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Review Article

The depressor axis of the renin–angiotensin system and brain disorders: a translational approach

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All the components of the classic renin–angiotensin system (RAS) have been identified in the brain. Today, the RAS is considered to be composed mainly of two axes: the pressor axis, represented by angiotensin (Ang) II/angiotensin-converting enzyme/AT1 receptors, and the depressor and protective one, represented by Ang-(1–7)/ angiotensin-converting enzyme 2/Mas receptors. Although the RAS exerts a pivotal role on electrolyte homeostasis and blood pressure regulation, their components are also implicated in higher brain functions, including cognition, memory, anxiety and depression, and several neurological disorders. Overactivity of the pressor axis of the RAS has been implicated in stroke and several brain disorders, such as cognitive impairment, dementia, and Alzheimer or Parkinson's disease. The present review is focused on the role of the protective axis of the RAS in brain disorders beyond its effects on blood pressure regulation. Furthermore, the use of drugs targeting centrally RAS and its beneficial effects on brain disorders are also discussed.

There is a growing increase in the number of patients suffering cognitive dysfunction, dementia, Alzheimer's disease (AD), anxiety, and depression among others. The prevalence of dementia may be increased 3-fold in 2050 [1]. In addition, the number of patients with depression increased 50% in the last two decades [2]. However, an effective treatment for dementia is still lacking and only 30% of the depressed population responds to antidepressive treatment. Hypertension is one of the main causes of cerebral vascular damage. In 2014, the Alzheimer's Disease International [1] recognized hypertension as the main modifiable vascular risk factor for cognitive decline or dementia. Several lines of evidence have shown that hypertension increases the risk for dementia development [3-7]. Thus, an antihypertensive treatment may have a beneficial effect on cognitive dysfunction [8]. Basic research has shown the key role of the renin–angiotensin system (RAS) in the physiopathology of hypertension and in cognitive function as well as in the development of neurological disorders at the central level. The present review is focused on the role of the protective axis of the RAS in brain disorders beyond its effects on blood pressure regulation. Furthermore, the use of drugs targeting centrally RAS and its beneficial effects on brain disorders are also discussed.

An overview of the depressor axis of the RAS in the brain

The RAS is of profound physiological significance in the central nervous system (CNS). All the essential components of the RAS have been identified in different brain areas inside the blood–brain barrier (BBB) of the mammalian brain [9-11] and have been suggested to be involved in additional functions and disorders besides blood pressure regulation [12]. However, a recent report has suggested that brain angiotensin (Ang) II represents Ang II taken up from blood rather than locally synthesized Ang II [13].

Despite the fact that it was long thought that Ang II was the main bioactive component of the RAS, today it is well known that others components of the RAS are biologically active and exert effects that may be similar, opposite, or distinct from those displayed by Ang II (Figure 1). Like Ang II, Ang-(1–12),

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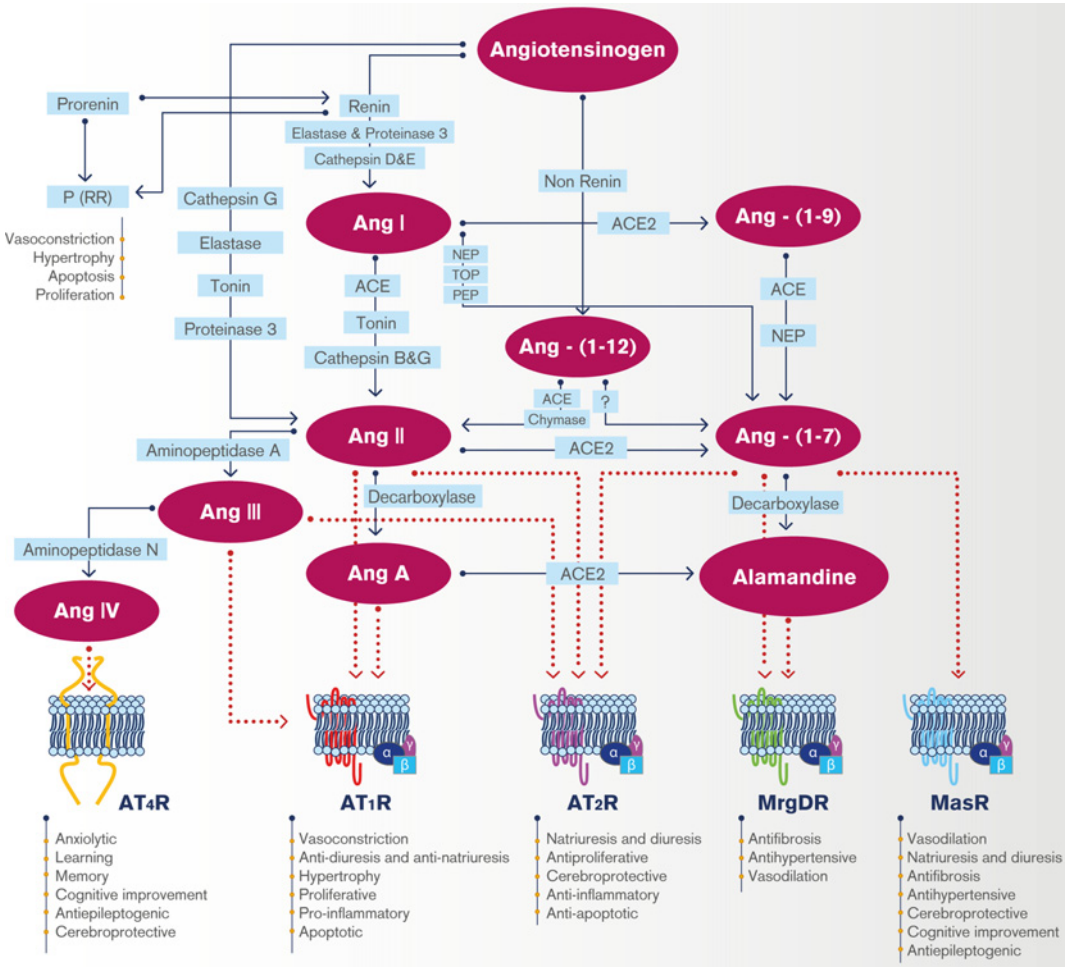

Figure 1. The brain renin–angiotensin system

Abbreviations: ACE, angiotensin-converting enzyme; ACE2, angiotensin-converting enzyme 2; AT_1 R, angiotensin type 1 receptor; AT_2 R, angiotensin type 2 receptor; AT_4 R, angiotensin type 4 receptor; Mas R, Mas receptor; MrgD, Mas related G protein-coupled receptors; NEP, neutral endopeptidase (neprilysin); PEP, prolyl endopeptidase; (P)RR, prorenin receptor; TOP, thimet oligopeptidase.

Ang A and Ang III bind primarily to angiotensin II type 1 (AT1) receptor and cause vasoconstriction, accumulation of inflammatory markers to subendothelial region of blood vessels and activate smooth muscle cell proliferation [10,14,15]. In contrast, Ang III induces natriuresis responses through angiotensin II type 2 (AT2) receptor stimulation and contributes to blood pressure regulation [16]. Other peptides like Ang-(1–9), Ang-(1–7), alamandine, and Ang IV help in protecting from cardiovascular diseases by binding to their respective receptors [14,15]. Today, the RAS is considered to be composed mainly of two axes. The pressor one represented by angiotensin-converting enzyme (ACE), the main enzyme involved in Ang II generation, Ang II and the AT1 receptor, which mediates the pressor and trophic effects of Ang II. The other axis, the depressor and protective one, is represented by ACE2, the enzyme that catalyzes the conversion of Ang II into Ang-(1–7), Ang-(1–7), and the Mas receptor [17].

One of the components of the depressor axis of the RAS is Ang-(1–7). Ang-(1–7) is generated from Ang I by an ACE-independent pathway. Neutral endopeptidase (EC 3.4.24.11, EP 24.11, neprilysin, thimet oligopeptidase (EC 3.4.24.15) and prolyl oligopeptidase (EC 3.4.21.26) cleave the bond at residues Pro^7-Phe^8 of Ang I generating Ang-(1–7). Ang-(1–7) may also be formed from Ang-(1–9) by cleavage of the dipeptide phenylalanine–histamine through the catalytic activity of ACE and neprilysin, or from Ang II by cleaving Phe^8 through the enzymatic activity of ACE2 (Figure 1) [10,18]. Ang-(1–7) has been shown to be present in the cerebellar cortex [19,20], hippocampus [19-22], hypothalamus [23,24], substantia nigra [25], medulla oblongata and amygdala, although the content of this peptide in these two last areas was 40–70% lower than that determined in the hypothalamus [24].

The other component of the depressor axis of the RAS is the Mas receptor. Mas receptor is a G protein-coupled receptor specific for Ang-(1–7), which is expressed in different tissues, including the brain [17,26]. Mas receptors have been demonstrated to be present in hippocampus, amygdala, cortex, and hypoglossal nucleus as well as in cardiovascular-related areas of medulla and forebrain from normotensive rats [19,27]. Within the murine brain, strongest Mas protein expression was detected in the dentate gyrus of the hippocampus and within the piriform cortex [28]. Regarding the cells of the CNS, Mas receptor expression was detected in neurons [27,29-31] and not in astroglia, and to exist in both non-nuclear and nuclear compartments of neurons [29]. Mas immunostaining was reported in neurons of cerebral cortex, hippocampus, amygdala, basal ganglia, thalamus, and hypothalamus [28-30,32]. In addition, Mas receptor protein expression was greater in neurons from hypothalami of spontaneously hypertensive rats (SHR) compared with normotensive Wistar-Kyoto rats [30]. Recently, Mas receptor labeling was observed in dopaminergic neurons and glial cells in rat mesencephalic primary cultures; substantia nigra of rats, monkeys, and humans; and human induced pluripotent stem cells derived from healthy controls and sporadic PD patients [25]. Mas receptors were shown to be located in mitochondria and nuclei of neurons and glial cells [25]. The localization of Mas receptor was not only restricted to neurons since it has also been detected in microglia [32]. Weak Mas immunoreactivity was also observed within endothelial cells of small cerebral vessels and was abundant within the endothelium of large vessels such as the middle cerebral artery [32].

Regarding ACE2, ACE2 is widespread in the mouse brain, predominantly in neurons, in regions involved or not in the central regulation of cardiovascular function. Doobay et al. [33] have reported a detailed localization of ACE2 in the mouse brain. ACE2 has also been detected in the rat hippocampus [22] and cerebral cortex [34]. An increase in ACE2 protein expression in the ischemic brain cortex after ischemic stroke has been reported [34] while a lower expression of the enzyme was observed in rostral ventrolateral medulla (RVLM) and nucleus of the solitary tracts of SHR [35]. ACE2 staining is present in the cytoplasm of neuronal cell bodies but not in glial cells [33]. Conversely, it has reported ACE2 gene expression in cultured astrocytes isolated from neonatal rat cerebellum or medulla oblongata [36].

The present review is focused on the role of the depressor axis of the RAS in cerebral dysfunction like those elicited by an ischemia or a neurocognitive disorder, i.e. its actions beyond blood pressure regulation.

The protective axis of the RAS and stroke

Hypertension affects cerebrovascular flow and is a major vascular risk factor for stroke. Fifty percent of strokes may be attributed to hypertension, and they constitute the main vascular risk factor for cognitive impairment or poststroke dementia [37]. The mechanisms include pathological remodeling of the cerebral arteries, diminished cerebrovascular autoregulation, and cerebrovascular inflammation. This reduces the capacity of the brain to adjust its regional blood flow to energy requirements, oxygen and nutrient supply, eventually leading to chronic hypoxia and cellular injury [38]. Enhanced AT1 receptor activity is a major factor in the hypertension-induced cerebrovascular pathology [38]. Overactivation of the ACE/Ang II/AT1 receptor axis is thought to contribute to the pathogenesis of acute ischemic stroke through its vasoconstrictor effects on cerebral vessels as well as its proinflammatory, profibrotic, and increased oxidative stress effects in the parenchyma [39].

The first evidence demonstrating that Ang-(1–7) exerts beneficial effects against CNS damage and neurological deficits produced by cerebral ischemic stroke were reported by the group of Sumners and colleagues [29]. They showed in the cerebral ischemia model elicited by endothelin-1-induced middle cerebral artery occlusion that central administration of Ang-(1–7) or pharmacological activation of ACE2 significantly attenuated the cerebral infarct size and neurological deficits measured 72 h after the insult [29]. The same group recently has shown that oral delivery of Ang-(1–7) poststroke attenuates cerebral damage and improves neurological functions induced by middle cerebral artery occlusion in rats, without affecting blood pressure or cerebral blood flow [40]. The mechanism of the Ang-(1–7) protective action was mediated by Mas receptor and included blunting of inducible NOS expression, several proinflammatory cytokines, like interleukin (IL) 1α, IL6 and chemokine receptor type 4, and the marker of macrophage/microglial activation CD11b indicating a decrease in microglial activation [29,32]. Altogether this report suggests that the cerebroprotective action of Ang-(1–7) involves an anti-inflammatory effect, possibly via interruption of the excessive activation of microglia that occurs during stroke [32].

Stroke induced by middle cerebral artery occlusion elicited significant pressor response, accompanied by activation of Ang II/AT1 receptor and AT2 receptor signaling, depression of Ang-(1–7)/Mas receptor, alongside augmentation of monocyte chemoattractant protein-1 (MCP-1)/ chemokine receptor 2 (CCR2) signaling and neuroinflammation in the RVLM, a key brain stem site that maintains blood pressure [41]. In addition, the stroke-elicited pressor response as well as the stroke-activated MCP-1/CCR2 signaling was eliminated by applying Ang-(1–7) into the RVLM

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[41]. In accordance, intracerebroventricular infusion of Ang-(1–7) significantly reduced infarct volume and improved neurological deficits in a rat model of permanent middle cerebral artery occlusion [42]. Ang-(1–7) decreased the levels of oxidative stress and suppressed nuclear factor-κB (NF-κB) activity, which was accompanied by a reduction in proinflammatory cytokines and cyclooxygenase-2 in the peri-infarct regions [42].

In another model of stroke, the stroke-prone SHR which is a model of hemorrhagic stroke, central administration of Ang-(1–7) increases lifespan and improves the neurological status of these rats, as well as decreases microglial numbers in the striatum, implying attenuation of cerebral inflammation and a tendency to increase neuron survival at the same site. This protective effect was coupled to Mas receptor stimulation [43].

The Ang-(1–7)/Mas axis has been shown to undergo dynamic changes in ischemic stroke. The cerebral ischemic lesion in rat brain resulted in a significant increase in regional cerebral flow and circulating Ang-(1–7) [34]. Both ACE2 and Mas expression were markedly enhanced compared with the control in the ischemic tissues, suggesting that the Ang-(1–7)/Mas/ACE2 axis would play a pivotal role in the regulation of acute neuron injury in ischemic cerebrovascular diseases [34].

ACE2 catalyzes the generation of Ang-(1–7) from Ang II [17]. Serum activity of ACE2 is decreased in patients with acute ischemic stroke [44]. A study comparing different acute stroke subtypes showed an increase in serum ACE2 level in patients with cardioembolic stroke compared with lacunar infarction [45].

Reinforcing the protective role of Ang-(1–7) on stroke, it has been shown that neuronal overexpression of ACE2 protects the brain from ischemic injury. This is evidenced by lower neurological deficit scores and smaller stroke volumes following middle cerebral artery occlusion-induced stroke in transgenic mice overexpressing neuronal ACE2 [46]. The protective effect of ACE2 was greater for older animals [46]. Furthermore, neuronal ACE2 overexpression decreases ischemic stroke in mice with Ang II overproduction. ACE2 protects brain from ischemic injury via the regulation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase/endothelial NOS (eNOS) pathways by changing Ang (1–7)/Ang II ratio, independently of mean arterial pressure changes [47]. In accordance, treatment after stroke with systemically applied diminazene, an ACE2 activator, resulted in decreased infarct volume and improved neurological function without apparent increases in cerebral blood flow and this effect was mediated via Mas signaling in a blood flow-independent manner [48].

Ang-(1–7) elicits a protective effect in stroke not only by itself but also by balancing Ang II actions. Ang-(1–7) counteracts the effects of Ang II on intracerebral hemorrhagic stroke via modulating NF-κB inflammation pathway in human brain vascular smooth muscle cells and cerebral microvessels [49]. Ang-(1–7) decreases the Ang II-induced proliferation and migration of human brain vascular smooth muscle cells through down-regulation of NF-κB, up-regulation of IκBα, and decreasing the levels of tumor necrosis factor-α (TNF-α), MCP-1 and IL8. In addition, infusion of Ang-(1–7) decreases Ang II-induced middle cerebral artery remodeling and hemorrhage volume and improved neurological function after intracerebral hemorrhagic stroke. These beneficial effects of Ang-(1–7) were mediated by Mas receptor [49]. Supporting this result, it has been shown that ACE2 overexpression in the human monocyte cell line macrophages attenuates Ang II-induced MCP-1 production and that this reduction is probably mediated by increased Ang-(1–7) level [50], reinforcing the involvement of the depressor axis of the RAS.

The protective effect of Ang-(1–7) in stroke may be related to its proangiogenic action. Infusion of Ang-(1–7) for 4 weeks promoted brain angiogenesis via a Mas/eNOS-dependent pathway, which attenuated the reduction in regional cerebral blood flow and improved stroke outcome after permanent middle cerebral artery occlusion [51]. These findings highlight brain Ang-(1–7)/Mas signaling as a potential target in stroke prevention [51].

The protective axis of the RAS, cognitive function, and Alzheimer's disease

Deficits in cerebral blood flow are linked to cognitive decline, and they have detrimental effects on the outcome of ischemia [52]. Hypertension causes alterations in cerebral artery structure and function that can impair blood flow, particularly during an ischemic insult or during periods of low arterial pressure [52]. AT1 receptor blockers (ARBs) protect cerebral blood flow and reduce injury to the BBB and neurological and cognitive loss in animal models of brain ischemia, traumatic brain injury, and AD [53]. Cerebral hypoperfusion results from chronic disruption of cerebral blood flow and is associated with cognitive decline in aging and vascular dementia. Ang-(1–7) protects against cognitive dysfunction in rats subjected to cerebral hypoperfusion. This neuroprotective effect was associated with increased NO generation, attenuated neuronal loss, and suppressed astrocyte proliferation in the hippocampus [54]. In agreement, ACE2 deficiency resulted in impaired cognitive function, at least in part because of enhanced oxidative stress and a decrease in brain-derived neurotrophic factor [55].

AD is an age-related neurodegenerative disorder characterized by progressive memory loss and cognitive function deficits. There are two major pathological hallmarks that contribute to the pathogenesis of AD which are the presence of extracellular amyloid plaques composed of amyloid-β (Aβ) and intracellular neurofibrillary tangles composed of hyperphosphorylated tau [56]. Besides Aβ and tau, the neuroinflammatory reaction mediated by cerebral innate immune cells has also be considered in this disease [57].

Hyperactivity of the pressor axis of the RAS, mediated by Ang II activation of the AT1 receptor has been implicated in the pathogenesis of AD [58-60]. Central Ang II induced Alzheimer-like tau phosphorylation [61] and promotes Aβ production [62]. Recently, it has been shown that both Ang II and Ang III levels were significantly higher in human postmortem brain tissue in the midfrontal cortex from AD patients compared with age-matched controls and that Ang III, rather than Ang II, was strongly associated with Aβ load and tau load whereas Ang II levels did not [63]. In addition, an increased ACE expression and activity has been reported in AD [64-68]. In contrast, ACE2 enzyme activity was significantly reduced by approximately 50% in the midfrontal cortex in postmortem human brain tissue of patients with AD compared with age-matched controls [69]. The decreased ACE2 activity was associated with increased Aβ and phosphorylated tau levels. In addition, ACE2 was inversely correlated with ACE, and the ratio of ACE to ACE2 was increased in AD. Ang II/Ang (1–7) ratio was increased in midfrontal cortex in AD compared with age-matched controls: Ang II levels were significantly increased whereas Ang-(1–7) levels were unchanged [69]. The ratio of Ang II to Ang-(1–7) (a proxy measure of ACE2 activity) was increased in AD, indicating reduced conversion of Ang II to Ang (1–7) [69]. In accordance, Ang-(1–7) levels were reduced in cerebral cortex and hippocampus in a mouse model of sporadic AD in association with hyperphosphorylation of tau [20]. Furthermore, in AD patients, the plasma concentration of Ang-(1–7) was significantly reduced compared with matched controls, suggesting that plasma Ang-(1–7) may represent a potential biomarker for AD diagnosis [70].

Abnormal accumulation of Aβ is considered a key pathogenic mechanism in AD. Currently, three Aβ species, Aβ40, Aβ42 and Aβ43, have been identified as accumulating in amyloid plaques of human brain. The two longer species Aβ42 and Aβ43 are highly amyloidogenic and neurotoxic. In contrast, the shorter species Aβ40 inhibits amyloid plaque formation and the neurotoxicity of Aβ42. It has been shown that ACE2 converts Aβ43 to Aβ42, which in turn is cleaved by ACE to less toxic Aβ40 and Aβ41 species [71].

Diabetes mellitus is associated with cognitive deficits and an increased risk of AD. In a model of diabetes-induced cognitive deficits, Ang-(1–7) treatment attenuated cognitive impairments and ameliorated damage to the ultrastructure of hippocampal synapses, reduced the expression of hippocampal phosphorylated tau, and decreased Aβ oligomer and both soluble and insoluble Aβ42 and Aβ40 levels. These protective effects were significantly reversed by the coadministration of the Mas receptor antagonist, indicating Mas receptor mediated effects [72].

The protective axis of the RAS and anxiety

The brain is the central organ involved in perceiving and adapting to social and physical stressors via multiple interacting mediators, from the cell surface to the cytoskeleton to epigenetic regulation and nongenomic mechanisms [73]. Stress is an antecedent and is a causative factor for the development of anxiety and depression [74]. The concept of anxiety disorders encompasses various subtypes of psychiatric entities, such as generalized anxiety, panic, and post-traumatic stress disorders. They are currently seen as malfunctions of brain defensive systems due to a misbalance of certain neurotransmitters, including amino acids, monoamines, and neuropeptides [73,75]. A variety of cognitive disorders is worsened by mood disorders and stress exposure and involves dysfunction of the prefrontal cortex. Exposure to acute, uncontrollable stress increases catecholamine release in prefrontal cortex, reducing neuronal firing and impairing cognitive abilities [76]. The other two regions of the brain shown to have important roles in behavior and cognitive function are amygdala and hippocampus [73].

Overactivation of the brain pressor axis of the RAS has been implicated in the etiology of stress-associated anxiety disorders [22,74,77]. Ang II and its two subtypes of receptors, AT1 and AT2, are localized on stress-responsive brain areas including the hypothalamus–adrenal–pituitary axis. The different types of stressors increase the levels of Ang II and change the expression of its receptors [74]. While the development of anxiety has been associated with activation of AT1 receptors, central AT2 receptor may have a role in attenuating stress-associated anxiety [74].

Looking at the other axis of the RAS, the first evidence of the involvement of this axis in anxiety was that reported by Walther et al. [78] who demonstrated that genetic deletion of the Mas receptor increases anxiety-like behavior in mice. The lack of Mas protein influences spatial learning and anxiety in a sex-specific manner: no differences were found in anxiety-like behavior between control and Mas-deficient females [79].

Ang-(1–7) central administration induces anxiolytic-like effects in adult rats as demonstrated by the increase percentage of time spent and frequency of entries in the open arms of the elevated plus maze, as well as increased

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head-dipping behavior in the open arms and decreased stretching in closed arms [80]. These effects were accompanied by a decreased oxidative stress in the amygdala, which is one of the key brain regions involved in mediating anxiety [80]. In accordance, Ang-(1–7) attenuates the anxiety and depressive-like behavior in transgenic rats with low brain angiotensinogen [81]. These transgenic rats show depression-related behavior which may be due, at least in part, to the decreased levels of Ang-(1–7) and serotonin in the brain [81]. In hypertensive (mRen2)27 transgenic rats (TGRs), which exhibit high levels of Ang II in different tissues, including the brain, Ang-(1–7) can modulate anxiety- and depression-like behaviors [82]. Hypertensive TGRs presented a decreased percentage of entries in the open arms of the elevated plus maze, which is an anxious-like behavior and this anxious phenotype was reversed by systemic treatment with enalapril [83] or intracerebroventricular infusion of Ang-(1–7) [82]. Pretreatment with A779, a selective Mas receptor antagonist, prevented the anxiolytic-like effect induced by the ACE inhibitor (ACEi) suggesting that Ang-(1–7) mediates, at least in part, the effect of an ACEi on anxiety-type behavior in TGRs [82]. Furthermore, transgenic rats overexpressing Ang-(1–7) show reduced anxiety-like behavior and this phenotype may result from an increased Mas receptor activation [75]. Altogether these data suggest that the Ang-(1–7)/Mas receptor pathway counteracts behavioral responses to various type of aversion stimuli. Supporting this, it has been recently demonstrated that increasing ACE2 in the brain reduces anxiety-like behavior by activating central MasR [22]. Male mice overexpressing ACE2, the enzyme that degrades Ang II to generate Ang-(1–7), explored the open arms of the elevated plus maze significantly more than wild-type mice, suggesting that increasing ACE2 activity is anxiolytic. Central delivery of diminazene aceturate, an ACE2 activator, to C57BL/6 mice also reduced anxiety-like behavior [22]. Centrally administering a Mas receptor antagonist to mice overexpressing ACE2 abolished their anxiolytic phenotype, suggesting that ACE2 reduces anxiety-like behavior by activating central Mas. ACE2 may reduce anxiety-like behavior by activating central Mas receptor that facilitates γ-aminobutyric acid release onto pyramidal neurons within the basolateral amygdala [22]. Altogether, the Ang-(1–7)/Mas receptor signaling may be further investigated as an additional strategy for the treatment of anxiety-related disorders.

Hypertension is associated with depression with anxiety in humans [84-87], and depression is probably an independent risk factor of hypertension [88]. Reduction in the central angiotensin function has both antidepressant-like and anxiolytic-like actions [89,90]. Depression was associated with a 30% increased odds of hypertension in women [91]. Several reports have shown that ACEi (captopril and enalapril) improves mood in depressed and hypertensive patients [92]. The score of Beck Depression Inventory and Hopkins Symptom Check-list, two different scores of depression in humans, was higher in untreated hypertensive patients than enalapril-treated hypertensive patients or normotensive subjects [92]. Patients treated with an ACEi or an ARB showed significantly lower doses of antidepressant [93].

Using medical information from Grady Memorial Hospital's outpatient population (n=505), ACEi or ARBs treatment were associated with decreased post-traumatic stress disorders symptoms [94]. To date, no randomized controlled trial has assessed the effects of ACEis or ARBs in depression [95]. In the Norwegian HUNT (Nord-Trøndelag Health) study, the depressive symptoms of a large population of 55472 patients with systemic hypertension taking an ACEi were compared with those of patients with untreated systemic hypertension. Results showed an important trend in favor of the depressive symptom-reducing effects of ACEis, as assessed by the Hospital Anxiety and Depression Rating Scale [96]. Thus, ACEi and ARBs may be considered as potential treatment against mood disorders.

The protective axis of the RAS and other neurodegenerative diseases

The two components of the RAS which show the greatest association with neurodegenerative diseases are receptors for RAS hormones: the AT1 receptor subtype for Ang II and the prorenin receptor, which is now recognized to signal via mitogen-activated protein kinases (MAPKs) in response to prorenin and renin, thereby paralleling some of the pathophysiological effects of Ang II at the AT1 receptor [97]. The AT1 receptor signals via the activation of NADPH oxidase, thereby generating reactive oxygen species creating oxidative stress in neurons which could contribute to the neuronal cell death associated with neurodegenerative diseases [97].

Several lines of evidence have suggested a link between reduced activities of the ACE-2/Ang (1–7)/Mas axis and neurodegenerative conditions. Multiple sclerosis (MS) is a complex, chronic inflammatory, and demyelinating disease of the CNS. Despite the fact that Ang II levels were reduced in the cerebrospinal fluid of patients with MS, ACE levels were elevated whereas ACE2 levels were significantly reduced [98].

Parkinson's disease (PD) is characterized by progressive loss of dopaminergic neurons in the substantia nigra pars compacta and the accumulation of abnormal aggregates of α-synuclein (called Lewy bodies) in the remaining neurons [99]. Enhanced levels of Ang II, via AT1 receptors, exacerbate dopaminergic cell death and may play a synergistic role in the pathogenesis and progression of PD [12]. Furthermore, an association of the gene AGTR, which encodes the AT1 receptor, and PD and AD was observed [97]. Injury mechanisms associated with AT1 receptor overactivity include activation of the NADPH oxidase complex mediating several key events in oxidative stress, enhanced uncontrolled inflammatory processes, increased TNF-α production, regulation of α-synuclein, stimulation of brain-derived neurotrophic factors and glial cell line-derived neurotrophic factor, and activation of the protective peroxisome proliferator-activated receptor γ nuclear receptor [38]. The Ang-(1–7)/Mas receptor axis is present in dopaminergic neurons and counteracts the pro-oxidative effects of the Ang II/AT1 axis [25]. An intracellular Ang-(1–7)/Mas axis that modulates mitochondrial and nuclear levels of superoxide may be involved in this counteracting effect. Furthermore, the Ang-(1–7)/Mas receptor axis is down-regulated in the aged nigra, which may contribute to the aging-related vulnerability to neurodegeneration [25]. Rocha et al. [100] have measured circulating Angs levels in PD patients. PD patients exhibited lower plasma levels of Ang I, Ang II and Ang-(1–7) than controls, which were associated with increased severity of depressive symptoms [100]. Circulating levels of both ACE and ACE2 were similar in PD patients and controls [100]. Despite the fact that peripheral Ang levels were evaluated, it remains to be elucidated if they reflect CNS changes.

Regarding epilepsy, it has been shown an increased expression of AT1 and AT2 receptors in the hippocampus of patients with temporal lobe epilepsy, supporting the idea of an up-regulation of RAS in this disease [101]. The ACEi enalapril and the ARB losartan were able to decrease seizures [102]. In acute and silent periods of an epilepsy model, Ang II levels were very low as well as AT1 receptor expression, whereas the chronic phase was characterized by an increased level of Ang II and by its AT1 receptor. In contrast, Ang-(1–7) levels increased in acute and silent phases, decreasing importantly in the chronic phase [103]. In chronic phase, the ratio between Ang II/Ang I was increased, showing a predominant form of Ang II. Differently, the ratio Ang-(1–7)/Ang II was decreased into the chronic phase [103].

RAS is a promising target for symptomatic and neuroprotective therapies in PD. But even, it is premature to infer the data from basic research to clinical practice. In a proof-of-concept, randomized, double-blind, crossover study in PD patients, perindopril enhanced the effect of levodopa without inducing dyskinesias [104]. There has not been any clinical trial exploring the neuroprotective effect of RAS drugs, but one cohort study in hypertensive patients suggested a protective effect of ACEi on PD risk [104].

Table 1 summarizes the expression of RAS components in different brain disorders.

Possible mechanisms of the centrally protective actions of Ang-(1–7)

The molecular mechanisms of Ang II-induced cerebrotoxicity have been reviewed [60]. Established mechanisms of Ang II-induced toxicity include increased NADPH oxidase activity, leading to intracellular generation of reactive oxygen species. Subsequently, increased reactive oxygen species production activates redox-sensitive signaling molecules, such as MAPKs, e.g. p38 mitogen-activated protein kinases, NH_2-terminal kinases, and extracellular signal-regulated kinases 1 and 2. In addition, Ang II directly enhances cellular and mitochondrial oxidative stress. Ang II-induced activation of transcription factors such as NF-κB promotes increased production of inflammatory cytokines such as of IL1β, TNFα and IL-6, and chemokines such as MCP-1. The result is a significant inflammatory response and increased apoptosis [60]. In addition, many cytokines, such as IL-1β and IL-12, have been related to the progression of AD pathology. Another regulator of inflammation is tumor growth factor-β (TGF-β). Increased TGF-β has been observed in amyloid plaques and in the cerebrospinal fluid of patients with AD [57]. In contrast with Ang II and supporting the protective role of Ang-(1–7) in the brain, it has been shown that centrally Ang-(1–7) induces a decrease in the proinflammatory cytokines IL1α, IL6, IL8, TNFα, MCP-1 and NF-κB [29-32, 41, 42], counteracting in this way the proinflammatory action of Ang II.

The locus coeruleus (LC) is the norepinephrine (NE)-containing nucleus in the brainstem and innervates into widespread brain regions. This LC–NE system plays a critical role in a variety of brain functions, including attention, arousal, emotion, cognition, and the sleep–wake cycle [105, 106]. The LC–NE system is one of the few regions in the brain that exhibits neurofibrillary tangles, an AD-related neuropathology. Accumulating evidence indicates that neurofibrillary tangles pathology as well as neuron loss in the LC play a critical role in the pathogenesis of AD [105]. It has been proposed that the basal AT2 receptors localized on the brain stem (particularly on the LC) exhibit anxiolytic phenotype and their up-regulation produces antistress effects due to a decrease in tyrosine hydroxylase and central

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Table 1 Expression of RAS components in different brain disorders

Stroke		
Human	↑ AT1R	[38]
Human	↑ ACE/Ang II/AT1R axis	[39]
Human	↓ Serum ACE2 activity (patients with acute ischemic stroke)	[44]
Human	↑ Serum ACE2 (patients with cardioembolic stroke compared with lacunar infarction)	[45]
Rat	↑ Ang II/AT1R and AT2R signaling	[41]
Rat	↓ Ang-(1–7)/MasR	[41]
Rat	↑ Cerebral and circulating Ang-(1–7)	[34]
Rat	↑ ACE2 and MasR expression	[34]
Anxiety		
Human	↑ ACE activity	[77]
Human	↑Ang II levels	[77]
Human	↑ Ang II levels	[74]
Human	↑ AT1R	[74]
Hypertensive (mRen2)27 transgenic rats	↑ Ang II levels	[82]
Alzheimer's disease		
Human	↑ ACE expression and activity	[64-67]
Human	↓ ACE2 activity in mid-frontal cortex	[69]
Human	↑ Ang II levels in mid-frontal cortex	[69]
Human	↓ Plasma concentration of Ang-(1–7)	[70]
Human	↑ Ang II and Ang III levels in brain	[63]
Mouse model of sporadic AD	↓ Ang-(1–7) levels in cerebral cortex and hippocampus	[20]
Multiple sclerosis		
Human	↓ Ang II levels in the cerebrospinal fluid	[98]
Human	↑ ACE levels	[98]
Human	↓ ACE2 levels	[98]
Parkinson's disease		
Human	↑ Ang II levels	[12]
Human	↓ Ang I, Ang II, and Ang-(1–7) levels	[100]
Epilepsy		
Human	↑ AT1R and AT2R in hippocampus	[101]
Pilocarpine-induced model of epilepsy acute and silent phase	↓ Ang II levels	[103]
Pilocarpine-induced model of epilepsy acute and silent phase	↓ AT1R	[103]
Pilocarpine-induced model of epilepsy acute and silent phase	↑Ang-(1–7) levels	[103]
Pilocarpine-induced model of epilepsy chronic phase	↑ Ang II and AT1R	[103]
Pilocarpine-induced model of epilepsy chronic phase	↓Ang-(1–7) levels	[103]
Pilocarpine-induced model of epilepsy chronic phase	↑ Ang II/Ang I	[103]
Pilocarpine-induced model of epilepsy chronic phase	↓ Ang-(1–7)/Ang II	[103]

sympathetic drive from the brain [74]. We have previously shown in neurons from hypothalamus and brainstem of normotensive and SHR that Ang-(1–7) through an AT_2 receptor-mediated mechanism down-regulates tyrosine hydroxylase, reducing in consequence NE biosynthesis [30]. In addition, Ang-(1–7) through Mas and AT2 receptors elicits a decrease in NE release in hypothalami from normotensive and hypertensive rats in a bradykinin/NO-dependent manner [107, 108]. Thus, we could not disregard that the neuroinhibitory effect of Ang-(1–7) on the hypothalamic and brainstem NE system may mediate its anxiolytic and protective effects on neurological disorders.

Microglia are phagocytic cells and can ingest Aβ through a range of cell surface receptors. It has been suggested that, in AD, a key factor in the accumulation of Aβ throughout the brain is the failure of microglia to remove extracellular amyloid. Similar to microglia, reactive astrocytes can polarize their processes around amyloid plaques and are capable of amyloid plaque degradation [57]. The involvement of oligodendrocytes in AD remains poorly understood, although there is emerging evidence that these cells contribute to the pathogenesis and progression of neurodegenerative disorders, including AD [57, 109]. Focal loss of oligodendrocytes has been observed in sporadic cases of AD. Aβ can impair the survival and maturation of oligodendrocyte progenitor cells and the formation of the myelin sheath [57]. Ang-(1–7) elicits a protective effect on cells of the CNS. Through Mas receptor stimulation, Ang-(1–7) prevented

neurodegeneration, axon demyelination, alterations in synapse and oligodendrocyte, and astrocyte damage induced by shigha toxin 2 [110]. This protective effect may be elicited in neurological disorders.

Clinical evidences

What do we know about RAS on brain disorders from clinical research? Regarding stroke, data from the CAPPP (Captopril Prevention Project) randomized trial demonstrated that captopril versus diuretics or β-blockers reduced the rate of stroke by 25% [111]. The HOPE (Heart Outcome Prevention Evaluation) study carried out with 9297 patients with vascular disease or diabetes and an additional vascular risk factor followed over 4.5 years have demonstrated a total stroke risk reduction of 32% with the ACEi ramipril [112]. In primary prevention, the LIFE (Losartan Intervention For Endpoint reduction in hypertension) randomized trial showed in 9193 participants aged 55–80 years with essential hypertension a significant difference in stroke rate in favor of losartan compared with atenolol despite similar reductions in blood pressure [113]. The PROGRESS (Perindopril Protection Against Recurrent Stroke Study) was designed to investigate the usage of an ACEi in the secondary prevention of stroke recurrence. The study was carried out with 6105 patients with a history of stroke or transitory ischemic attack and showed that the ACEi perindopril, in combination or not with the diuretic indapamide, prevented the recurrence of stroke in normotensive and hypertensive patients from 5% to 43%. According to the PROGRESS investigators, a 10 mm Hg in systolic blood pressure fall is expected to decrease the risk of stroke recurrence by only 28% in this population [114]. The SCOPE (The Study on Cognition and Prognosis in the Elderly) study carried out with 4937 elderly hypertensive patients showed that candesartan reduced the non-fatal stroke in 28% [115]. The ACCESS study (Acute Candesartan Cilexetil Therapy in Stroke Survivors) suggested that an ARB is safe in the hypertensive acute phase of patients with stroke and improves mortality independent from blood pressure control. In secondary stroke prevention, there are very few antihypertensive trials [116].

The population-based follow-up study in Taiwan evaluated 5445 subjects (Taiwan's National Health Insurance data) and concluded that ARBs could be used, from the perspective of stroke prevention as a first-line antihypertensive drug for patients with both hypertension and diabetes. The group with ARBs regimen reduces 26% of stroke in contrast with the group with ACEi regimen [117]. Altogether, the different trials showed that an ACEi or an ARB may have a beneficial action on stroke. The clinical and experimental observation support the hypothesis that the stroke may be mediated by AT2 receptors, then ARBs could be better in the prevention of the stroke.

Hypertension, particularly midlife, has been associated with an increased risk for cognitive impairment and dementia in the late-life, vascular dementia or AD. The Nun Study was the first evidence of the association between cerebral vascular injury, AD, and risk of cognitive impairment or dementia [118]. The BBB disruption could be the key point in the sporadic AD pathophysiology (decreased Aβ clearance and accumulation in the intraneuronal space brain). Thus, targeting the pressor arm of the RAS may have a preventive effect on cognitive function. Enalapril and, to a lesser extent, captopril reversed these deficits [92]. Some authors affirm that a higher availability of Ang-(1–7) in patients treated with ACEi might underlie some improvement of cognitive processes [119, 120]. Studies have revealed reduced rates of cognitive decline, in elderly patients, who were treated with centrally active ACEi such as captopril, fosinopril, lisinopril, perindopril, ramipril, and trandolapril, which are lipid soluble and have an ability to cross the BBB and penetrate cerebral tissues [59, 121]. They thus exert an effect on cognition via possible anti-inflammatory mechanisms independent of their blood pressure-lowering action. In contrast, noncentrally active ACEi (without these cerebral properties), including benazepril, enalapril, moexipril, and quinapril, which work mainly by lowering blood pressure, do not have such an effect on cognitive function [121]. The ARBs losartan, candesartan, ibersartan, olmesartan, valsartan, and telmisartan have also been shown to improve cognitive dysfunction and dementia. The effect of the antihypertensive treatment on cognitive function and prevention of dementia differ between drugs classes and possibly ARBs are the most effective [122].

Up to date there are no specific formal randomized controlled trials of RAS drugs testing dementia incidence as a primary outcome. The first randomized trial that showed that the treatment of hypertension decreases the incidence of dementia was the Syst-Eur (Systolic Hypertension in Europe) performed in the context of the Vascular Dementia Project [123], a project whose objective was the prevention of vascular dementia. Nitrendipine (calcium channel blocker) plus enalapril and/or hydrochlorothiazide (diuretic) reduced the incidence of dementia by 50% and 55% in the extended phase (Syst-Eur2) [124]. Although the project was aimed at the prevention of vascular dementia, 64% of registered cases of dementia (41/62 cases) were diagnosed as AD.

The HOPE and the PROGRESS study were not designed to evaluate cognitive function in hypertensive patients, although the subanalysis showed a reduction in cognitive decline associated with stroke by 41% with ramipril [112] and 45% with perindopril with a 34% reduction in the risk of dementia poststroke [125].

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The HYVET-COG (Hypertension in Very Elderly Trial) performed in elderly patients treated with perindopril [126] and the SCOPE study carried out with patients treated with candesartan [115] showed a reduction in the incidence of dementia and cognitive decline without statistical significant. However, when the study was included in a meta-analysis [PROGRESS, Syst-Eur, SHEP (Systolic Hypertension in the Elderly Program) and HYVET], the risk of dementia was significantly reduced by 13% [126].

Three studies have been performed with telmisartan: Prevention Regimen for Effectively Avoiding Second Strokes trial (PRoFESS), Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease (TRANSCEND) and Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET), being this last one performed in combination with ramipril. A reduction in 11% (n=20332) and 17% (n=5926) in cognitive deterioration was observed in the PRoFESS and the TRANSCEND studies, respectively, although this decrease was not statistical significant. The ONTARGET study (n=25650) showed that different approaches to blocking of the RAS had no clear effects on cognitive outcomes in patients with cardiovascular disease or diabetes. Although patients with the lowest systolic blood pressure had the greatest preservation of cognitive function, meta-regression analyses did not show any benefits of blood pressure lowering on cognition over several years of treatment [127]. In contrast, another study (n=160) showed that telmisartan was superior compared with lisinopril in improving some of the components of cognitive function, particularly episodic memory and visuospatial abilities [128]. The same group demonstrated that losartan improves the performance of short- and long-term memory compared with the β-blocker atenolol [129] and that valsartan is more effective than enalapril in improving some of the components of cognitive function, particularly episodic memory [130]. In addition, in the Antihypertensives and Vascular, Endothelial, and Cognitive Function (AVEC) study, candesartan has been shown to be superior to hydroclorotiazide and lisinopril in the preservation of the executive function [131]. The cerebral smaller vessels disease induces demyelination of the subcortical white matter and disconnection between the cortical and subcortical circuit. The disconnection between dorsolateral prefrontal cortex and basal ganglia—caudate, globus pallidus, and thalamus—gives rise to a cognitive clinical syndrome called "executive dysfunction" [132,133]. The executive function is the domain more affected in patients with hypertension (cerebral subcortical damage) [134,135].

The impact of treatment with ARBs on the neuropathology of AD was evaluated in the National Alzheimer Coordinating Center database, which included aggregated data and brain autopsies (n=890) from 29 AD centers throughout the United States. Brain from hypertensive patients treated with ARBs showed less Aβ deposition markers compared with those treated with other antihypertensive medications [136]. Database of the U.S. Veteran Affairs (n=819491) showed that ARBs are associated with a significant reduction in the incidence (55% reduction) and progression (70% reduction) of AD and dementia compared with the ACEi lisinopril or other cardiovascular drugs in a predominantly male population [137]. A Health Data Analysis in Taiwan Research Group demonstrated that ARBs reduce the risk of dementia. ARB may be associated with a reduced risk of dementia in high vascular risk individuals. Patients exposed to ARBs for higher cumulative doses experienced more protection from dementia and the subtypes [138].

A quantitative meta-analysis was performed to evaluate the association of RAS blockade use with the incidence of cognitive impairment of aging and AD. ARBs treatments, regardless of the drug class, have benefits on prevention of AD, and the effects of ACEi may analogous to ARBs. However, the benefit differs according to drug classes for cognitive impairment of aging, with ARBs use, rather than ACEi use, being a potential treatment for reducing the incidence of cognitive impairment of aging [139].

Until recently there have been no specific formal randomized controlled trials of RAS drugs on AD. Some ongoing clinical trials have now begun to explore various questions regarding the role of RAS in the development and pathology of AD [140]. The first such trial to commence and likely first to finish is the U.K.-based (with a recruitment target of n=228) Phase II multi-center RADAR (Reducing Pathology in Alzheimer's Disease through Angiotensin TaRgeting) trial of losartan compared with placebo in hypertensive and normotensive AD patients where the primary outcome is changed to magnetic resonance imaging-based measurement of brain structure and volume after 12 months of treatment [141]. A similar design and sized (SARTAN-AD) Phase II trial in hypertensive AD patients will compare perindopril with telmisartan. The smaller pilot Phase I (n=66) HEART study will compare two doses of telmisartan against placebo for effects on cerebrospinal fluid levels of RAS components in African Americans at increased risk of AD [140,142]. A similarly sized (n=72) CEDAR study will compare the effect of candesartan and placebo on a number of cardiovascular outcome measures in people with mild cognitive impairment, while the CALIBREX study will compare lisinopril with candesartan for effects on the primary outcome of executive function in people with hypertension and mild cognitive impairment. Finally, the rrAD study will compare the effects of losartan and amlodipine in conjunction with aerobic exercise training on cognitive performance in older adults who have high risk for AD [140]. They serve as the first formal gold-standard tests of RAS as a target for intervention in AD patients and also elderly with mild cognitive impairment [140].

The CHS (Cardiovascular Health Study Cognition Substudy*)* demonstrated that the administration of central ACEi to hypertensive subjects during 6 years (follow-up) was associated with a reduced risk of cognitive decline by 65% per year and the cumulative dosage of no-central ACEi was associated with more incidence of dementia [143]. In agreement, central ACEi (especially perindopril) showed a 25% reduction in the rate of cognitive decline in patients with mild to moderate AD [144]. Recently, a pharmacogenetic interaction with ACEi use and rates of cognitive decline has been shown. ACEis slowed cognitive decline in one year independently of reductions in blood pressure in patients with AD, more remarkably for APOE4- carriers of specific ACE genotypes (T allele of rs1800764 or the T allele of rs4291 or both) [145]. Treatment with brain-penetrating ACEi could slow the rate of cognitive decline in mild to moderate AD patients in comparison with other antihypertensive drugs independent of the significant differences in the levels of blood pressure [146]. ARB users, other antihypertensive drug users and normotensives were compared [147]. Hypertensive participants demonstrated worse baseline memory and executive function, as well as greater memory decline, over the 3-year follow-up than normotensives, unless they were ARB users, who showed preserved memory compared with those taking other antihypertensive drugs. Users of BBB-crossing ARBs showed superior memory performance over time compared with other antihypertensive drug users. Users of BBB-crossing medications (ARBs or ACEis) showed better list-learning memory performance over time than all other groups, including normotensives, than users of non-BBB-crossing medications. These findings demonstrate that ARBs, especially those of the BBB-crossing variety, are associated with greater memory preservation than other antihypertensive medications [147]. Altogether, these data showed that some but not all antihypertensive treatments may benefit cognition and risk for AD, independent of stroke. The ARBs have been highlighted as one antihypertensive drug class that may confer greatest benefit.

Clinical evidence shows that the blockade of the pressor arm of the RAS with an ACEi or an ARB is beneficial to improve cognitive impairment. How this fact may be translated to the basic research? ACE inhibitor therapy caused an increase in plasma Ang-(1–7) levels and decreased plasma Ang II while ARB treatment increased plasma levels of both Ang II and Ang-(1–7) [148-151]. Treatment with azilsartan, a new AT1R antagonist, increased plasma Ang-(1–7) levels comparably (∼2- to 3-fold) in both normotensive and Ang II-infused hypertensive rats [152]. In agreement to that reported in animals, chronic administration of the ACEi captopril to essential hypertensive patients induced an increase in Ang-(1–7) levels in venous blood [153]. In contrast, subjects with essential hypertension administered placebo, losartan (50 mg OD) or eprosartan (600 mg OD) in randomized order in a double-blind, 3-period, 3-treatment, crossover trial, arterial blood Ang-(1–7) levels were unchanged [154]. Unfortunately, no enough clinical evidence were reported. Furthermore, those reports showed circulating Ang-(1–7) levels and not those present in cerebrospinal fluid. Although the predominant effect of ACE inhibition may result from the combined effect of reduced Ang II formation and Ang-(1–7) metabolism, the antihypertensive action of AT1 antagonists may in part be due to increased Ang II metabolism by ACE2 [155]. Altogether, the available data demonstrate that under an ACEi or an ARB therapy, an increase in Ang-(1–7) levels occurs and this may contribute to the antihypertensive effect of a combined therapy of an ACEi and an ARB. For instance, the acute infusion of a specific antibody raised against Ang-(1–7) reversed the antihypertensive effect produced by lisinopril and losartan in awake SHR [156] and the hypothalamic hypotensive effect of captopril in sinoaortic denervated rats [157]. No data on the possible contribution of Ang-(1–7) to the beneficial effect of an ACEi or ARB on brain disorders are available. Unfortunately, the clinical evidence did not clearly show that improvement in cognitive function caused by blockade of the pressor arm of the RAS is due to an involvement of the depressor arm of the RAS, but the data reported in animals suggest that this arm may at least in part contribute to an ACEi or ARB therapy. Ongoing trials [139] certainly will show the contribution of the depressor axis of the RAS in brain disorders.

Conclusions

The RAS is phylogenetically one of the oldest homeostatic systems. The complexity of this evolutionary system is far away from the vision of a system regulating water and salt. Newly discovered effects of the RAS on brain tissue include neuroprotection, cognition, angiogenesis, and cerebral vasodilation. A number of brain biochemical pathways are influenced by the brain RAS. Several lines of evidence show that activation of ACE2, resulting in production of Ang-(1–7) and stimulation of its receptor Mas, exerts protective actions in a number of cardiovascular diseases, including ischemic stroke, and in neurocognitive disorders. Thus, the depressor axis of the RAS may be a potential therapeutic target in the treatment of neurological disorders. Furthermore, therapies that induce an increase in centrally Ang-(1–7) levels may be thought as possible approaches as neuroprotectives.

On the other hand, drugs that modulate RAS responses seem to be superior to other antihypertensive drugs as strategies to preserve and improve cognitive function. Some of these drugs that have the ability to cross the BBB

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improve cognitive function independent of their blood pressure-lowering action. Although the clinical evidence are not enough to recommend the usage of ACEi or ARBs to prevent cognitive decline or dementia, sometimes it is necessary to accept the demonstration from experimental research. The delay in obtaining true data may decrease the impact in its application and may lead to irreversible situations.

Competing Interests

The authors declare that there are no competing interests associated with the manuscript.

Abbreviations

ACE, angiotensin-converting enzyme; ACEi, angiotensin-converting enzyme inhibitor; AD, Alzheimer's disease; Ang, angiotensin; ARB, angiotensin type 1 receptor blocker; AT1 receptor, Ang II type 1 receptor; AT2 receptor, Ang II type 2 receptor; BBB, brain–blood barrier; CCR2, chemokine receptor 2; CNS, central nervous system; eNOS, endothelial NOS; IL, interleukin; LC, locus coeruleus; MCP-1, chemoattractant protein-1; MS, multiple sclerosis; NADPH, nicotinamide adenine dinucleotide phosphate; NE, norepinephrine; NF-κB, nuclear factor-κB; NO, nitric oxide; NOS, nitric oxide synthase; PD, Parkinson's disease; RAS, renin–angiotensin system; RVLM, rostral ventrolateral medulla; SHR, spontaneously hypertensive rats; TNF-α, tumor necrosis factor-α.

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