The renin-angiotensin system (RAS) is a crucial signalling system for adjusting sodium homeostasis, body fluid volume, and maintaining arterial blood pressure. The classical RAS is described as a process of renin splitting inactive angiotensinogen to yield angiotensin (Ang-I). Ang-I is then converted by angiotensin-1 converting enzyme (ACE) into angiotensin II (Ang-II). Using PubMed, Google Scholar, and other means, we searched the peer-reviewed literature from 1990 to 2013 for articles on newly discovered findings related to the RAS, especially focusing on how the system influences the central nervous system (CNS). The classical RAS is now considered to be only part of the picture; the discovery of additional RAS pathways in the brain and elsewhere has yielded a vastly improved understanding of how the RAS influences the CNS. Newly discovered effects of the RAS on brain tissue include neuroprotection, cognition, and cerebral vasodilation. A number of brain biochemical pathways are influenced by the brain RAS. Within various pathways, there are potential opportunities for classical pharmacologic interventions as well as the possibility of controlling gene expression.

1. Introduction

The renin-angiotensin system (RAS) is a crucial signalling system for adjusting sodium homeostasis, body fluid volume, and maintaining arterial blood pressure. The classical RAS is described as a process of renin splitting inactive angiotensinogen to angiotensin (Ang-I). Angiotensin-I is then converted by angiotensin-I converting enzyme (ACE) to angiotensin II (Ang-II) (Fig. 1).

The discovery of a separate brain RAS at Jacques Genet’s laboratory in Montreal, Canada in 1971 has changed our traditional understanding of the RAS system [1], with additional brain RAS components such as angiotensin III, angiotensin IV, and a newly discovered RAS member with seven amino acids, angiotensin [1–7], enhancing our understanding of RAS functions in the brain. Most of the classically described functions of the RAS—like vasoconstriction, hypertension, and neurotoxicity—are mediated by angiotensin II (Ang-II) via its action on the angiotensin 1 receptor (AT1R). However, newly discovered effects of the RAS relate to neuroprotection, cognition, and cerebral vasodilation. The goal of this review is to present the reader with new developments concerning the RAS in the central nervous system.

2. Angiotensin IV (Ang IV) and angiotensin IV receptor (AT4 receptor)

Angiotensin IV (Ang IV) effects occur via the AT4 receptor, which is primarily distributed in the caudate putamen, cerebellum, anterior pituitary globus pallidus, neocortex, lateral geniculate body, CA1–CA3 pyramidal layers and the nucleus basalis of Meynert. Receptor density is also high in the ventral lateral thalamic nucleus, motor cortex, and in motor neurons of the brain stem and ventral horn of the spinal cord [2].

The AT4 receptor has been recognized as an Insulin Regulator Aminopeptidase (IRAP) using [125I]-IRAP radioligand binding assay [3]. IRAP is a member of the M1 family of zinc

Abbreviations: ACE, angiotensin – converting enzyme; ACE2, angiotensin – converting enzyme-2; Ang-(17), angiotensin – (17); Ang-I, decapeptide precursor of Ang-II (and eventually, Ang-(19) & Ang-(17)); Ang-II, octapeptide precursor of Ang-(17); Ang-III, angiotensin – III; Ang-IV, angiotensin – IV; AT1 receptor, angiotensin receptor-1; AT2 receptor, angiotensin receptor-2; ATIP, AT1-receptor interacting protein; ATRAP, AT1-receptor associated protein; CAD, coronary artery disease; CNS, central nervous system; GPCR, G-protein coupled receptor; IL-6, interleukin-6; MAPK, mitogen-activated protein kinase; NO, nitric oxide; PLC, phospholipase C; PPAR-γ, peroxisome proliferator-activated receptor gamma; RAS, renin angiotensin system; ROS, reactive oxygen species.

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metallopeptidases that also contains aminopeptidases A, N, and B. IRAP splits the N-terminal amino acid from peptides such as vasopressin, oxytocin, somatostatin, eNOS (endothelial nitric oxide synthase), and many others [2]. IRAP also has a second functional domain that apparently regulates intracellular trafficking through the insulin-responsive glucose transporter 4 (GLUT4) in the pyramidal cell of the hippocampus and cerebral cortex, thereby reducing glucose uptake in these regions [4]. Ang IV is a natural inhibitor to IRAP, so that attachment of Ang IV to IRAP provokes:

a. Enzymatic competitive inhibition of the catalytic activity of IRAP extends the half-life of a number of peptides, including vasopressin, oxytocin, somatostatin, and eNOS;

b. Inhibition of intracellular GLUT4 vesicular trafficking induced by IRAP, thus enhancing memory by increasing neuronal glucose uptake [2,4].

The interaction between AngIV/AT4 and hepatic growth factor (HGF) takes place via Type 1 tyrosine kinase receptor (c-Met) [5]. Stimulation of c-Met blunts neurodegenerative changes [6] facilitating long-term potentiation (LTP) apart from the NMDA-dependent LTP pathway [7,8] and increasing dendritic arborisation in the hippocampus [9]. Ang IV stimulates the c-Met receptor, which is considered as a subtype of AT4 and may also facilitate HGF docking at c-Met [2].

3. Angiotensin 1 and 2 receptors (ATR1 and ATR2)

Both ATR1 and ATR2 have the 7-transmembrane domain typical of G-protein-coupled receptors. Despite this, ATR2 shares only approximately 32–34% of the amino acid sequence present in ATR1. ATR1 appears to be more sensitive to Ang II, while ATR2 is most receptive to Ang III. Both Ang-(1–7) and Ang II also serve as ligands at ATR2 [2].

The potentially injurious effects of Ang II on the brain (e.g., hypertension, inflammation, increased oxidative stress, blood brain barrier disruption and neurotoxicity) are mainly mediated via action on the ATR1A subtype. In contrast, activation of ATR2 enhances the repair of damaged DNA and differentiation in the nervous system through induction of methyl methane sulfonate sensitive 2 (MMS2), an ubiquitin conjugating enzyme variant [10]. Ang II induces nitric oxide (NO) production, neurite outgrowth, and brain development through ATR2 activation [11]. It was therefore unsurprising that in the TROPHY (TRial Of Preventing Hypertension) study, the angiotensin II type 1 receptor blocker (ARB) valsartan protected against ischemic brain injury after middle cerebral artery occlusion in mice given non-hypotensive doses of valsartan. Treatment with valsartan for two weeks, followed by interruption for two weeks, protected against subsequent ischemic brain damage—at least partially because capillary density increased [12].

4. Angiotensin–(1–7) and angiotensin converting Enzyme-2

The discovery of angiotensin converting enzyme-2 (ACE2), which converts the octapeptide Ang-II into the heptapeptide angiotensin–(1–7) [Ang-(1–7)], has enhanced understanding of alternate RAS in the brain. The actions of Ang-(1–7) are mainly produced by Mas receptors, and to a lesser extent via ATR2. Moreover, Ang-(1–7), it also affects non-cardiovascular functions in the brain. Those functions include learning, memory, and neuroprotection which are produced by Ang-(1–7), via its action on Mas receptors. The action of Ang-(1–7) via Mas receptors augments NO production through neuronal nNOS (nNOS) activation in the brain. The production of neuronal NO is considered an essential step for object recognition memory and long-term potentiation (LTP) in the hippocampus and amygdala [13,14]. The genetically engineered knockout Mas receptor rats, for example, have deficient object recognition memory, highlighting the indispensable role of Ang-(1–7) and Mas axis in learning and memory [15].

Ang-(1–7) could have an significant neuroprotective effect against ischemic stroke. Ang-(1–7) enhances the production of both nNOS and eNOS. In addition it reduces expression of inducible NOS (iNOS) in animals [16]. Moreover, the antioxidative effects of the ACE2/Ang-(1–7) and Mas axis help maintain normal endothelial function in cerebral vessels. The ACE2 and Ang-(1–7) axes have also been identified in human retina glial cells. The administration of Ang-(1–7) in the vitreous decreases intra-ocular pressure in rabbits. Furthermore, the administration of ACE2 genes intraocularly in diabetic rats protect against diabetic retinopathy [17,18].
5. The central sympathetic system and blood pressure control

Central sympathetic tone and blood pressure control is a complicated process that results in part from intricate interactions between the hypothalamic and medullary nuclei. The hypothalamic paraventricular nucleus (PVN) is the single most crucial aspect of the central autonomic network. The PVN also functions as the central neuro-circuitry of the renal sympathetic nerve activity (RSNA) and cardiac sympathetic afferent (CSAR), controlling sympathetic activity through projections to the rostral ventrolateral medulla (RVLM) and the intermediolateral column (IML) of the spinal cord. RVLM activation augments arterial pressure via increases in peripheral resistance, cardiac output, and catecholamines. In contrast, stimulation of the caudal ventrolateral medulla (CVLM) provokes hypotension and bradycardia by reducing sympathetic tone. Another entity controlling this process is the nucleus of the solitary tract (NTS) that is responsible for baroreceptor sensitivity control [Figs. 2 and 3].

The main function of the PVN is to moderate tonic sympathetic activity, especially the cardiac sympathetic afferent (CSAR) and RSNA. Both endogenous Ang-(1–7) and Ang II in the PVN enhance CSAR as well as RSNA. In addition, Ang-(1–7) in the PVN enhances sensitivity to Ang II in the cardiac sympathetic afferent (CSAR) pathway as well as sympathetic outflow in renovascular hypertension. The Mas receptor is essential for Ang-(1–7) stimulatory action in the PVN [19–21]. However, concentrations of Ang II and ATR1 in the PVN are enhanced in numerous hypertension animal models [22].

In patients with hypertension, Ang II up-regulates ACE and down-regulates ACE2 [23]. Therefore, induced hypertension from an Ang II infusion in rats decreases ACE2 and MAS gene expression, and increases ATR1 and ACE expression. Ang II also increases gene expression of pro-inflammatory cytokines in the PVN such as IL-1β, TNF-α, and IL-6. These effects were reversed when ACE2 in the PVN was over-expressed by transfection with adenovirus encoding human ACE2 genes, with consequent anti-hypertensive activation of RAS (ACE2/Ang-(1–7)/Mas). Moreover, the overexpression of ACE2 in PVN attenuated Ang II–mediated hypertension that was induced by Ang II infusion [24]. Therefore, it appears while Ang-(1–7) normally maintains tonic sympathetic activity in PVN, the balance is shifted towards Ang II with hypertension which then becomes the predominant PVN angiotensin peptide.

Ang-(1–7) and Ang II have comparable stimulatory outcomes on RVLM sympathetic outflow in both normotensive and hypertensive rats. The effects of Ang-(1–7) in RVLM are not produced via ATR1, nevertheless by Mas receptors instead [25–27]. In the caudal ventrolateral medulla, however, Ang-(1–7) reduces blood pressure via a reduction in the RVLM-mediated pressor response [28].

Ang-(1–7) acts tonically in NTS to enhance the sensitivity of baroreflex-mediated changes of heart rate in normotensive rats [29]. However, in transgenic hypertensive rats with over-expression of the mouse Ren2 gene in the brain results in increased Ang II and reduced Ang-(1–7) in brain medullary nuclei. The endogenous Ang-(1–7) does not offer tonic input to the NTS, possibly contributing to impaired baroreflex control in those animals [30,31]. However, transgenic ASrAOGEN rats (AS) with high Ang-(1–7) tone have reduced resting systolic pressure and increased baroreflex sensitivity [32,33].

Antenatal steroid exposure is linked with hypertension during adolescence, possibly because tonic Ang-II overcomes Ang-(1–7) effects in the NTS [34,35]. However, the effect diminishes in elderly hypertensive patients [36].

Ang-(1–7) restrains central sympathetic nerve activity via Mas receptor activation which in turn enhances neuronal nitric oxide synthase (nNOS) and nitric oxide (NO) production. Increased NO activates hyperpolarizing voltage-gated outward potassium current (IKv) in catecholaminergic neurons [14,37]. The augmented chronotropic action of ANG-II in hypertensive rat neurons is produced by phosphatidylinositol 3-kinase (PI3-kinase).

Ang-(1–7) counters the chronotropic effects of ANG-II by enhancing phosphatase and tensin homolog (PTEN) gene expression. The protein encoded by this gene dephosphorylates...
phosphatidylinositol 3 (PI(3)) and thereby antagonizes the chronotropic effects of ANG-II [38,39]. There is thus an intricate equilibrium balancing Ang-II and Ang-(1–7) in the CNS that normally maintains baroreceptor reflex sensitivity and blood pressure.

6. Parkinson's disease

Parkinson's disease is a very common neurodegenerative condition that affects nearly 1.5% of the world's population aged over 65 years [40]. James Parkinson first described the disease in 1867; it is now known to be the result of a loss of dopaminergic neurons in the substantia nigra pars compacta.

The relationship between brain RAS and Parkinson's disease was first defined by Allen et al. [41]. Stimulation of Ang-II induces the NADPH oxidase complex and high concentrations of reactive oxygen species (ROS) by inflammatory cells (microglia) in the basal ganglia, resulting in dopaminergic neuronal death; although Ang-II stimulation did not increase dopaminergic neuronal death in the absence of microglial cells [42]. Also, simulation of AT1 receptor by Ang-II results in the stimulation of the nuclear factor kappa light chain enhancer of activated B cells (NF-κB) signal pathway, thus increasing cytokine production in the basal ganglia. The pro-oxidative and proinflammatory states produced by AT1 stimulation may contribute to dopaminergic neuronal death and Parkinson’s disease.

The treatment of patients with Parkinson’s disease using the ACEI perindopril has improved their motor responses to the dopaminergic precursor 3,4-dihydroxy-L-phenylalanine [43]. The harmful effects of Ang-II and AT1 in dopaminergic neurons are usually balanced by anti-inflammatory, neuroprotective and anti-oxidative functions of ATR2. In aged rats, a reduction of AT2 expression promotes inflammation. Inhibition of ATR1 with the selective antagonist candesartan decreases susceptibility of aged rats to dopaminergic neurotoxins, and decreases expression of nigral proinflammatory cytokines [44]. Interestingly, oestrogen protects against the development of Parkinson’s disease by maintaining the balance between ATR1 and ATR2 in the substantia nigra. Similarly, hormonal replacement therapy in ovariectomized rats’ upregulates ATR2 while down regulating ATR1, and the NADPH complex in the substantia nigra [45,46].

Ang IV protects against Parkinson’s disease by activating the HGF/c-Met pathway. HGF is a plasminogen family member and produces its actions via the Type 1 tyrosine kinase receptor c-Met [47]. Stimulation by c-Met blunts neurodegenerative changes and inhibits the dopaminergic neuron loss in the substantia nigra in rats. Ang IV either directly stimulates c-Met receptors that might be considered subtypes of Ang IV receptors, or helps HGF bind c-Met. The protective effect of ATR1 antagonist on Parkinson’s disease results from increased Ang-II concentrations, which are converted into Ang IV and stimulate the HGF/c-Met pathway. Administration of small Ang IV analogues that are able to pierce the blood brain barrier and thus stimulate the HGF/c-Met pathway is a novel potential treatment for PD [2,40,48,49].

In the same context, Kitamura et al. discovered administration of recombinant human HGF (rhHGF) enhances the operative recovery in primates after a spinal cord insult. However, the use of HGF is not without problems as HGF is a potent angiogenic factor that can stimulate the MET receptor. Therefore, it can enhance protein overexpression and constitutive kinase activation that can induce human primary tumours [47].

7. Alzheimer's disease and dementia

A serious health problem today is dementia, which imposes a heavy burden on health services. The prevalence of dementia is predicted to grow to 42 million by 2020 and to more than 81 million by 2040 [50]. Alzheimer’s disease and vascular dementia are the major causes of dementia and account for 85–90% of all cases...
of dementia [51]. Alzheimer’s disease is common in population over 65 years. Of note, 40% of the individuals over 65 years of age are at increased risk for Alzheimer’s disease. The price tag for taking care of these patients in US could cost more than $70 billion annually, and is likely to increase considerably [52,53].

Ang II constrains the potassium-facilitated release of acetylcholine (Ach) from slices of rat entorhinal and human temporal cortex [54]. Additionally, Ang II has proinflammatory and prooxidant effects that damage the BBB, reduce CBF, and increase amyloid β-peptide (Aβ) deposition, contributing to the pathogenesis of Alzheimer’s disease [55]. The Ang II injection inhibits long-term memory potentiation in both the hippocampus and lateral nucleus of the amygdala. These effects, however, can be reversed by losartan [56,57], [Fig. 4]

Losartan reverses cognitive deficits brought by scopolamine, an effect potentiated by co-administration of an anticholinesterase to antagonize the otherwise detrimental effects of ethanol on memory and learning [58–60]. Blocking ATR1 by ARBs increases Ang II levels, which promotes their translation to Ang III and Ang IV. Ang IV, in turn, stimulates ATR4 and dopamine to release in the striatum and Ach to release in the hippocampus, which facilitate long-term memory potentiation and neuroprotection, [8,61,62]. Ang IV inhibits aminopeptidase activity of ATR4, thereby increasing brain concentrations of vasopressin and oxytocin. Both vasopressin and oxytocin are critical for development of memories [63,64].

The ACE genes have at least 78 polymorphisms, with the most important being an inclusion or omission of a 287 base pair sequence of the ACE gene’s sixteenth intron [65]. The inclusion decreases ACE expression, with omission/omission homozygotes having 65% more ACE activity than inclusion/inclusion homozygotes [66]. Nevertheless, the relationship between ACE gene polymorphism and Alzheimer’s disease remains highly controversial and beyond the scope of this review [58,67]. However, increased ACE activity is associated with omission/omission genotype in other pathological conditions, such as diabetes, chronic obstructive pulmonary disease, hypertension, renal disease, and rheumatoid arthritis [68–71].

Enhanced ACE activity has opposing effects on Aβ, it both enhances aggregation, and degradation. However, ACE degrades nephrilysin which acts as an Aβ degrading enzyme [72]. Therefore, increased ACE activity could possibly be helpful in the brief period—but prolonged increases in Ang-II production and consequent reduction of nephrilysin activity may impair cognitive function. This theory remains speculative, though, pending suitable clinical trials.

In Japanese patients, prolonged therapy with ACEIs, such as captopril or perindopril that are capable of crossing the blood-brain barrier decreased the occurrence of Alzheimer’s disease. Moreover, it enhanced memory function in patients with mild-to-moderate Alzheimer’s disease [73,74]. Secondary analyses of data from the Systolic Hypertension in Europe (SYST-EUR) trial with enalapril and the Perindopril Protection Against Stroke Study (PROGRESS) trial showed that use of ACEIs reduced dementia and cognitive decline [75–78].

Amenta et al., in a review of clinical trials that examined the outcomes of antihypertensive medications on cognitive functions, concluded that the use of ACEIs resulted in improved cognitive function and a reduction in the vascular dementia following haemorrhagic or ischemic cerebrovascular events [79,80]. Furthermore, the ACEI perindopril improved cognitive function as measured by the Cambridge Neuropsychological Test Automated Battery. This battery measures visuospatial, attention, and verbal memory, problem-solving, learning, and reasoning [81].

Tedesco et al. showed that losartan improved cognitive efficiency measured by the Sandoz Clinical Assessment Geriatric (SCAG) and MMSE (mini–mental state examination) scores. Furthermore, Fogari et al. confirmed positive impacts of losartan on cognition in hypertensive patients [82,83]. Moreover, the use of
candesartan diminished the incidence of non-fatal stroke. In addition, it showed trend towards improved cognitive function [84]. These data indicate that antagonism of the classical RAS pathway potentially results in either cognitive improvement and/or protection of neural tissue.

8. Neuroprotection

The RAS and alternate RAS are promising new targets for neuroprotection via their actions on NO production. The production of NO by endothelial NO synthase (eNOS) during the ischemiareperfusion periods reduces apoptosis and promotes vasodilation. Moreover, it enhances cerebral blood flow in the penumbra region of the ischemic region. However, pathological concentrations of NO from other NOS isoforms could increase apoptosis. Therefore, reduction of eNOS activity could have detrimental effects after cerebral ischemia. [85,86] In contrast, the increased eNOS activity and thereby NO production has been demonstrated by Ang-(1–7) infusion in rats models of focal cerebral ischemia. [16].

Ang-(1–7) enhances NO release and eNOS expression via the Ang-(1–7)/Mas axis and the bradykinin–NO dependent pathway [87]. For example, when Ang-(1–7) is applied in brain before and after strokes caused by middle-cerebral artery occlusion in rats, it inhibits inducible nitric oxide synthase (iNOS). The increased production of NO by the enhanced activity of iNOS in glia and neurons will enhance the concentration of peroxynitrite (a powerful oxidant) and may increase the tissue damage following cerebral ischemia [88]. Ang-(1–7) suppresses NF-kB via Mas receptors. Therefore, Ang-(1–7) could be a useful neuroprotective agent via its anti-inflammatory effects after cerebral ischemia [89]. Deficiency of ACE2, and therefore of Ang-(1–7) production, impairs endothelial function in cerebral arteries and increases oxidative stress [90] [Fig. 3]. The Ang-(1–7)/Mas axis therefore appears to be an exciting and novel method for neuroprotection management.

Ang IV and its ATR4 pathway might be another neuroprotective target in the RAS. ATR4 metabolizes oxytocin, vasopressin and eNOS. Ang IV is considered the natural inhibitor of the IRAP receptor and increases NO levels in the brain resulting in increased cerebral blood flow. Intravenous administration of Ang IV in rats after subarachnoid haemorrhage increases cerebral blood flow 45–80% above baseline [91]. Moreover, intracarotid Ang IV in a rat model of embolic stroke significantly reduces infarct size. That could be explained by relocation of blood flow to ischemic areas [92]. Consistent with these results, omission of the IRAP gene defends the brain from ischemic injury analogous to the effects of Ang IV [93]. Moreover, deletion of IRAP in mice reduces sensitivity to pentylentetrazol–induced generalized seizures [94].

Use of HF1419 that is specific non-peptide IRAP inhibitors may identify the extent to which IRAP inhibitors contribute to neuroprotection [95]. AngIV also exerts a neuroprotective via its action in the HGF/c-Met pathway. A subtype of ATR4 or Ang IV facilitates the attachment of HGF to its receptor c-Met [96,97]. Therefore, the RAS and alternate RAS could be the new promising targets for neuroprotection in humans and the focus of clinical trials to prove their efficacy as neuroprotective agents.

9. Conclusion

Many pathways are influenced by the brain RAS, and within each there are potential opportunities for classical pharmacologic intervention, and possibly interventions related to the control of gene expression. As the knowledge of the brain RAS improves, there will surely be efforts to develop novel approaches to treat Parkinson’s disease, dementia, and a host of other neurological conditions. RAS-related interventions may also protect the brain against physiological and pharmacological insults.

Advances in understanding the brain RAS also open new venues for improving perioperative care. The prophylactic effect of RAS antagonists against stroke and Alzheimer’s disease may help in our search for neuroprotective agents for the perioperative period. But in the meantime, the use of RAS antagonists as cardiovascular and pulmonary therapeutic agents will continue to attract interest [98,99].

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Contribution attestation

Ehab Farag contributed to the analysis and interpretation of the literature. Dr. Farag also participated in drafting the article and revising it critically. He was also involved in the final approval of the manuscript.

Daniel I. Sessler participated in revising the article critically. Dr. Sessler approved the final version of the manuscript.

Zeyd Ebrahim contributed to the analysis and interpretation of the literature. Dr. Ebrahim has also participated in drafting the article and revising it critically. He was also involved in the final approval of the manuscript.

Andrea Kurz participated in revising the article critically. Dr. Kurz was also involved in the final approval of the manuscript.

Joseph Morgan contributed to the analysis and interpretation of the literature. Dr. Morgan has also participated in drafting the article and revising it critically. He was also involved in the final approval of the manuscript.

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