrades A β and converts A β 1-42 to A β 1-40 chronic inhibition of ACE with captopril enhances predominant A β 1-42 deposition. ACE exhibits polymorphic variation, Deletion (D) and Insertion (I). These different genotypes are important in athleticism: blood pressure of D carriers increase soon and have increased risk of cardiovascular diseases. The major function of ACE2 is to counter-regulate ACE activity by reducing Ang II bioavailability and increasing Ang-(1-7) formation. The main ACE responsible for emergence of Ang-(1-7) is ACE2 [16]. ACE2 could either directly convert Ang II to Ang-(1-7), or by acting firstly on Ang I and converting it to Ang1-9, which latter converts to Ang-(1-7) under the influence of ACE. Ang-(1-7) could also be directly derived from Ang I under the effect of neprilysin and



Prolyl-Endo-Peptidase (PEP) (Figure 1). ACE2 is primarily epithelial and is developmentally regulated in the mouse lung [17]. ACE2 activity increases with increased $[Cl^-]$. An increase in $[Cl^-]$ above 100 mm, which is the physiological concentration in human plasma, increases Ang I and decreases Ang II cleavage by ACE2. The latter effect has an effect on the localized concentration of Ang II in the kidney, where ACE2 has a high level of expression and extracellular chloride ion levels fluctuate. It is assumed that the function of the anion, chloride activation in ACE provides high substrate specificity ACE2 functions predominantly as a monocarboxypeptidase [18]. ACE2 activity is unaffected by inhibitors of ACE (captopril, lisinopril and enalaprilat) or carboxypeptidase A (benzylsuccinate and potato carboxypeptidase inhibitor) [19]. ACE2 improves endothelial function [20].

RAS Receptors and Their Cellular Signals

RAS is found in the JGCs, and exists as local RAS in various tissues. Ang II produces its effects *via* its several receptors. Ang II could directly recognize two GPCRs-dependent receptor type 1 (AT1R) and type 2 (AT2R) forming the ACE/Ang II/AT1 receptor axis that is implicated in a variety of diseases such as vasoconstriction, inflammation, proliferation, angiogenesis, fibrosis, cellular growth and migration and fluid retention [21,22]. The Ang II-AT1R axis may attenuate ACE2 expression but increase A Disintegrin and Metalloproteinase (ADAM) levels. Moreover, AT2R is predominantly expressed in fetal tissues. Ang II binding increases apoptosis causes vasodilation and is involved in fetal tissue development [23]. Ang II under the effect of APA is converted to Ang III which latter cleaves to Ang IV. Ang IV evokes hypertrophy, vasodilatation and vascular inflammatory response. It binds to AT1R and AT2R with low affinity, but binds with high affinity and acts on its own specific receptor AT4R. AT4R expression has been localized in both endothelial and smooth muscle cells [24,25]. AT4Rs regulate blood flow *via* a mechanism mediated by AT4R and nitric oxide and play an important role in normal pregnancy [26,27]. Metabolically stable Ang IV had been found to significantly improve motor performance [28].

Multi-system effects of Ang-(1-7) *via* Mas receptors

a) Anti-inflammation: Decrease TNF- α , RAGE, neutrophil and macrophage. Increases RAGE.

b) Anti-fibrosis: Increase apoptosis, decrease collagen deposition, hydroxyproline and TGF- β .

c) Reproduction: Increase ovulation, spermatogenesis and sex steroid synthesis.

d) Anti-cancer: Decrease tumor cell proliferation, Placental

Growth Factor (PIGF), soluble fraction of Vascular Endothelial Growth Factor (VEGF) receptor 1 (sFlt-1), MMP2/9, MAPK/ERK, HAC1. Increase FOXO1.

e) Metabolism: Increase insulin, glucose uptake and lipolysis. Decrease insulin resistance and dyslipidemia.

f) Brain: Increase LTP, decrease ischemia-infarct. Improve behavioral deficits.

Ang II could influence the vascular contractility/relaxation by two ways: after conversion to Ang-(1-7), the latter produces endothelium-dependent vasodilation. This pathway becomes prominent at high Ang II levels or following ACE inhibition. On the other hand, activation of AT1 receptors by low concentrations of angiotensin II causes vasoconstriction. As could be seen from Figure 1, Ang II stimulates AT2R in addition to AT1R. Stimulation of AT2R leads to intracellular acidification, which together with MasR stimulation by Ang-(1-7) increase kininogenase and bradykinin synthesis. Bradykinin stimulates its B2 receptors. The B2 receptors are localized differentially in different parts of the cardiovascular system: the arterioles have smooth muscle-localized B2 receptors, and large elastic vessels have endothelium-localized receptors. Stimulation of the B2 receptors by bradykinin produces vasorelaxation, which in turns results in the activation of the NO-cGMP pathway, vasodilator cyclooxygenase product(s), and voltage dependent and Ca^{2+} -activated large-conductance K^+ channels [29]. The Prorenin Receptors (PRR) is increasingly gaining significance. They are involved in cardiac and renal fibrosis and hypertrophy. It has been suggested that blocking the PRR may be a new target for renal and cardiac end-organ protection. PRRs activate renin. Antagonists of PRRs, known as Hand region peptide, act as decoy receptors and prevent binding of prorenin and renin to PRR. Renin bound to the PRR displays an increased catalytic efficiency of AGT conversion to Ang I compared with free renin [18]. The G-protein coupled MasR is the functional receptor for Ang-(1-7) and its derivative Ang-(1-5) [30]. Thus, Ang-(1-7) is now considered a biologically active member of the RAS. Ang-(1-7) is both a substrate and an inhibitor of ACE. Ang-(1-7) is derived directly from Ang II by the action of ACE2. It is also derived from Ang I either directly (by NEP and PEP) or indirectly after conversion of Ang I to Ang1-9 (ACE2) and the latter to Ang-(1-7) (by ACE/NEP). It has been reported that combination of ACE inhibition and low sodium diet appeared to shift the balance between Ang-(1-7) and Ang II towards Ang-(1-7), which in turn might contribute to the therapeutic benefits of ACEIs [31]. However, MasR undergoes endocytosis on stimulation with Ang-(1-7), and this event may explain the desensitization of MasR responsiveness [32]. Ang-

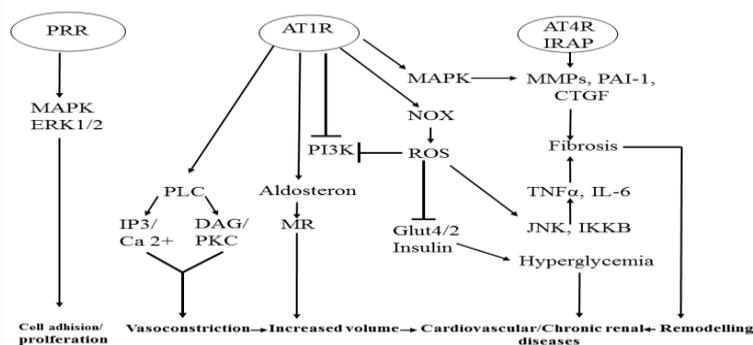


Figure 3: Schematic representation of the cellular signaling pathways and the clinical impact for the deleterious arm components of RAS. AT1R inhibits ACE2, but increases ADAM (A Disintegrin and Metalloproteinase). CTGF: connective tissue growth factor; DAG: Diacyl Glycerol; Glut: Glucose Transporter; IKK- β : Inhibitor of Nuclear Factor-Kappa-B Kinase; IP3: Inositol Triphosphate; JNK: c-Jun N-terminal Kinases; MAPK: Mitogen-Activated Protein Kinase; MMPs: Matrix Metalloproteinases; MR: Mineralocorticoid Receptor; NOS: Nitric Oxide Synthase; NOX: NADPH Oxidase; PAI-1: Plasminogen Activator Inhibitor-1; PI3K: Phosphoinositide 3-Kinase; PKC: Protein Kinase C; PLC: Phospho Lipase C; PRR: Prorenin Receptor; ROS: Reactive Oxygen Species; TNF- α : Tumor Necrosis Factor Alpha.

(1-7) and alamandine act on Mrg-D receptors. Mrg-D receptors are positively modulated by Beta alanine, GABA, Beta-aminoisobutyric acid. Mrg-D regulates two intracellular regulatory pathways *via* Gi and Gq: activity *via* Gi decreases adenylate cyclase and cyclic AMP, whereas that *via* Gq increases Ca^{2+} influx in response to beta-alanine. Mrg-D also mediates mechanic (not cold/heat) pain [33,34]. Ang-(1-7) is converted to Ang-(1-5) by the activity of ACE. Ang-(1-5) increases Atrial Natriuretic Peptide (ANP) secretion *via* MasR and PI3K-Akt-NOS pathway [35]. Ang-(1-7) metalloendopeptidase in Cerebrospinal Fluid (CSF) and brain medulla metabolizes Ang-(1-7) to Ang-(1-4) [36]. $G_{i/o}$ coupling links MR-G to KCNQ2/3 channels, and inhibition of KCNQ2/3 activity is mainly responsible for the MR-G-inhibition of noninactivating potassium currents, M-currents and enhanced neuronal activity [37,38]. The other receptor type is the Insulin Regulated Amino Peptide (IRAP)/AT₄ receptors. The ligands that act on these receptors display their effects *via* either one of these mechanisms: (1) The peptides bind to the catalytic site of IRAP and inhibit its enzymatic activity thereby prolonging the half-life of its neuropeptide substrates with memory-enhancing properties, or (2) Upon binding to IRAP, the AT₄ ligands regulate the level of GLUT4 expressed at the cell surface resulting in an increase in glucose uptake into neurons [39].

Physiological and Health Impact of RAS

The protective angiotensins: Ang-(1-7) and other components (Figure 2): Ang-(1-7) is the endogenous substrate for Mas-R [28]. Ang-(1-7) reduces hypertrophy and ERK [40]. Ang-(1-7), has vasodilator, antidiuretic antithrombotic effects that involve MAS1-mediated release of nitric oxide from platelets. Moreover, it has been reported that Ang-(1-7) increase ovulation, spermatogenesis, glucose uptake, lipolysis while decreases insulin resistance and dyslipidemia [41]. We have also reported that Ang-(1-7) reversed the effect of adjuvant-arthritis; it decreased aortic RAGE and TNF- α (but not IL-1 β) expression, but increased the sRAGE in blood. Ang-(1-7) also decreased phenylephrine and KCl contractility, especially in the endothelial-denuded aorta, whereas increased acetylcholine relaxation in the endothelial-intact aorta [42].

Ang-(1-7) activates the molecular mechanisms that inhibit angiogenesis and tumorigenesis. It inactivates histone deacetylase 1, while activates the transcriptional factor FOXO1 and consequently

its translocation to the nucleus of endothelial and tumor cells [43]. FOXO1 is responsible for triggering the activation of genes involved in apoptosis, cell-cycle arrest and oxidative stress resistance [44]. Ang-(1-7) has been detected in retinal glial cells [45]. Mast cells in eye mediate the diminution of intraocular pressure without modifying aqueous humor outflow, and conferring protection against diabetic retinopathy [46,47].

The Deleterious Angiotensins (Figure 3): Ang II acts directly on vascular smooth muscle as a potent vasoconstrictor. It affects cardiac contractility and heart rate through its action on the sympathetic nervous system, and alters renal sodium and water absorption through its ability to stimulate the zona glomerulosa cells of the adrenal cortex to synthesize and secrete aldosterone. Ang II stimulates aldosterone release, with subsequent fluid and salt retention and volume increase. Moreover, Ang II stimulates sympathetic outflow (increase norepinephrine). In the cardiovascular system, it induces hypertrophy (heart) with remodeling in both heart musculature and vascular bed (Figure 3).

Role of RAS in CNS Function and Neurodegenerative Disorders

In addition to the role played by RAS in a variety of physiological and pathological conditions in renal system and cardiovascular system, leukocyte recruitment and activation, fibrogenesis and remodeling, the paracrine RAS takes place within the CNS [48]. It has been reported that Signaling of the renin receptor *via* ERK1/2 activation is important for brain development and maintenance of normal function of CNS [49]. The central RAS could act largely independently of the peripheral one. Whereas peripheral angiotensin regulates blood pressure, thirst, and secretion of antidiuretic and adrenocorticotrophic hormones, accumulating evidence implicates the central brain angiotensin system operating independently of the circulating renin-angiotensin system in regulation of the above-mentioned activities [50]. It is now well established that brain possesses all the required substrates and the enzymes required for synthesis of various components of RAS including Ang II, Ang III, Ang IV, Ang-(1-7), Ang-(3-7). However, various members could produce effects opposing those of some others. Ang II activates two types of receptors, AT1R (vasoconstriction, endothelial dysfunction, and vascular remodeling) and AT2R (vasodilatation, neuronal

differentiation, decreased inflammation, and axonal regeneration). Ang II impairs memory and LTP [51]. The ARBs block the AT1R, but not AT2R, whereas centrally active ACEIs decrease activation of both receptors [52]. It has been suggested that blockade of AT1R by the ARBs allows greater AT2R binding, thus exerting their effects by both interrupting AT1R activity and promoting AT2R activity [53]. Moreover, it has been reported that centrally active ACEIs and ARBs might lower dementia risk, independently of their blood pressure lowering properties [54]. Ang-(1-7) is the main angiotensin peptide in the CNS. It is expressed in different regions of the brain, including the hypothalamus, hippocampus, amygdala and many others [55-57]. Ang-(1-7) influences different non-cardiovascular functions in the brain such as learning, memory and provides cerebroprotection against ischemia [58]. The strongest Mas protein expression had been detected in the dentate gyrus of the hippocampus and within the piriform cortex [59]. Ang-(1-7) has been shown to facilitate hippocampal LTP [60]. Ang-(1-7) reduces not only the anxiety *per se*, but also the cardiovascular risks consequent to the emotional stress [61]. We have also found a memory improving activity of Ang-(1-7) in an amyloid peptide-induced Alzheimer's disease model (data not published). Although the exact mechanism of the memory improving effect of Ang-(1-7) has not yet been pinpointed, several possible mechanisms had been put forward: increased eNOS/nNOS contributing to protection against cerebral ischemia, reducing iNOS leading to decrease in ischemia-infarct size and improving the behavioral deficits [40,62]. The other mechanism is proposed to be mediated by the anti-inflammatory effects of Ang-(1-7) through a reduction of oxidative stress and pro-inflammatory cytokines and suppression of NF- κ B [63]. Moreover, it has also been reported that NO together with COX mediate the jejunal water absorption induce by Ang-(1-7) [64]. Other members of RAS are also detected in brain. Of these, Ang-(3-7) is formed in brain from Ang II, Ang IV, and Ang-(1-7) [65]. Ang-(3-7) induces dopamine release in dorsal striatum and it may be involved in the dopamine release induce by Ang-(1-7). Moreover, Ang-(3-7) exerts a neuromodulator effect in the rostral ventrolateral medulla by activity displayed on AT4R [66,67]. The other member Ang IV is also found in brain. It has been localized in structures known to mediate cognitive processing including the neocortex, hippocampus, and basal nucleus of Meynert [68]. Ang IV improves memory and learning, facilitates LTP and reverses scopolamine-induced amnesia [69,70]. The RAS in brain is implicated in processes of learning and memory [71]. The Centrally active ACEIs regulate cerebral blood flow independently from the peripheral RAS. They play a key role in linking arterial hypertension to cognitive functions [51]. AT1R blockade has been shown to influence the Hypothalamic-Pituitary-Adrenal (HPA) axis [72]. ACEI/ARB decrease symptoms in patients with Post-Traumatic Stress Disorder, PTSD. This property could enhance the extinction of fear memory and therefore might be involved in the therapeutic efficacy of ACEI/ARBs in PTSD patients, who have impairments in extinction of aversive memories [73,74].

RAS and alzheimer's disease: The cholinergic and amyloidogenic hypotheses only partially describe the main cause of AD, and the drugs effective on either one are only of partial benefit. One very attractive potential upstream contributor to dementia is the brain RAS. Various components of RAS are either primarily involved in, or contribute to a possible connection between the blood vessel functional condition and AD pathology. However, the precise role(s) played by the members of RAS are overlapping and even contradictory: Ang II has

been shown to disrupt learning and memory, while Ang-(1-7) and Ang IV facilitates memory acquisition and consolidation. Moreover, the effect of ACE's on AD is still highly debated. Both ACE itself and its inhibitors had been reported to exert beneficial effects in brain. Although these effects seem contradictory, they could be attributed to medication in patients with different genetic traits. In individuals with the ApoE4 allele, ACE inhibitor use may accelerate or poorly delay AD development compared with ApoE2 or ApoE3; if an individual is an ApoE4 non-carrier, an ACE inhibitor may effectively delay AD development [75]. AD usually show higher ACE levels in their brain. Higher levels of ACE can prevent AD proportionally to the cerebral load of amyloid beta [76]. Moreover, ACE is increased in brain areas responsible for memory, cognitive, and executive functions, and primarily affected in patients with AD [77].

ARBs improve memory by

- CBF improvement, protection against inflammation and ischemia, Improvement of neuronal function
- Structural protection by preserving frontal-subcortical connections,
- Stymieing effects of cerebral small vessel disease and/or Alzheimer's disease pathology
- Anti-inflammatory activity and free radical scavenging,
- AT2 receptors Blockade, promoting AT1 receptors
- Increased n/e NO, decrease iNOS.
- Others (AChR, Glutamate)?

It is assumed that ACE can degrade beta-amyloid in brain blood vessels and therefore help prevent the digression of the disease [78]. However, the ACEIs enhance cognitive processing in humans and animals [79,80]. c-ACEI potentiates acetylcholine esterase inhibitors-produced-cognition-improvement in AD [81]. Some studies suggest that c-ACE inhibitors could enhance the activity of major amyloid-beta peptide degrading enzymes like neprilysin in the brain resulting in a slower development of AD. More recent research suggests that ACE inhibitors can reduce risk of AD, but in the absence of apolipoprotein E4 alleles (ApoE4), but will have no effect in ApoE4- carriers [74]. However it should be noted that ACE converts A β 1-42 to A β 40. Since A β 1-42 is responsible for brain amyloid deposition, long treatment with ACEI could, overtime, result in greater accumulations of amyloid plaques [82]. The ARBs confer protective effects on cognition in hypertensive patients to a greater extent than the other antihypertensives, including ACE inhibitors [83]. This may be attributed to the fact that while ACEIs reduce the amount of free angiotensin II and decrease damaging angiotensin II receptor type 1 (AT1) receptor activity, they also reduce beneficial angiotensin II receptor type 2 (AT2) receptor activities. On the other hand, given that ARBs block AT1 receptors and not the production of angiotensin II, they promote AT2 receptor activity and are ACE-sparing," in theory allowing ACE to continue its suggested A β -degrading function, unlike ACEIs [84], or itself (as reported for valsartan) decrease amyloid β -mediated cognitive dysfunction [85]. Moreover, it has been reported that when ARB users were combined with users of ACEIs, beneficial effects on memory and WMH volume disappeared [86]. The anti-inflammatory properties of ARBs could also contribute to their beneficial therapeutic activity in lowering incidence and progression of Alzheimer's disease [87]. The efficacy of

ARBs is related to the capacity of the medications to cross blood brain barrier [52,88,89]. The blood brain barrier crossers and centrally acting ARBs (valsartan, telmisartan, and candesartan) and ACE inhibitors (captopril, fosinopril, lisinopril, perindopril, Ramipril, trandolapril, or zofenopril) display more cognition improving activities than non-crosser ARBs (irbesartan, olmesartan, losartan, and eprosartan) and ACE inhibitors (benazepril, enalapril, imidapril, moexepil, quinapril, and ramipril).

RAS and parkinson's disease: ACE is present in the nigro-striatal pathway and basal ganglia structures. Patients who are poor responders to neuroleptic treatment have high activity ACE phenotype [90]. There is a negative correlation between RAS activity and Dopaminergic neuronal degeneration. This may confer the significance of RAS in other neurodegenerative disorders such as Parkinson's disease. ACEIs increase striatal dopamine synthesis and release. It has been reported that Parkinson's disease patients treated with the ACEI perindopril revealed elevated striatal dopamine levels and improved motor activity [91]. Treatment with ACEI improves response to dopamine precursors, reduces AT1-induced Nicotinamide Adenine Dinucleotide Phosphate (NADPH)-ROS, migration of inflammatory cells and chemokine, and provides protection for the dopaminergic neurons. Although ARBs share some of the properties of ACEIs, exacerbated motor dysfunction had been reported for Losartan [92]. Angiotensin receptors take place and exhibit differential activities in the nigrostriatal dopaminergic pathway. AT2Rs are decreased in the substantia nigra and striatum in post mortem brains of Parkinson's disease patients [93]. An increase in the expression of AT1Rs and decreased expression of AT2Rs has been reported in aged rats [94]. This observation is of major importance given the potentially deleterious consequences of AT1Rs activation on basal ganglia structures. AT1R is increased in chronic haloperidol which may indicate a change consequent to chronic antipsychotic use, and possibly indicate validity of prescribing ACEIs to treat adverse reactions that emerge during long-term treatment of psychosis with the antipsychotics [95]. On the other hand, activation of the AT2Rs has been shown to enhance differentiation of dopamine neurons, and inhibit NADPH oxidase activation [96].

Conclusion

AAMA integrity and activity play an important role in balancing the deleterious arm, Ang II-AT1R, of RAS. AAMA is also important in maintaining neuronal function. Drugs with specific activities on AAMA but devoid of the side/adverse effects of the relevant drugs in use and act on RAS could be a promising tool in treatment of the neurodegenerative disease and, in case of combination, may improve the effects of drugs used in treatment of these disorders.

References

1. Kehoe K, Brouns R, Verkerk R, Engelborghs S, De Deyn PP, Hendriks D, et al. Prolyl carboxypeptidase activity decline correlates with severity and short-term outcome in acute ischemic stroke. *Neurochem Res.* 2015;40(1):81-8.
2. Ferreira AJ, Santos RA. Cardiovascular actions of angiotensin-(1-7). *Braz J Med Biol Res.* 2005;38(4):499-507.
3. Ahmad S, Varagic J, Groban L, Dell'Italia LJ, Nagata S, Kon ND, et al. Angiotensin-(1-12): a chymase-mediated cellular angiotensin II substrate. *Curr Hypertens Rep.* 2014;16(5):429.
4. Chan KH, Chen YH, Zhang Y, Wong YH, Dun NJ. Angiotensin-[1-12] interacts with angiotensin type I receptors. *Neuropharmacology.* 2014;81:267-73.
5. Persson PB. Renin: origin, secretion and synthesis. *J Physiol.* 2003;552:667-71.
6. Jankowski V, Vanholder R, van der Giet M, Tölle M, Karadogan S, Gobom J, et al. Mass-spectrometric identification of a novel angiotensin peptide in human plasma. *Arterioscler. Thromb Vasc Biol.* 2007;27(2):297-302.
7. Lautner RQ, Villela DC, Fraga-Silva RA, Silva N, Verano-Braga T, Costa-Fraga F, et al. Discovery and characterization of alamandine: a novel component of the renin-angiotensin system. *Circ Res.* 2013;112(8):1104-11.
8. Hrenak J, Paulis L, Simko F. Angiotensin A/Alamandine/MrgD Axis: Another Clue to Understanding Cardiovascular Pathophysiology. *Int J Mol Sci.* 2016;17(7):1098.
9. Wilson TW. Renal prostaglandin synthesis and angiotensin-converting enzyme inhibition. *J Cardiovasc Pharmacol.* 1992;6:S39-44.
10. Gard PR, Daw P, Mashhour ZS, Tran P. Interactions of angiotensin IV and oxytocin on behaviour in mice. *J Renin Angiotensin Aldosterone Syst.* 2007;8(3):133-8.
11. Ring RH, Malberg JE, Potestio L, Ping J, Boikess S, Luo B, et al. Anxiolytic-like activity of oxytocin in male mice: behavioral and autonomic evidence, therapeutic implications. *Psychopharmacology (Berlin).* 2006;185(2):218-25.
12. Shapiro R, Holmquist B, Riordan JF. Anion activation of angiotensin converting enzyme: dependence on nature of substrate. *Biochemistry.* 1983;22(16):3850-7.
13. Bünnig P. The catalytic mechanism of angiotensin converting enzyme. *Clinical and Experimental Hypertension. Part A, Theory and Practice.* 1983;5(7-8):1263-75.
14. Fillardi P. ACEI and ARBS in Hypertension and Heart Failure. In: Filardi PP, editor. *Current Cardiovascular Therapy.* Switzerland: Springer International Publishing. 2015;5:10-3.
15. Hemming ML, Selkoe DJ. Amyloid beta-protein is degraded by cellular angiotensin-converting enzyme (ACE) and elevated by an ACE inhibitor. *J Biol Chem.* 2005;280(45):37644-50.
16. Donoghue M, Hsieh F, Baronas E, Godbout K, Gosselin M, Stagliano N, et al. A novel angiotensin-converting enzyme-related carboxypeptidase (ACE2) converts angiotensin I to angiotensin 1-9. *Circ Res.* 2000;87(5):E1-9.
17. Wiener RS, Cao YX, Hinds A, Ramirez MI, Williams MC. Angiotensin converting enzyme 2 is primarily epithelial and is developmentally regulated in the mouse lung. *J Cell Biochem.* 2007;101(5):1278-91.
18. Bünnig P. The catalytic mechanism of angiotensin converting enzyme". *Clin Exp Hypertens. Part A: Theory and Practice.* 1983;7-8(5):1263-75.
19. Guang C, Phillips RD, Jiang B, Franco, Milani F. Three key proteases - angiotensin - I - converting enzyme (ACE), ACE2 and renin - within and beyond the renin-angiotensin system. *Arch Cardiovasc Dis.* 2012;105(6-7):373-85.
20. Fraga-Silva RA, Costa-Fraga FP, Murça TM, Moraes PL, Lima AM, Lautner RQ, et al. Angiotensin - converting enzyme 2 activation improves endothelial function. *Hypertens.* 2013;61:1233-8.
21. Inagami T. A memorial to Robert Tiegerstedt: the centennial of renin discovery. *Hypertens.* 1998;32(6):953-7.
22. Kim S, Iwao H. Molecular and cellular mechanisms of angiotensin II-mediated cardiovascular and renal diseases. *Pharmacol Rev.* 2000;52(1):11-34.
23. Grishko V, Pastukh V, Solodushko V, Gillespie M, Azuma J, Schaffer S. Apoptotic cascade initiated by angiotensin II in neonatal cardiomyocytes:

- role of DNA damage. *Am J Physiol Heart Circ Physiol.* 2003;285(6):H2364-72.
24. Hall KL, Venkateswaran S, Hanesworth JM, Schelling ME, Harding JW. Characterization of a functional angiotensin IV receptor on coronary microvascular endothelial cells. *Regul Pept.* 1995;58:107-15.
25. Hall KL, Hanesworth JM, Ball AE, Felgenhauer GP, Hosick HL, Harding JW. Identification and characterization of a novel angiotensin binding site in cultured vascular smooth muscle cells that is specific for the hexapeptide (3-8) fragment of angiotensin II, angiotensin IV. *Regul Pept.* 1993;44(2):225-32.
26. Coleman JK, Krebs LT, Hamilton TA, Ong B, Lawrence KA, Sardinia MF, et al. Autoradiographic identification of kidney angiotensin IV binding sites and angiotensin IV-induced renal cortical blood flow changes in rats. *Peptides.* 1998;19(2):269-77.
27. Williams PJ, Mistry HD, Innes BA, Bulmer JN, Pipkin FB. Expression of AT1R, AT2R and AT4R and their roles in extravillous trophoblast invasion in the human. *Placenta.* 2010;31(5):448-55.
28. Wright JW, Kawas LH, Harding JW. A Role for the brain RAS in Alzheimer's and Parkinson's diseases. *Front Endocrinol (Lausanne).* 2013;4:158.
29. Fukada SY, Tirapelli CR, de Godoy MAF, de Oliveira AM. Mechanisms Underlying the Endothelium-Independent Relaxation Induced by Angiotensin II in Rat Aorta. *J Cardiovasc Pharmacol.* 2005;45(2):136-43.
30. Santos RA, Simoes e Silva AC, Maric C, Silva DM, Machado RP, de Buhr I, et al. Angiotensin - (1-7) is an endogenous ligand for the G protein-coupled receptor Mas. *Proc Natl Acad Sci USA.* 2003;100(14):8258-63.
31. Kocks MJ, Lely AT, Boomsma F, de Jong PE, Navis G. Sodium status and angiotensin - converting enzyme inhibition: effects on plasma angiotensin - (1-7) in healthy man. *J Hypertens.* 2005;23(3):597-602.
32. Gironacci MM, Adamo HP, Corradi G, Santos RA, Ortiz P, Carretero OA. Angiotensin (1-7) induces mas receptor internalization. *Hypertens.* 2011;58(2):176-81.
33. Bader M, Alenina N, Andrade-Navarro MA, Santos RA. MAS and its related G protein-coupled receptors, Mrgprs. *Pharmacol Rev.* 2014;66(4):1080-105.
34. Shinohara T, Harada M, Ogi K, Maruyama M, Fujii R, Tanaka H, et al. Identification of a G protein-coupled receptor specifically responsive to beta - alanine. *J Biol Chem.* 2004;279(22):23559-64.
35. Yu L, Yuan K, Phuong HTA, Park BM, Kim SH. Angiotensin-(1-5), an active mediator of renin-angiotensin system, stimulates ANP secretion via Mas receptor. *Peptides.* 2016;86:33-41.
36. McCollum LT, Gallagher PE, Ann Tallant E. Angiotensin-(1-7) attenuates angiotensin II-induced cardiac remodeling associated with upregulation of dual-specificity phosphatase 1. *Am J Physiol Heart Circ Physiol.* 2012;302:H801-10.
37. Crozier RA, Ajit SK, Kaftan EJ, Pausch MH. MrgD activation inhibits KCNQ/M - currents and contributes to enhanced neuronal excitability. *J Neurosci.* 2007;27(16):4492-6.
38. Solinski HJ, Gudermann T, Breit A. Pharmacology and signaling of MAS-related G protein-coupled receptors. *Pharmacol Rev.* 2014;66(3):570-97.
39. Chai SY, Fernando R, Ye S, Peck GR, Albiston AL. Insulin-Regulated Aminopeptidase. In: Hooper NM, Lendeckel U, editors. *Aminopeptidases in Biology and Disease. Proteases in Biology and Disease.* Boston, MA: Springer. 2004;2:61-81.
40. Alzayadneh EM, Chappell MC. Angiotensin-(1-7) abolishes AGE-induced cellular hypertrophy and myofibroblast transformation via inhibition of ERK1/2. *Cell Signal.* 2014;26(12):3027-35.
41. Passos-Silva DG, Verano-Braga T, Santos RA. Angiotensin-(1-7): beyond the cardio-renal actions. *Clin Sci (Lond).* 2013;124(7):443-56.
42. Açikalin Ö, Bölükbasi Hatip FF, Tan RF, Hatip-al-Khatib I. Effect of angiotensin-(1-7) on aortic response, tnf- α , il-1 β and receptor for advanced glycation end product in rat's adjuvant-induced arthritis. *Pharmacology.* 2016;97(5-6):207-17.
43. Verano-Braga T, Schwammle V, Sylvester M, Passos-Silva DG, Peluso AA, Etelvino GM, et al. Time-resolved quantitative phosphoproteomics: new insights into angiotensin-(1-7) signaling networks in human endothelial cells. *J Proteome Res.* 2012;11(6):3370-81.
44. Calnan DR, Brunet A. The FoxO code. *Oncogene.* 2008;27(16):2276-88.
45. Senanayake P, Drazba J, Shadrach K, Milsted A, Rungger-Brandle E, Nishiyama K, et al. Angiotensin II and its receptor subtypes in the human retina. *Invest Ophthalmol Vis Sci.* 2007;48(7):3301-11.
46. Vaajanen A, Vapaatalo H, Kautiainen H, Oksala O. Angiotensin (1-7) reduces intraocular pressure in the normotensive rabbit eye. *Invest Ophthalmol Vis Sci.* 2008;49(6):2557-62.
47. Verma A, Shan Z, Lei B, Yuan L, Liu X, Nakagawa T, et al. ACE2 and Ang-(1-7) confer protection against development of diabetic retinopathy. *Mol Ther.* 2012;20(1):28-36.
48. Simões e Silva AC, Silveira KD, Ferreira AJ, Teixeira MM. ACE2, angiotensin-(1-7) and Mas receptor axis in inflammation and fibrosis. *Br J Pharmacol.* 2013;169(3):477-92.
49. Nguyen G. Renin/prorenin receptors. *Kidney Int.* 2006;69(9):1503-6.
50. Ciobica A, Bild W, Hritcu L, Haulica I. Brain renin-angiotensin system in cognitive function: pre-clinical findings and implications for prevention and treatment of dementia. *Acta Neurol Belg.* 2009;109(3):171-80.
51. Denny JB, Polan-Curtain J, Wayner MJ, Armstrong DL. Angiotensin II blocks hippocampal long-term potentiation. *Brain Res.* 1991;567(2):321-4.
52. Horiuchi M, Mogi M, Iwai M. The angiotensin II type 2 receptor in the brain. *J Renin Angiotensin Aldosterone Syst.* 2010;11(1):1-6.
53. Furiya Y, Ryo M, Kawahara M, Kiriya T, Morikawa M, Ueno S. Renin-angiotensin system blockers affect cognitive decline and serum adipocytokines in Alzheimer's disease. *Alzheimers Dement.* 2013;9(5):512-8.
54. Hajjar J, Hart M, Milberg W, Novak V, Lipsitz L. The rationale and design of the antihypertensives and vascular, endothelial, and cognitive function (AVEC) trial in elderly hypertensives with early cognitive impairment: Role of the renin angiotensin system inhibition. *BMC Geriatr.* 2009;9:48.
55. Cato MJ, Toney GM. Angiotensin II excites paraventricular nucleus neurons that innervate the rostral ventrolateral medulla: an in vitro patch-clamp study in brain slices. *J Neurophysiol.* 2005;93:403-13.
56. Becker LK, Etelvino GM, Walther T, Santos RA, Campagnole-Santos MJ. Immunofluorescence localization of the receptor Mas in cardiovascular-related areas of the rat brain. *Am J Physiol Heart Circ Physiol.* 2007;293(3):H1416-24.
57. Metzger R, Bader M, Ludwig T, Berberich C, Bunnemann B, Ganten D. Expression of the mouse and rat mas proto-oncogene in the brain and peripheral tissues. *FEBS Lett.* 1995;357(1):27-32.
58. Holy Z, Braszko J, Kupryszewski G, Witczuk B, Wisniewski K. Angiotensin II--derived peptides devoid of phenylalanine in position 8 have full psychotropic activity of the parent hormone. *J Physiol Pharmacol.* 1992;43(2):183-92.
59. Freund M, Walther T, von Bohlen und Halbach O. Immunohistochemical localization of the angiotensin-(1-7) receptor Mas in the murine forebrain. *Cell Tissue Res.* 2012;348(1):29-35.
60. Hellner K, Walther T, Schubert M, Albrecht D. Angiotensin-(1-7) enhances LTP in the hippocampus through the G-protein-coupled receptor Mas. *Mol Cell Neurosci.* 2005;29(3):427-35.
61. Fontes MA, Martins Lima A, Santos RA. Brain angiotensin-(1-7)/Mas

- axis: A new target to reduce the cardiovascular risk to emotional stress. *Neuropeptides*. 2016;56:9-17.
62. Feng Y, Xia H, Cai Y, Halabi CM, Becker LK, Santos RA, et al. Brain-selective overexpression of human angiotensin-converting enzyme type 2 attenuates neurogenic hypertension. *Circ Res*. 2010;106(2):373-82.
63. Jiang T, Gao L, Guo J, Lu J, Wang Y, Zhang Y. Suppressing inflammation by inhibiting NF- κ B pathway contributes to the neuroprotection of angiotensin-(1-7) in rats with permanent cerebral ischemia. *Br J Pharmacol*. 2012;167(7):1520-32.
64. Borges EL, Cabral BM, Braga AA, Neves MJ, Santos RA, Rogana E. Effect of angiotensin-(1-7) on jejunal absorption of water in rats. *Peptides*. 2002;23(1):51-6.
65. Chappell MC, Brosnihan KB, Diz DI, Ferrario CM. Identification of angiotensin-(1-7) in rat brain. Evidence for differential processing of angiotensin peptides. *J Biol Chem*. 1989;264(28):16518-23.
66. Stragier B, Hristova I, Sarre S, Ebinger G, Michotte Y. In vivo characterization of the angiotensin-(1-7)-induced dopamine and gamma-aminobutyric acid release in the striatum of the rat. *Eur J Neurosci*. 2005;22(3):658-64.
67. Ferreira PM, dos Santos RAS, Campagnole-Santos MJ. Angiotensin-(3-7) pressor effect at the rostral ventrolateral medulla. *Regulatory Pept*. 2007;141(1-3):168-74.
68. Chai SY, Bastias MA, Clune EF, Matsacos DJ, Mustafa T, Lee JH, et al. Distribution of angiotensin IV binding sites(AT4 receptor) in the human forebrain, midbrain and pons as visualized by in vitro receptor autoradiography. *J Chem Neuroanat*. 2000;20(3-4):339-48.
69. Braszko JJ, Kupryszewski G, Witezuk B, Wisniewski K. Angiotensin II-(3-8)-hexapeptide affects motor activity, performance of passive avoidance and a conditioned avoidance response in rats. *Neuroscience*. 1988;27(3):777-83.
70. Albiston AL, Pederson ES, Burns P, Purcell B, Wright JW, Harding JW, et al. Attenuation of scopolamine induced learning deficits by LVV-hemorphin-7 in rats in the passive avoidance and water maze paradigms. *Behav Brain Res*. 2004;154:239-43.
71. Llorens-Cortes C, Mendelsohn FA. Organisation and functional role of the brain angiotensin system. *J Renin-Angiotensin-Aldosterone Syst*. 2002;3:S39-48.
72. Armando I, Volpi S, Aguilera G, Saavedra JM. Angiotensin II AT1 receptor blockade prevents the hypothalamic corticotropin-releasing factor response to isolation stress. *Brain Res*. 2007;1142:92-9.
73. Khoury NM, Marvar PJ, Gillespie CF, Wingo A, Schwartz A, Bradley B, et al. The renin-angiotensin pathway in posttraumatic stress disorder: angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are associated with fewer traumatic stress symptoms. *J Clin Psychiatry*. 2012;73(6):849-55.
74. Marvar PJ, Goodman J, Fuchs S, Choi DC, Banerjee S, Ressler KJ. Angiotensin type 1 receptor inhibition enhances the extinction of fear memory. *Biol Psychiatry*. 2014;75(11):864-72.
75. Qiu WW, Lai A, Mon T, Mwamburi M, Taylor W, Rosenzweig J, et al. Angiotensin converting enzyme inhibitors and Alzheimer disease in the presence of the apolipoprotein E4 allele. *Am J Geriatr Psychiatry*. 2014;22(2):177-85.
76. Zou K, Michikawa M. Angiotensin-converting enzyme as a potential target for treatment of Alzheimer's disease: inhibition or activation? *Rev Neurosci*. 2008;19(4-5):203-12.
77. Savaskan E, Hock C, Olivieri G, Bruttel S, Rosenberg C, Hulette C, et al. Cortical alterations of angiotensin converting enzyme, angiotensin II and AT1 receptor in Alzheimer's dementia. *Neurobiol Aging*. 2001;22(4):541-6.
78. Hu J, Igarashi A, Kamata M, Nakagawa H. Angiotensin-converting enzyme degrades Alzheimer amyloid beta-peptide (A beta); retards A beta aggregation, deposition, fibril formation; and inhibits cytotoxicity. *J Biol Chem*. 2001;276:47863-8.
79. Ohrui T, Matsui T, Yamaya M, Arai H, Ebihara S, Maruyama M, et al. Angiotensin-converting enzyme inhibitors and incidence of Alzheimer's disease in Japan. *J Am Geriatr Soc*. 2004;52(4):649-50.
80. Yamada K, Horita T, Takayama M, Takahashi S, Takaba K, Nagata Y, et al. Effect of a centrally active angiotensin converting enzyme inhibitor, perindopril, on cognitive performance in chronic cerebral hypoperfusion rats. *Brain Res*. 2011;1421:110-20.
81. Fazal K, Perera G, Khondoker M, Howard R, Stewart R. Associations of centrally acting ACE inhibitors with cognitive decline and survival in Alzheimer's disease. *BJ Psych Open*. 2017;3(4):158-64.
82. Wright JW, Harding JW. The brain RAS and Alzheimer's disease. *Exp Neurol*. 2010;223(2):326-33.
83. Davies NM, Kehoe PG, Ben-Shlomo Y, Martin RM. Associations of anti-hypertensive treatments with Alzheimer's disease, vascular dementia, and other dementias. *J Alzheimers Dis*. 2011;26(4):699-708.
84. Kehoe PG, Miners S, Love S. Angiotensins in Alzheimer's disease - friend or foe? *Trends Neurosci*. 2009;32(12):619-28.
85. Wang J, Ho L, Chen L, Zhao Z, Zhao W, Qian X, et al. Valsartan lowers brain beta-amyloid protein levels and improves spatial learning in a mouse model of Alzheimer disease. *J Clin Invest*. 2007;117(11):3393-402.
86. Ho JK, Nation DA. Alzheimers Disease Neuroimaging Initiative. Memory is preserved in older adults taking AT1 receptor blockers. *Alzheimers Res Ther*. 2017;9(1):33.
87. Royea J, Zhang L, Tong XK, Hamel E. Angiotensin IV receptors mediate the cognitive and cerebrovascular benefits of losartan in a mouse model of alzheimer's disease. *J Neurosci*. 2017;37(22):5562-73.
88. Sink KM, Leng X, Williamson J, Kritchevsky SB, Yaffe K, Kuller L, et al. Angiotensin-converting enzyme inhibitors and cognitive decline in older adults with hypertension: results from the Cardiovascular Health Study. *Arch Intern Med*. 2009;169(13):1195-202.
89. Ohrui T, Tomita N, Sato-Nakagawa T, Matsui T, Maruyama M, Niwa K, et al. Effects of brain-penetrating ACE inhibitors on Alzheimer disease progression. *Neurology*. 2004;63(7):1324-5.
90. Illi A, Kampman O, Anttila S, Roivas M, Mattila KM, Lehtimäki T, et al. Interaction between angiotensin-converting enzyme and catechol-O-methyltransferase genotypes in schizophrenics with poor response to conventional neuroleptics. *Eur Neuropsychopharmacol*. 2003;13(3):147-51.
91. Reardon KA, Mendelsohn FA, Chai SY, Horne MK. The angiotensin converting enzyme (ACE) inhibitor, perindopril, modifies the clinical features of Parkinson's disease. *Aust N Z J Med*. 2000;30:48-53.
92. Sarma GRK, Kamath V, Mathew T, Roy AK. A case of parkinsonism worsened by losartan: a probable new adverse effect. *Mov Disord*. 2008;23(7):1055.
93. Ge J, Barnes NM. Alterations in angiotensin AT1 and AT2 receptor subtype levels in brain regions from patients with neurodegenerative disorders. *Eur J Pharmacol*. 1996;297(3):299-306.
94. Villar-Cheda B, Valenzuela R, Rodriguez-Perez AI, Guerra MJ, Labandeira-Garcia JL. Aging-related changes in the nigral angiotensin system enhances proinflammatory and pro-oxidative markers and 6-OHDA-induced dopaminergic degeneration. *Neurobiol Aging*. 2012;33:204.e1-11.
95. Jenkins TA, Chai SY, Mendelsohn FA. Upregulation of angiotensin II AT1 receptors in the mouse nucleus accumbens by chronic haloperidol treatment. *Brain Res*. 1997;748(1-2):137-42.
96. Sohn HY, Raff U, Hoffmann A, Gloe T, Heermeier K, Galle J, et al. Differential role of angiotensin II receptor subtypes on endothelial superoxide formation. *Br J Pharmacol*. 2000;131(4):667-72.