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Review Article

Renin Angiotensin System in Cognitive Function and Dementia

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Angiotensin II represents a key molecule in hypertension and cerebrovascular pathology. By promoting inflammation and oxidative stress, enhanced Ang II levels accelerate the onset and progression of cell senescence. Sustained activation of RAS promotes end-stage organ injury associated with aging and results in cognitive impairment and dementia. The discovery of the angiotensin-converting enzyme ACE2-angiotensin (1–7)-Mas receptor axis that exerts vasodilator, antiproliferative, and antifibrotic actions opposed to those of the ACE-Ang II-AT_1 receptor axis has led to the hypothesis that a decrease in the expression or activity of angiotensin (1–7) renders the systems more susceptible to the pathological actions of Ang II. Given the successful demonstration of beneficial effects of increased expression of ACE2/formation of Ang1–7/Mas receptor binding and modulation of Mas expression in animal models in containing cerebrovascular pathology in hypertensive conditions and aging, one could reasonably hope for analogous effects regarding the prevention of cognitive decline by protecting against hypertension and cerebral microvascular damage. Upregulation of ACE2 and increased balance of Ang 1–7/Ang II, along with positive modulation of Ang II signaling through AT_2 receptors and Ang 1–7 signaling through Mas receptors, may be an appropriate strategy for improving cognitive function and treating dementia.

1. Cognition and Dementia

Cognition is a general term that refers to all mental processes, such as perception, thinking, memory, movement, attention, emotions, ability to understand the intentions and thoughts of other people, decision making, and self-awareness. Anecdotal evidence of age-related decline in cognitive functions is amply supported by a wealth of objective data. Mild cognitive impairment (MCI) is a widely used term to indicate a syndrome characterized by a mild memory or cognitive impairment that cannot be accounted for by any recognized medical or psychiatric conditions [1]. The general criteria for MCI require a subjective complaint of memory loss, an objective impairment of memory function for age and education (1 or 2 SD below the mean score of the examined sample) assessed by formal neuropsychological testing, with no evidence of dementia, but preservation of intact activities of daily living and other cognitive domains [1]. In contrast to MCI, a diagnosis of dementia is made when cognitive impairment is greater than that found in normal aging and it affects two or more cognitive domains that comprise orientation, attention, verbal linguistic capacities, visuospatial skills, calculation, executive functioning, motor control, praxia, abstraction, and judgement and the person's ability to function. In fact, an essential condition to establish the diagnosis of dementia is that the cognitive failure must be severe enough to impair the usual social and occupational daily activities, excluding those deficits that are caused by the motor consequences of stroke. A schematic flow diagram for assessing mild cognitive impairment and dementia is shown in Figure 1. Patients with disturbances of consciousness, delirium, psychosis, serious aphasia, or sensory motor alterations that preclude correct execution of neuropsychological testing are not considered dementia deficits. Additionally, there cannot be present other cerebral or systemic pathologies that could produce a dementia syndrome, such as congestive heart failure and end-stage renal disease. The most common forms of dementia are Alzheimer's disease (AD) and vascular dementia (VaD) due to microangiopathy, associated with poorly controlled hypertension, with respective frequencies

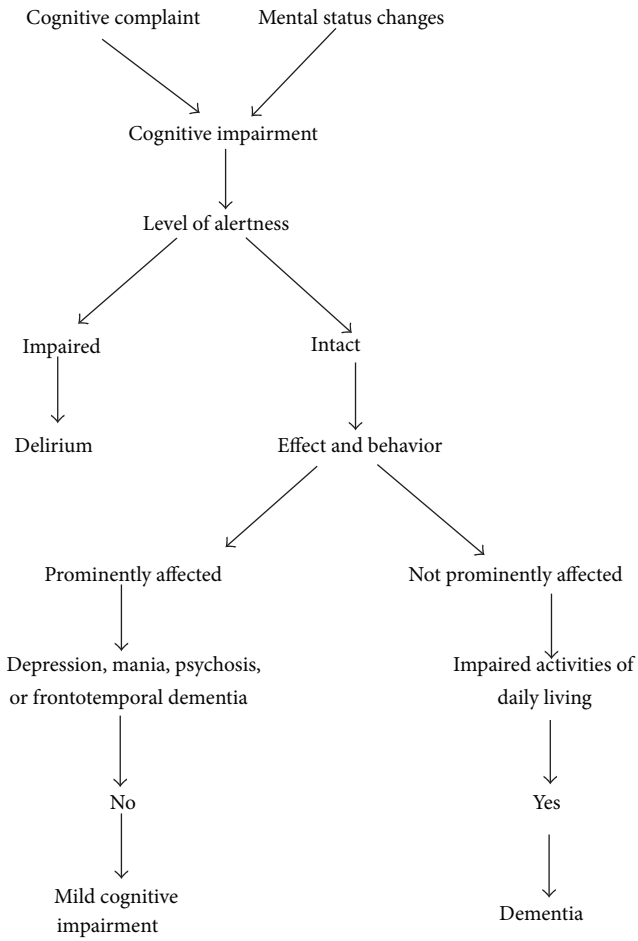

Figure 1: A schematic flow diagram for assessing mild cognitive impairment and dementia.

of 70 and 15% of all forms of dementia [2]. The term vascular dementia refers to a group of pathologies that involve cerebral damage of a vascular etiology, with the presence of focal neurological signs compatible with a diagnosis of cerebral ischemia and neuroradiological evidence of cerebral lesions arising because of multiple infarcts from the occlusion of large vessels, strategic single infarcts of the angular gyrus, thalamus, brain stem or cerebral anterior and posterior territories and ischemic lacunae of the subcortical white matter, and periventricular leukoaraiosis [3]. A schematic flow diagram for differential assessment of dementia is given in Figure 2.

1.1. Aging and Cognition. Cognitive impairment and dementia are common interlinked disorders among elderly persons influencing the individual's ability to function independently. Due to the aging population, the prevalence of cognitive impairment and dementia is increasing [4]. It is also recognized that there is variability in the magnitude and rate of decline in cognitive abilities among aging individuals. A similar phenomenon exists for dementia, where individuals with similar neuropathologic burden present themselves with varying degrees of cognitive impairment. Various potentially modifiable lifestyle factors, social resource factors, and dietary factors have the capacity to modulate the cognitive function in individuals, in addition to genetic, demographic, and other health factors [5]. In this regard, it is important to note that there is increased prevalence of cardiovascular, renal, and other malignant diseases in the aging population. More pertinent is the increase in the prevalence of hypertension, where there is a likelihood of cardiac enlargement (hypertrophy), reduction in ventricular function, and thromboembolic stroke. One of the long-term complications of hypertension is presented clinically as dementia (such as Alzheimer's disease) or vascular dementia, associated with degenerative central nervous system (CNS) diseases. The temporal correlation between the dementia and the large cerebrovascular pathology implicates that the onset of dementia is within the three months following the diagnosis of ictus, or there is a history of abrupt onset and stepwise progression of the cognitive decline. Hypertension has been known to increase target organ complications such as cardiac enlargement, progressive hypertensive retinopathy, nephropathy, and stroke. Persistent hypertension that results in a decrease in cerebral blood flow, in addition to frequent episodes of stroke or transient ischemic attacks, is associated with vascular dementia and results in cognitive decline, a clinically gradual progression downhill [5]. The principle

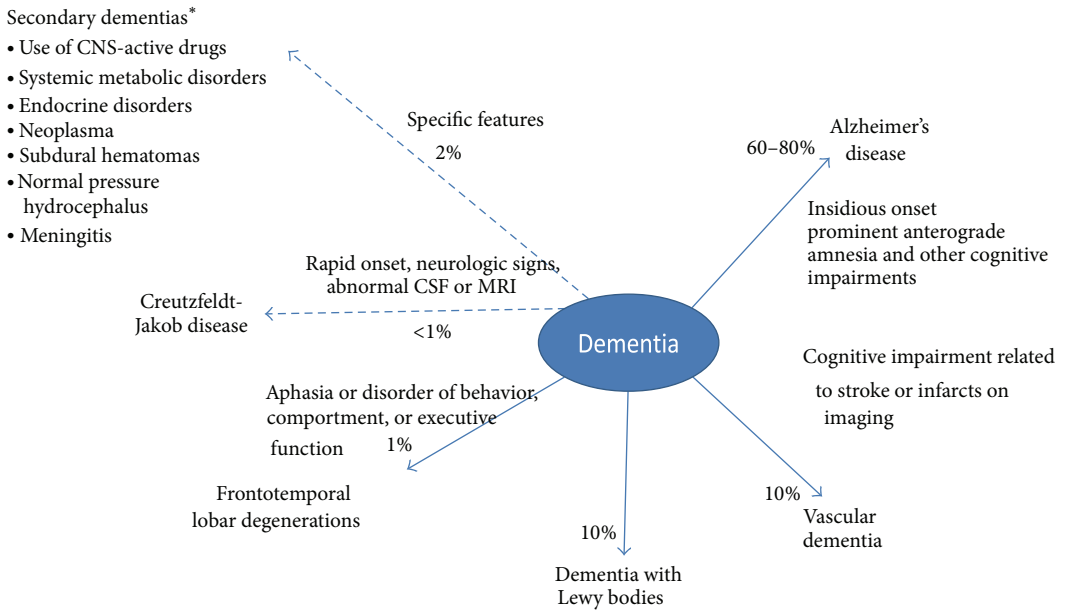

Figure 2: A flow diagram for the differential assessment of dementia, showing the approximate percent contribution of each diagnosis. The list of secondary dementias is not exhaustive. CSF: cerebrospinal fluid; MRI: magnetic resonance imaging.

effect of aging is the progressive elongation of cerebral vessels, which become more tortuous, increasing the minimal blood pressure required to maintain adequate perfusion of the white matter, thereby increasing the susceptibility to ischemia. Although the cerebral autoregulation is designed to maintain constant blood flow independent of variations in perfusion pressure, metabolic factors (the perivascular pH) and mechanical factors (variations in the tone of smooth muscle in the vascular wall) can potentially modify the autoregulation process. The compromise of autoregulation of the cerebral blood flow from systemic hypertension is of a long standing nature and is characterized by alterations in the cerebral vasculature, including vasoconstriction and increased pathological growth with proliferation of smooth muscle, decreased lumen, and decreased vascular compliance [6]. These changes shift the cerebrovascular autoregulation towards the right, in the direction of high blood pressure [7]. As a consequence, there is a decreased capacity of cerebral blood vessels to dilate during hypoperfusion, increasing the vulnerability to brain ischemia and stroke. The mechanisms by which high blood pressure determines a decline in the cognitive function are not completely understood, even though knowledge in this field is increasing [8]. High blood pressure can cause different types of cerebral vascular damage, associated with an increase in atherosclerosis in the larger vessels and in the oxidative stress at the level of the vascular wall [9]. Hypertension is the most important factor that negatively affects the modalities of cerebral aging [10, 11] and is associated with cognitive compromise in aging individuals. This observation has led to the hypothesis that hypertension is one of the factors responsible for the compromise of cognitive function in the elderly, even to the point of dementia. Thus, it is hypothesized that aging leads to hyperactivity of systemic and tissue renin-angiotensin system

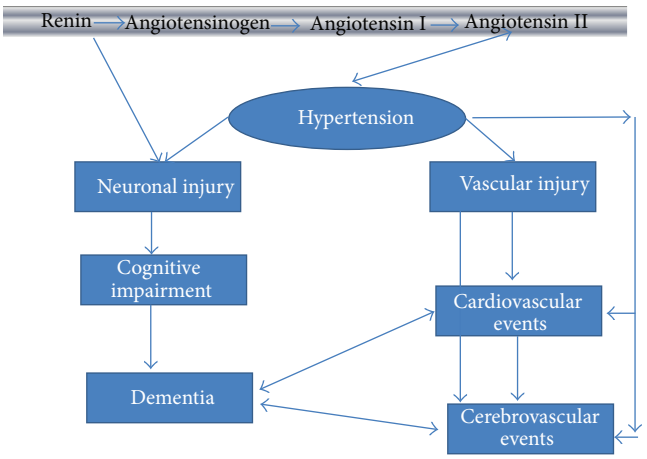

Figure 3: A schematic illustrating the role of renin-angiotensin system in causing hypertension and in mediating cognitive impairment and dementia.

(RAS) and an increase in neurogenic hypertension, while evidence connecting brain RAS with Alzheimer' disease, memory, and learning, cognitive functions is evolving [12]. A diagrammatic sketch of the role of renin angiotensin system in inducing hypertension and in mediating cognitive impairment and dementia is shown in Figure 3.

2. Systemic and Brain Renin Angiotensin System

The renin angiotensin system (RAS) is a peptide hormone cascade that controls fluid homeostasis, blood pressure, and hormone secretion, as well as behavioral and cognitive

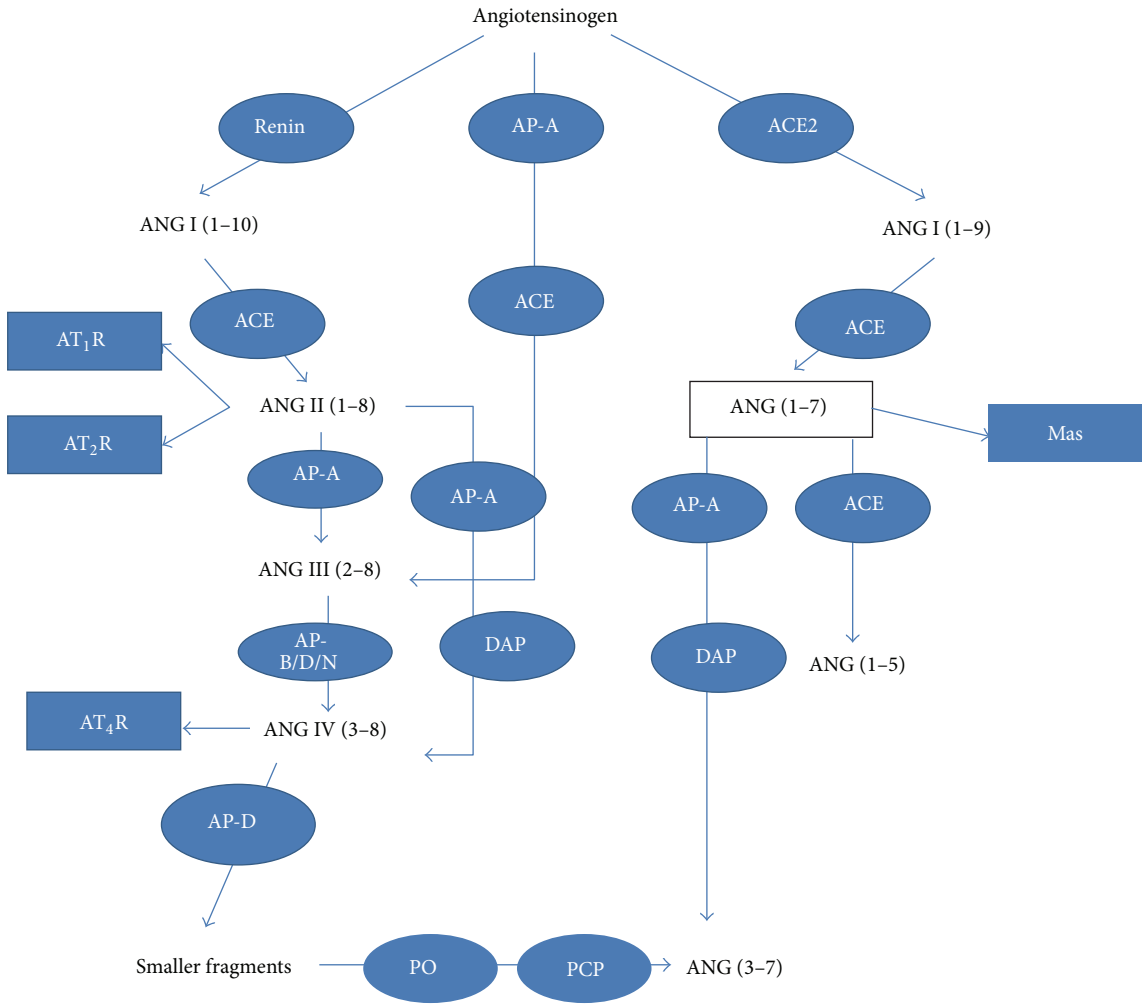

Figure 4: A schematic representation of the renin-angiotensin system. Additional components of the renin-angiotensin system (RAS) pathway have been identified in recent years, increasing its complexity. Angiotensin metabolites are prefixed by Ang, with the number of amino acids present relative to the 14 amino acid angiotensinogen sequence order. Arrows between peptide fragments denote enzymatic conversion steps catalyzed by a host of enzymes denoted by coloured circles or boxes according to the abbreviations listed below. Arrows from peptides to boxes denote receptor binding routes. Note that the Ang II metabolite Ang III is currently considered to be the main and a more potent mediator of many recognized Ang II functions, and the binding of Ang IV to its receptor is believed to affect cognitive function. Also note the ACE2-Ang(1–7)-Mas (receptor) axis, which is now currently believed to be a RAS internal regulatory mechanism to attenuate Ang II-mediated functions (large red arrow centrally located in pathway; ACE2 is a recently discovered ACE homologue). ACE: angiotensin-1 converting enzyme; AP: aminopeptidase; DAP: dipeptidyl aminopeptidase; PCP: carboxypeptidase; PO: propyl oligopeptidase; REN: renin.

responses through a complex enzymatic pathway generating several peptides [13]. A schematic representation of the renin angiotensin system with key players is presented in Figure 4. Renin, a proteolytic enzyme released from the juxtaglomerular apparatus of the kidney, in response to a decrease in arterial blood pressure, acts on the inactive precursor angiotensinogen to form the decapeptide angiotensin (Ang) I. Liver is the principal site for angiotensinogen (55–60 kDa, ~452 aa) synthesis and secretion; mRNA for angiotensinogen is stimulated by corticosteroids, estrogens, thyroid hormones, and angiotensin II in fat, certain regions of the central nervous system, and kidney [14]. There is evidence within the brain of renin mRNA [15] and cells in the pituitary, choroid plexus, medulla oblongata, and hypothalamus are positive for renin immunoreactivity. The renin present in the cells of the choroid plexus would be positioned for release and has the ability to act on the angiotensinogen in the extracellular milieu. Renin immunoreactivity is localized in neurons, but in the medulla oblongata and subfornical organ, it has been demonstrated in glial elements as well. However, renin mRNA, as an indicator of synthesis of the protein, is predominant but not exclusive in neurons [16, 17]. Both secreted and nonsecreted forms of renin are present in the brain of rodents and humans [18, 19] and their overexpression results in a hypertensive phenotype, adding credence to the notion that brain RAS indeed exists and plays an important role in the regulation of blood pressure. The concentration of angiotensinogen in the circulation is approximately equal

to the K_m of renin (1.25 μM), and therefore, angiotensinogen availability is an important determinant of the rate of angiotensin formation [20]. Angiotensinogen synthesis in astrocytes and its secretion into the interstitial space and cerebrospinal fluid were shown to be the major source of substrate for brain Ang II formation [21]. It is well known that angiotensinogen is an extracellular component of cerebrospinal/interstitial fluid and constitutes one of the most abundant proteins in cerebrospinal fluid [22] and the production of the precursor protein is primarily glial [23]. Overexpression of antisense to angiotensinogen behind a glial-fibrillary acidic protein (GFAP) promoter results in loss of 90% of the brain angiotensinogen [23]. However, angiotensinogen is also found in neurons [23], most often in brain centers involved in cardiovascular regulation such as the subfornical organ, paraventricular nucleus, nucleus of the solitary tract, and rostroventrolateral medulla. In addition, angiotensinogen immunoreactivity is present at sites other than those associated with blood pressure (BP) and fluid and electrolyte homeostasis providing evidence that the brain RAS may serve in other capacities and is not limited to cardiovascular regulatory functions.

2.1. Formation of Ang II. The 14 amino acids at the N-terminus are the relative portion of angiotensinogen from which Ang I is derived by the active renin. Ang I, in turn, is hydrolyzed at the carboxy terminal by the action of angiotensin-converting enzyme (ACE), an ectoenzyme and a zinc metalloproteinase, to form the active octapeptide, Ang II. Expression of local Ang II was reported in the hypothalamic paraventricular nucleus (PVN), supraoptic nucleus, circumventricular organs (CVOs), and nucleus of the tractus solitarii (NTS) neuronal cell bodies [24]. ACE mRNA was detectable in choroid plexus, caudate putamen, cerebellum, brain stem, hippocampus, and pineal gland. In addition, quantitative autoradiography established the presence of relatively high levels of ACE protein in the choroid plexus, blood vessels, subfornical organ, and organum vasculosum of the lamina terminalis and relatively low levels in the thalamus, hypothalamus, basal ganglia, and posterior pituitary gland. Most convincingly, ACE could be colocalized with renin in synaptosomal fractions of the brain [25]. Human ACE contains 1277 amino acid residues with 2 homologous catalytic sites and a region for binding Zn^{2+} [26]. Human ACE is made up of a large extracellular domain, a short intracellular carboxy-terminal domain, and a 17 amino acid hydrophobic stretch that allows the ACE to anchor to the cell membrane. ACE is widely distributed in the body, with relatively high levels in the lungs and kidneys, but is also present in the brain. Membrane ACE that has undergone proteolysis at the cell surface by a secretase is associated with the luminal surface of vascular endothelial cells and is in close contact with the circulation [27]. Membrane-bound ACE, rather than soluble ACE, is believed to be responsible for the regional or local tissue conversion of Ang I into Ang II. This process follows first-order kinetics, since the angiotensin I levels in circulation or the interstitium are approximately six orders of magnitude below the K_m for angiotensin I (16 M). First-order kinetics will apply even at angiotensin I levels that are 10,000-fold higher than normal. Accordingly, Ang II formation from Ang I is similar over a wide range of arterial Ang I levels. Ang II results in elevation of blood pressure by promoting vasoconstriction, upregulates renal sodium and water absorption, increases cardiac output, sympathetic tone, and arginine vasopressin release, and stimulates the sensation of thirst in the central nervous system [28, 29]. ACE, which is present in the endothelial cells of the blood vessels, has an additional effect of degrading bradykinin, an active vasodilator [30].

2.2. Mechanisms of Ang II Action. Ang II binds to one of the G-protein coupled receptors, termed AT_1 or AT_2. AT_1 is the primary receptor that mediates vasoconstriction, water intake, sympathetic nervous system activation, and aldosterone, vasopressin, and endothelin secretion. Ang II also contributes to vascular smooth muscle hypertrophy, migration, proliferation, and growth, which act in concert to raise the blood pressure [31]. In addition, AT_1 receptor mediates a number of other biological actions in cardiovascular and renal tissues that include cytokine production by monocytes and macrophages, leading to inflammation, plasminogen activator inhibitor-1 (PAI-1) biosynthesis, platelet activation, aggregation, and adhesion, leading to thrombosis; collagen biosynthesis leading to fibrosis; and low-density lipoprotein transport leading to atherosclerosis. Many of these actions of Ang II have an underlying common mechanism that increases the influx of extracellular Ca^{2+} and mobilization of intracellular Ca^{2+}. An increase in intracellular Ca^{2+} level activates acute contractile responses and also activates various cellular kinases, including mitogen-activated protein kinase (MAPK), to induce cell proliferation signaling. Ang II also generates reactive oxygen/nitrogen species, especially superoxide anion, via stimulation of NAD(P)H oxidase complex, with accompanying formation of peroxynitrite and, in the process, decreases the bioavailability of endogenous nitric oxide, an efficient vasodilator. Increased cardiac contractility, along with cardiac and vascular remodeling, and reduction in vascular compliance are widely reported effects of Ang II *in vitro* and *in vivo*. This classical axis can be called the ACE-Ang II-AT_1 receptor axis. These effects of Ang II can be attenuated or partially overcome by AT_1-mediated short-loop negative feedback suppression of renin biosynthesis and secretion at renal juxtaglomerular cells. In contrast, Ang II acting via AT_2 induces vasodilation of both resistance and capacitance vessels, natriuresis, and inhibition of cellular proliferation and growth [32, 33]. AT_2 receptors are present in brain, heart, adrenal medulla, kidney, and reproductive tissues. The AT_2 receptor is involved in fetal development and control of nocturnal arterial blood pressure in rats [34]. Both AT_1 and AT_2 receptors bind to Ang II with the same affinity but have contrasting effects. The relative balance between AT_1 and AT_2 receptor functions may be influenced by receptor expression patterns in tissues. AT_1 receptors are highly expressed in the cardiovascular, renal, endocrine, and nervous systems of adults. AT_2 receptor expression is quantitatively less and its tissue distribution is more limited

than in AT_1 receptors. Thus, the RAS plays an important role in normal cardiovascular homeostasis, and overactivity of the RAS has been implicated in the development of various cardiovascular diseases, such as hypertension, congestive heart failure, coronary ischemia, and renal insufficiency [35]. Therefore, ACE inhibitors and angiotensin receptor blockers (ARBs) that target ACE-AngII-AT_1 receptor axis are of great therapeutic benefit in the treatment of cardiovascular disease. Beneficial effects of ARBs are not only contributed by blocking AngII-AT_1 receptor binding, but also by enabling AngII-AT_2 receptor interactions, as the AT_2 receptor stimulation seems to antagonize the signaling associated with AT_1 receptor stimulation. It was long established that infusion of Ang II into the brain could increase blood pressure [36] and central injection of purified Ang II near the hypothalamus resulted in a drinking response [37, 38], suggesting the presence of specific receptors in brain tissue. The distribution of AT_1 and AT_2 receptors in brain has been well studied in rat and mouse models [39–49]. In the central nervous system, AT_1 receptors are localized to areas of the brain that are exposed to blood borne Ang II, such as the circumventricular organs, including the subfornical organ, median eminence, vascular organ of the lamina terminalis, anterior pituitary, and the area of postrema in the hindbrain [47, 50]. Other regions of the hypothalamus, nucleus of the solitary tract, and ventrolateral medulla in the hindbrain also contain a high density of AT_1 receptors [47]. In line with the existence of AT_1 receptors in brain, it is well documented that Ang II facilitates sympathetic transmission by enhancing the release of noradrenaline from peripheral nerve terminals as well as from the central nervous system [51, 52]. Moreover, Ang II stimulates the release of catecholamines from the adrenal medulla and aldosterone from the adrenal cortex [53]. Ang II also exerts diverse actions on the brain by modulating drinking behavior and salt appetite, central control of blood pressure, and stimulation of pituitary hormone release and has effects on learning and memory [29, 54, 55]. Furthermore, existence of alternative pathways for Ang II formation such as chymase, cathepsin G, chymostatin-sensitive Ang II-generating enzyme (CAGE), tissue plasminogen activator, and tonin is reported [56, 57]. The main feature of this system is its distinction from the other local or tissue RAS, since it is physically separated from the endocrine RAS by the presence of the blood-brain barrier, thus preventing the diffusion of Ang II from the circulation into the brain [58]. However, there exist several areas lacking a blood-brain barrier, called circumventricular organs (CVOs), located in the proximity of the 3rd and 4th ventricles, the vascular organ of the lamina terminalis, the subfornical organ, the median eminence, the intermediate and the posterior lobes of the hypophysis, the subcommissural organ, the pineal gland, and the area postrema [59, 60]. Most of these CVOs have fenestrated capillaries allowing molecules of large molecular weight to cross back and forth between the circulation and the cerebrospinal fluid; therefore circulating Ang II may still produce some effects inside the brain [61]. Thus, there appears to be two closely integrated central Ang II systems, one responding to Ang II generated within the brain and stimulating receptors inside the blood-brain barrier and another with Ang II receptors in circumventricular organs and in cerebrovascular endothelial cells, responding to circulating Ang II of peripheral and/or tissue origin [62–64]. Nevertheless, the local brain RAS is thought to play a functional role in the maintenance of the BBB. Angiotensinogen, but not renin, levels in the brain appear to be relevant for this function, since a decrease in density in granular layer cells of hippocampus resulted in an impaired blood-brain barrier function which is seen in angiotensinogen-deficient mice, whereas renin-deficient mice do not show this phenotype [65]. Other studies in knockout mice came to similar conclusions. Astrocytes of angiotensinogen knockout mice had significantly attenuated expression of glial fibrillary acidic protein and decreased laminin production in response to cold injury and ultimately incomplete reconstitution of impaired blood-brain barrier function [66]. These data are in contrast to reports by Rose and Audus [67] who suggested AT_1 receptor-mediated uptake and transport of Ang II at the site of the bovine blood-brain barrier. This has been questioned since there is no evidence that angiotensins cross the blood-brain barrier and penetrate noncircumventricular organ structures [68]. Monti et al. [69] found functional upregulation of the AT_1 receptors inside the blood-brain barrier in a transgenic rat line with specific downregulation of astroglial synthesis of angiotensinogen. The authors have found higher AT_1 receptor binding in most of the regions inside the blood-brain barrier in transgenic rats compared with controls. In contrast, in the circumventricular organs investigated, AT_1 receptor binding was significantly lower in transgenic rats.

2.3. Other Angiotensins. Alternatively, angiotensin III (Ang 2–8) is produced from Ang II by the actions of aminopeptidase A, a zinc metallopeptidase that cleaves the N-terminal aspartyl reside of Ang II. Further, action of aminopeptidase N on Angiotensin III results in the formation of Ang IV (Ang 3–8). Both aminopeptidases A and N are present in the rodent brain [70–72]. The AT_4 receptor is defined as the high affinity binding site that selectively binds Ang IV with 1–10 nM affinity [73]. AT_4 receptors are widely distributed in the guinea pig, rat, sheep, monkey, and human brain, and the distributions are highly conserved through these species [74–78]. The receptor sites occur in high abundance in the basal nucleus of the Meynert, in the CA1 to CA3 regions of the hippocampus, and throughout the neocortex, a distribution that closely resembles cholinergic neurons and their projections and is consistent with the memory enhancing properties of the AT_4 ligands. High levels of the receptors are also found in most brain regions involved in motor control. The AT_4 receptor was shown to be insulin-regulated aminopeptidase (IRAP), a type II integral membrane protein belonging to the M1 family of zinc-dependent metallopeptidase [79].

2.4. ACE2 and Ang 1–7. To add to this complexity, an enzyme that can act upon Ang I and Ang II to produce Ang 1–9 and Ang 1–7, respectively, has been identified as a new component of the renin-angiotensin system [80–82]. This enzyme, known as ACE2, exhibits a high catalytic efficiency for the conversion of Ang II to Ang 1–7, almost 500-fold

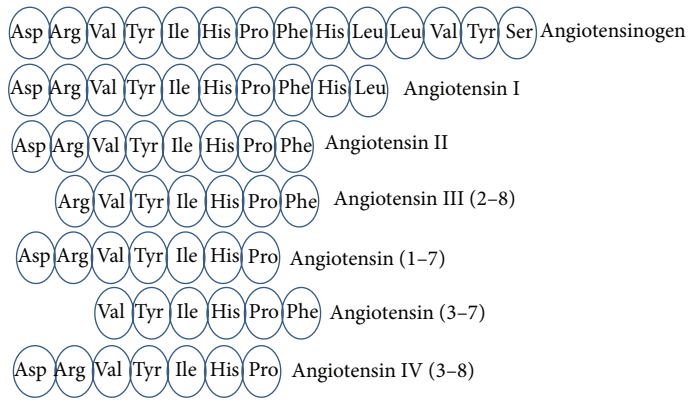

Figure 5: Amino acid sequences of different angiotensins generated by the action of various enzymes.

greater than that for the conversion of Ang I to Ang 1–9 [82]. ACE2 shares ~42% nucleotide sequence homology with ACE and conservation of active sites residues is an eminent feature [80, 83]. Similar to ACE, ACE2 is widely distributed in cells and tissues with high concentrations in cardiorenal and gastrointestinal tissues and limited expression in the central nervous system and lymphoid tissues [84, 85]. Low levels of ACE2 mRNA were shown in the human brain using quantitative real-time RT-PCR [85], while immunohistochemistry showed that ACE2 protein was restricted to endothelial and arterial smooth muscle cells of cerebral vessels [86]. In primary cultures, ACE2 was predominantly expressed in glial cells [87] and neurons [88]. Using a selective antibody, it was found that ACE2 is widespread throughout the brain, present in nuclei involved in the central regulation of cardiovascular functions like the cardiorespiratory neurons of the brainstem, as well as in noncardiovascular areas such as the motor cortex and raphe [88]. This observation was later confirmed by Lin et al. showing the presence of ACE2 mRNA and protein in the mouse brainstem [89]. Both ACE and ACE2 are type 1 glycoproteins with two domains, but ACE has two catalytic sites, whereas ACE2 has only one catalytic site. ACE2 is carboxymonopeptidase with a preference for hydrolysis between a proline and carboxyterminal hydrophobic or basic residues, whereas ACE cleaves two amino acids from its substrate [90]. A more clinically important finding is that the ACE2 activity is not directly affected by ACE inhibitors [80]. Figure 5 presents the amino acid sequences of different angiotensins produced from angiotensinogen by the action of cellular enzymes.

Consistent with the evidence that ACE2 is present in the brain, Ang 1–7 was shown to be present as an endogenous constituent of the brain, in areas including hypothalamus, medulla oblongata, and amygdale, as well as adrenal glands and plasma of normotensive rats [91]. It is likely that the synthesis of Ang 1–7 takes place most in the extracellular space since ACE2 is a transmembrane protein with its catalytic site located outside the cell [92]. However, because ACE2 conserves its activity even after shedding by A disintegrin and A metalloproteinase 17 (ADAM17), one can imagine that endocytosis of the secreted enzyme could lead to formation of the heptapeptide inside the cell. In line with this speculation, ACE2 enzyme was localized in the cytoplasm of neurons in the mouse brain [88]. Interestingly, Ang 1–7 can be further metabolized into Ang 1–5 by ACE [93] or Ang 1–4 by neprilysiN [94]. Ang 1–7 was shown to bind to a G-protein coupled receptor, Mas encoded by the Mas protooncogene. Mas, protein has seven hydrophobic transmembrane domains, whereas N- and C-terminal ends are hydrophilic and share strong sequence similarity with the GPCR subfamily of hormone receptor proteins [95]. More specifically, Mas belongs to the Class A orphan GPCRs. Mas is expressed in the brain, where its mRNA has been located in the hippocampus, dentate gyrus, piriform cortex, and amygdala [96–98]. In fact, brain was the first organ where *Mas* was found to be highly expressed [99]. High amounts of *Mas* transcripts are present in the hippocampus and cerebral cortex of rat brain [96]. Martin et al. [97] could show by *in situ* hybridization that *Mas* mRNA is expressed in a subpopulation of neurons in both the adult and developing rat central nervous systemS (CNS). In the adult CNS, *Mas* mRNA was most abundant in hippocampal pyramidal neurons and dentate granule cells but also presented at low levels in the cortex and thalamus. Recently, *Mas* expression was also discovered in cardiovascular regions of the brain by western blot and immunofluorescence [100]. Furthermore, brief seizure episodes led to a significant and transient increase in *Mas* mRNA in the rat hippocampus, which may contribute to anatomical and physiological plasticity associated with intense activation of hippocampal pathways [101]. In the mouse, the distribution of *Mas* mRNA in the brain is comparable to the rat being highest in the hippocampus and piriform cortex as detected by *in situ* hybridization [98].

ACE2 shares 42% sequence identity with the catalytic domain of ACE. In addition, ACE2 can convert Ang II into Ang (1–7). ACE2 shows 400-fold higher substrate preference for Ang II than for Ang I [82]. ACE2 is expressed in heart, kidney, liver, and intestine [83]. ACE2 may play a role as negative regulator of ACE. Furthermore, ACE2 acts as a tissue-specific negative feedback regulator of the activated RAS. This action is probably mediated by Ang (1–7) and bradykinin [102], which is in agreement with the reduced ACE2 level in several rat models of hypertension [103]. Deficiency of functional ACE2 resulted in severe cardiac dysfunction associated with

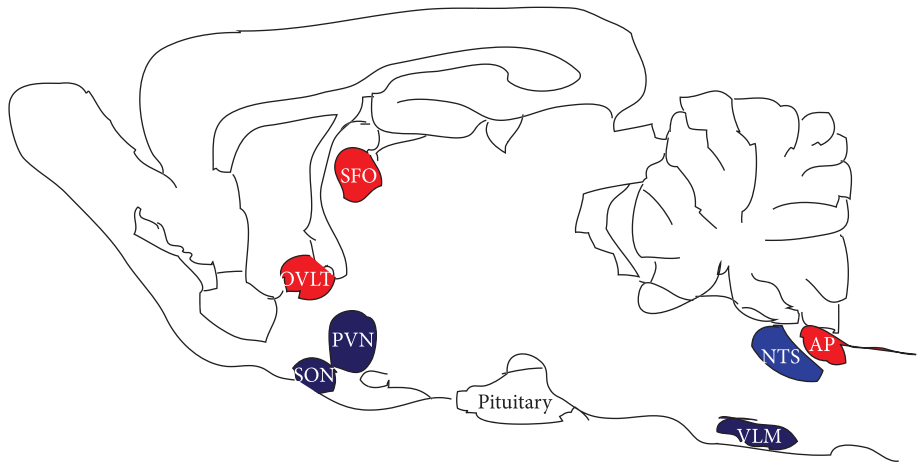

Figure 6: A diagrammatic sketch of the brain showing Ang-II-sensitive areas and inaccessible areas. In the brain, some areas (red), such as the subfornical organ (SFO), the organum vasculosum of the lamina terminals (OVLT), and the area postrema (AP), contain AT_1 receptors that are accessible to circulating Ang II. Other areas (blue), such as the supraoptic (SON) and the paraventricular nuclei (PVN) of the hypothalamus, the rostral (R) and caudal (C) ventrolateral medullae (VLM), and the nucleus tractus solitarii (NTS), also contain AT_1 receptors that cannot be reached by systemic Ang II owing to the blood-brain barrier. These regions are only accessible to Ang II synthesized locally in the brain.

an accumulation of cardiac Ang II [104]. Chronic treatment with AT_1 receptor antagonist induced ACE2 mRNA level in the SHR rats as well as increased Ang (1–7) level [105]. ACE inhibitors promote Ang II antiproliferation by increasing the generation of Ang (1–7) in the vasculature [106]. In addition, Ang 1–7 has vasodilator and antiproliferative properties [107–109]. ACE2 thus appears to have emerged to modulate pressor/mitogenic and depressor/growth inhibitory arms of the renin-angiotensin system by converting Ang II to Ang 1–7.

3. Cognitive and Behavioural Effects of Renin-Angiotensin System Components

Several studies provided convincing evidence in favor of hyperactive brain RAS in the development and maintenance of hypertension [110–114]. In normotensive models, Ang II acting on brain AT_1R [111, 112] induces an increase in blood pressure mediated by enhanced sympathetic outflow [115–117] and cardiac baroreflex resetting [118]. In spontaneous hypertensive rat (SHR), upregulation of brain RAS components (AGT, Ang-II, ACE, and AT_1R) precedes and sustains the development of hypertension [112, 118–122]. Although the precise mechanisms by which Ang II triggers hypertension are not known, it seems to involve increased sympathetic vasomotor tone and altered cardiac baroreflex function [123].

3.1. Actions of Ang II in the Brain. Angiotensin II (Ang II), initially described as a peripheral circulating hormone regulating blood pressure and fluid homeostasis, has been recognized as a brain neuromodulator inducing fluid and salt intake and blood pressure increase [62]. A diagrammatic view of the brain indicating Ang-II-sensitive areas is shown in Figure 6. There are two closely integrated central Ang II systems, one responding to Ang II generated in the brain and stimulating receptors inside the blood-brain barrier and another with Ang II receptors in circumventricular organs and in cerebrovascular endothelial cells, responding to circulating Ang II of peripheral origin or to locally generated Ang II, or both [62–64]. Ang II type 1 (AT_1) receptors located in selective forebrain and brain stem structures mediate the classical functions of brain Ang II, including the control of the hormonal and central sympathetic systems [63, 64]. The selective localization of large numbers of AT_1-receptors in sensory pathways, all limbic structures [124], and the endothelium of cerebral microvessels [125] indicated the possibility of several additional central roles for Ang II, including the regulation of the reaction to stress, brain development, neuronal migration, sensory information and motor activity, cognition, control of emotional responses, and cerebral blood flow.

The cognitive effects of Ang II, the dominant effector molecule of the RAS, are well recognised. Ang II inhibits acetylcholine release in fresh tissue slices of human temporal cortex [126] and rodent amygdala [127]. Acetylcholine (Ach) is critical for communication between neurons and muscle at the neuromuscular junction, is involved in direct communication in autonomic ganglia, and has been implicated in cognitive processing, arousal, and attention in the brain [128]. Ang II alters the sensory transmission in lateral geniculate neurons [129]. In addition, it suppresses long-term potentiation (LTP), a measure of synaptic excitability duration that can be stimulated to last from days to months, in the hippocampus and amygdala of rats, acting through the AT_1 receptor [127]. Ang II has also been found to interfere with memory acquisition in research animals [130]. Ang II administered in the brain disrupted an operant task in rabbits. On the other hand, it has been reported that centrally administered Ang II improves aversive memory [131], but using similar learning tasks, others have shown that this peptide either impairs or does not affect memory retention

[132, 133]. Ang II administered to the hippocampus affects memory by the activation of AT_1 [134] or AT_2 receptors [132]. The hippocampal Ang II [135–138] and specific receptor analogues of Ang II are reported to block LTP [139] and selectively impair olfactory and spatial learning [140], indicating that LTP is related to important cognitive processes through RAS. Moreover, antagonist action at AT_1 or AT_2 sites may exhibit cognitive enhancing effects [141–143]. A possible role for hippocampal Ang II receptors in voluntary exercise-induced enhancement of learning and memory in rat was proposed recently [144]. Similarly, when angiotensin II is injected directly into the dorsal neostriatum, retention of a stepdown shock avoidance response is impaired, whereas retrieval in a similar passive avoidance conditioning task improves the following intracerebroventricular administration of angiotensin II [145]. It was also reported that Ang II exhibits both inhibitory and stimulatory effects in 8-arm radial maze and Y maze tasks [133]. Recent studies demonstrated that Ang II modulates long-term depression (LTD) in the lateral amygdala of mice. This effect on synaptic plasticity may be dependent on AT_1 receptors, since losartan blocked the Ang-II-induced effect on LTD, whereas AT_2 receptors seem not to be involved. Also, the importance of L-type calcium channels in this process was demonstrated [146]. Role of brain RAS in retention impairment was also documented [147]. A recent report showed increased ACE activity and angiotensinogen levels in cerebrospinal fluid of patients with mild cognitive impairment and Alzheimer's disease [148]. Thus, several lines of evidence clearly established the contributions of renin-angiotensin system components towards modulating cognitive function.

3.2. AT_1 Receptor Blockers and AT_2 Receptor Agonists Affect Cognitive Function. Since AT_1 receptor is a major target for antihypertensive drugs, ACE inhibitors, which reduce the conversion of Ang I to Ang II, are believed to facilitate cognitive functioning, probably by decreasing Ang II and thus removing inhibitory influence upon acetylcholine release [130, 149]. ACE inhibitors in particular, such as captopril and perindopril, which affect the central RAS, have distinct cognitive effects. In addition, preventing the formation of Ang II releases inhibition of potassium-induced exocytosis of acetylcholine, resulting in facilitation of memory consolidation and retrieval [150]. Recent studies show that Ang II inhibitors help to preserve cognitive functions in patients with Alzheimer's disease through a mechanism that is independent of the blood-pressure-lowering effect [151]. Also, angiotensin-converting enzyme (ACE) inhibitors enhance conditioned avoidance and habituation memory and it has been shown that angiotensin-II-deficient mice present normal retention of spatial memory [152]. Chronic administration of ramipril to whole-brain irradiated F344 rats prevented perirhinal cortex-dependent cognitive impairment by attenuating microglial activation in the dentate gyrus and improving neurogenesis [153]. In an AD mouse model induced by intracerebroventricular injection of amyloid-β (Aβ) 1–40, administration of perindopril (brain penetrating ACE inhibitor) significantly inhibited hippocampal ACE activity and prevented cognitive impairment that was attributed to the suppression of microglial/astrocyte activation and attenuation of oxidative stress caused by iNOS induction and downregulation of extracellular superoxide dismutase [154]. In contrast, neither enalapril nor imidapril (non-brain-penetrating ACE inhibitors) prevented cognitive impairment and brain injury in this AD mouse. Mice lacking AT_2 receptor gene are significantly impaired in their performance in a spatial memory task and in a one-way active avoidance task [155].

Chronic activation of brain RAS with sustained production of angiotensin II induces cerebrovascular remodelling, promotes vascular inflammation and oxidative stress leading to endothelial dysfunction, and thereby impairs regulation of cerebral blood flow [156, 157]. It is also well known that CBF decreases with aging impairing cognitive function with the stimulation of AT_1 receptor with a decrease in CBF and increase in oxidative stress. Significant reduction in the incidence and progression of Alzheimer's disease and dementia was reported in a population aged 65 years or more with cardiovascular disease with the use of ARBs [158]. Administration of an ARB, olmesartan, attenuated the increase in blood pressure and ameliorated cognitive decline with the enhancement of cerebral blood flow and a reduction in oxidative stress in hRN/hANG-Tg mice carrying human renin and angiotensinogen genes [159]. Pretreatment with a low dose of olmesartan completely prevented beta-amyloid-induced vascular dysregulation and partially attenuated the impairment of hippocampal synaptic plasticity in young Alzheimer's disease model transgenic mice (APP23 mice) with cerebrovascular dysfunction [160].

AT(1) blocker, telmisartan, administered to hypertensive patients with probable Alzheimer's disease showed increased region cerebral blood flow in the right supramarginal gyrus, superior parietal lobule, cuneus, and lingual gyrus, without any changes in cognitive function test scores [161]. In normotensive young adults, acute administration of losartan improved performance on a task of prospective memory and reversed the detrimental effects of scopolamine in a standard lexical decision paradigm with the incorporation of a prospective memory component, highlighting the cognitive enhancing potential of losartan on compromised cognitive systems in normotensive subjects [162]. Antihypertensive mediations targeting AT_1 could therefore be successful in reducing the incidence of Alzheimer's disease (AD) and improving cognitive function.

The importance of relative AT_2 receptor stimulation during ARB treatment has been reported in terms of protection against brain damage, promoting cell differentiation and regeneration of neuronal tissue [163], through activation of mitogen-activated protein kinase [164] or nitric oxide [165]. Direct stimulation of AT_2 receptor by a newly generated agonist, compound 21 (C21), enhanced cognitive function in wild-type C57BL6 mice and an Alzheimer's disease mouse model with intracerebroventricular injection of amyloid-β (1–40) [166]. C21, an orally active nonpeptidergic highly selective AT_2 receptor agonist, promoted cerebral blood flow and neurite outgrowth of cultured hippocampal neurons [167].

It has been proposed that ARBs prevent or modulate accumulation of misfolded proteins, including the amyloid (Aβ) peptide responsible for oxidative and inflammatory damage that leads to energy failure and synaptic dysfunction [130]. The Ang II receptor antagonists, losartan and PD123177, which are selective for the AT_1 and AT_2 receptor subtypes, respectively, constitute important pharmacological tools for the assessment of behavioral consequences through the modulation of Ang II function [145, 168]. Several studies have shown that low doses of losartan and PD123177 improved scopolamine-impaired performance in a light/dark box habituation task. Similarly a countering effect was observed in the case of captopril and ceranopril [169].

3.3. Role of Ang IV and AT_4 Receptors in Cognition. In addition, the activation of AT_4 receptor by native Ang IV or AT_4 agonists improves learning and memory [130]. Central administration of Ang IV in rodents stimulates exploratory locomotor behaviour, enhances recall in passive avoidance situations, and facilitates memory retention [13]. Ang IV increases potassium-evoked acetylcholine release in the hippocampus, suggesting that the brain cholinergic system may underlie, at least in part, the mechanism of this AT_4 receptor-mediated memory enhancement [13].

3.4. Behavioural Effects of RAS Components. In addition to their cognitive effects, RAS components exert behavioural effects. A modulatory action of Ang II on anxiety has been reported, and the brain RAS may be involved in the course of affective disorders [13, 170]. ACE inhibitors, especially captopril, have mood-elevating effects in depressed patients. Dopaminergic pathways may play a role in the anxiety-modulating effects of Ang II, but additional involvement of GABAergic pathways has also been suggested, since Ang II was found to potentiate the actions of GABA.

AT_1 antagonist treatment reduced anxiety and improved learning, spatial working memory, and motor performance in the aged rat [132, 134, 171, 172]. Transgenic chimera mice with human renin and angiotensinogen genes mimicking continuous activation of the brain renin-angiotensin system showed impaired cognitive function as assessed by the shuttle avoidance test. The mice were found to show a decrease in cerebral surface blood flow, increased activity of p^{47}phox and Nox4, and an increase in oxidative stress. Administration of an angiotensin II type 1 receptor blocker, olmesartan, attenuated the increase in blood pressure and ameliorated cognitive decline with enhancement of cerebral blood flow and reduction of oxidative stress [159]. C57BL/6J mice prepared as a model of subcortical vascular dementia by subjecting to bilateral common carotid artery stenosis with microcoil to result in chronic cerebral hypoperfusion showed significantly increased brain renin activity and angiotensinogen expression that was attributed to increased renin in activated astrocytes and microvessels and the increased angiotensinogen in activated astrocytes of the white matter. The upregulation of renin and angiotensinogen resulted in increased NADPH oxidase activity, oxidative stress, glial activation, white matter lesions, and spatial working memory deficits. Pretreatment or posttreatment of these mice with a direct renin inhibitor, aliskiren, or a superoxide scavenger, tempol, ameliorated the brain damage and working memory deficits [173].

3.5. Modulation of RAS Affects Cognitive Function. Furthermore, treatment with an angiotensin receptor blocker (ARB) ameliorates the cognitive impairment in mice fed a high-salt and cholesterol diet, or type 2 diabetic mice [174, 175]. ARBs were also shown to decrease BBB permeability in diabetic rats [176], suggesting that activation of the brain RAS is involved in the pathogenesis of cognitive impairment. On the other hand, long-term inhibition of RAS improves memory function in aged, low-salt-treated, normotensive, Dahl salt-sensitive (DSS) rats [177]. In yet another study, DSS/hypertensive rats with leakage of brain microvessels in the hippocampus showed impaired cognitive function with a parallel increase in brain Ang II levels and a decrease in mRNA levels of tight junctions (TJs) and collagen-IV in the hippocampus, indicating disruption of BBB. Olmesartan treatment decreased brain Ang II levels, restored mRNA expression of TJs and collagen-IV, and restored the cognitive decline without altering the blood pressure [178]. It is assumed that Ang II stimulates the production of proinflammatory cytokines and activates matrix metalloproteinases (MMPs), which are involved in TJ disruption and BBB permeability changes, leading to cognitive dysfunction [179–181]. It is important to mention that few ARBs can partially penetrate the BBB at very low concentrations and selectively inhibit central AT_1 receptors that may or may not be sufficient enough to regulate brain RAS.

Ang III (2–8) binds with similar affinity to the AT_1 receptor as Ang II and acts as an agonist. Therefore, it is believed that Ang III behaves similarly to Ang II in eliciting responses in brain as well as in cardiovascular tissues. Ang III appeared twice as effective as Ang II in stimulating the firing rate of certain neurons in hypothalamic paraventricular and supraoptic nuclei, ventrolateral medulla, and nucleus of the solitary tract [182]. These studies provide evidence in favor of the pathophysiological overexpression of some of the RAS components in impairing cognitive function in experimental animal models and the beneficial effects of RAS inhibitors and blockers in ameliorating the cognitive decline.

Recently several large clinical studies [158, 183] have reported that antihypertensive drugs that modulate the RAS, that is, RAS blockers, such as angiotensin receptor blockers [ARBs] or angiotensin-converting enzyme [ACE] inhibitors, are associated with a decreased incidence of AD and reduced rates of cognitive decline in patients with mild cognitive impairment [184]. The RAS is implicated in hypertension and adipose tissue metabolism [185] and has recently attracted interest because of its potential involvement in the pathogenesis of AD [184]. The RAS exerts its effects through the generation and action of angiotensin II, which has potent vasoconstrictor, antinatriuretic, and dipsogenic properties. Angiotensin II is generated by the serial cleavage of angiotensinogen, first by renin and then by ACE. Angiotensin II exerts its well-known hypertensive

effects by binding to its two receptors (AT_1R and AT_2R) [145]. A potential relation between ACE and AD was first suggested by human genetic studies, which reported that an insertion/deletion polymorphism within intron 16 of the *ACE* gene is associated with AD [186]. In addition to vascular systems, accumulating evidence suggests that the brain has certain components of the RAS that may have crucial roles in learning and memory processes [177, 187]. For example, ACE is upregulated in the hippocampus, frontal cortex, and caudate nucleus of patients with AD [188, 189]. In adipose tissues, angiotensin II participates in adipocyte growth, differentiation, and metabolism, thereby reducing adiponectin secretion [190]. Treatment with RASB thus substantially increases adiponectin levels and may improve insulin sensitivity in hypertensive patients [191]. Therefore, RASB has been recently recommended as the antihypertensive drug of choice for Japanese patients with metabolic syndrome [192]. Because metabolic syndrome is one of the nongenetic risk factors for AD, RASB also may affect cognitive function beneficially by improving insulin resistance. In a recent retrospective study of Alzheimer's disease patients with and without hypertension, it was reported that RAS blockers in hypertensives showed increased visceral fat accumulation, adipocytokine secretion, and improved cognitive function [193]. In addition to endocrinological effects, direct effects of RASB on the central nervous system have been reported. RASBs decrease the production of angiotensin II, which inhibits potassium-mediated release of acetylcholine [150], BBB maintenance [194], and cell survival via AT_1R and AT_2R receptors [195]. These effects of RASB on brain RAS may improve neuronal metabolic functions and, consequently, decrease cognitive impairment in patients with AD.

Targeted disruption of the Mas protooncogene led to an increased durability of LTP in the dentate gyrus, without affecting hippocampal morphology, basal synaptic transmission, or presynaptic function. The permissive influence of Mas deletion on hippocampal synaptic plasticity was paralleled by behavioral changes such as anxiety behavior [196, 197]. In addition, cell numbers in the hippocampus are not changed in Mas-KO mice compared to their WT in contrast to that in AT_{1A}- and AT_2-deficient mice [198]. Direct effect of Ang 1–7 on limbic plasticity studies in WT and Mas-KO mice showed for the first time that Ang 1–7 enhances LTP in the hippocampus, which was abolished by Mas receptor antagonist A779, suggesting a role for Ang 1–7 in modulating learning and memory. Mas-KO mice exhibited more robust LTP than WT mice, without any change in the cell numbers and AT_1 receptor density or distribution in the hippocampus [198]. It has been demonstrated that Mas interacts with AT_1 receptor and inhibits the actions of Ang II, thus being a physiological antagonist of AT_1 receptor [199, 200].

The ability of angiotensin-converting enzyme (ACE) inhibitors to facilitate cognitive processes and to improve emotional feeling in patients [126, 201] may be, therefore, not only related to reduced availability of Ang II but might be also due to an increase in the level of Ang 1–7. Consequently, the pharmacological stimulation of ACE2/Ang 1–7/Mas axis could be a new promising target for the improvement of learning and memory in the older population but also in young patients with learning deficits. Brain-specific overexpression of ACE2 (neuron-targeted) effectively reversed the effects of chronic administration of Ang II, preventing neurogenic hypertension and enhancing drinking behavior in the Ang II "slow pressor" model. Infusion of a low concentration of Ang II is most effective at reaching the brain via the blood-brain barrier-deficient circumventricular organs and acting on nuclei controlling blood pressure rather than directly affecting peripheral vasculature, leading to neurogenic hypertension via increased sympathetic outflow [202]. In this model, it was shown that the pressor response to acute Ang II essentially involved ACE2-mediated Ang II hydrolysis and AT_1 receptor downregulation, further reducing Ang II downstream signaling [203], the reversal of neurogenic hypertension. Most importantly, blockade of Ang (1–7)/Mas receptors permitted the development of hypertension in this model, indicating that ACE2-expression-mediated decrease in neurogenic hypertension is indeed due to hydrolysis of Ang II to the form Ang(1–7), which in turn acted on Mas receptors. This is indeed supported by their observation that both Mas and AT_2 receptors were upregulated by ACE2 overexpression [204].

Central infusion of Ang IV facilitates memory retention and retrieval in rats in passive avoidance paradigms [205, 206]. Moreover, chronic infusions of the more stable analogue of Ang IV, Nle1-Ang IV, improved performance in rats in the spatial learning task, the Morris water maze [207]. In two rat models of memory deficit, induced by either scopolamine or bilateral perforant pathway lesion, the AT_4 receptor agonists reversed the performance deficits detected in the Morris water maze paradigm [207, 208]. It was shown recently that both Ang IV and LVV-H7 dose-dependently inhibited the catalytic activity of IRAP *in vitro* [79]. It was therefore proposed that the AT_4 ligands, Ang IV and LVV-H7, facilitate memory and enhance learning by binding to IRAP and inhibiting its enzymatic activity.

Animal studies have demonstrated that central ACE2 overexpression exerts a potential protective effect in chronic heart failure through attenuating sympathetic outflow. SYN-hACE2[SA] mice with brain selective overexpression of ACE2 subjected to permanent coronary artery ligation exhibited only a slight decrease in mean arterial pressure compared to WT mice and showed attenuated left ventricular end-diastolic pressure, decreased urinary norepinephrine excretion, and enhanced baroreflex sensitivity. The mice also exhibited lowered AT_1 receptor levels in medullary nuclei compared to WT CHF mice [209]. In a similar study, rats with chronic heart failure showed decreased expression of ACE2, Ang 1–7 receptor, Mas, and neuronal nitric oxide synthase (NOS) within the paraventricular nucleus. Overexpression of ACE2 using an adenovirus (AdACE2) significantly improved ACE2 levels and nNOS expression and attenuated the sympathetic outflow in chronic heart failure [210]. These data clearly suggest that ACE2 overexpression in the brain can attenuate neurogenic hypertension partially by preventing the decrease in both spontaneous barorelflex sensitivity and parasympathetic tone, which are mediated by enhanced NO release in the brain resulting from Mas and AT_2 receptor upregulation [204].

4. Summary and Conclusions

Cognition, therefore, is a not a unitary phenomenon as it is a complex of multiple integrated neurological and behavioural activities of which renin-angiotensin system has ample documentation as a key player. The therapeutic control of cognition remains an important and complex challenge. Patients suffering from mild cognitive impairment, Alzheimer's disease, and cognitive impairments from a host of other insults such as schizophrenia, Parkinson's disease, and neural trauma are all potential candidates for improved therapies. Therefore, it has been argued that a compound that positively modulates RAS systemically or locally in the brain would be valuable in correcting cognitive deficiencies for which these functions were reduced. Upregulation of ACE2 and increased balance of Ang 1–7/Ang II, along with positive modulation of Ang II signaling through AT_2 receptors and Ang 1–7 signaling through Mas receptors, may be an appropriate strategy for improving cognitive function and in treating dementia.

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