The renin-angiotensin system in neurodegenerative diseases

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Summary

The renin-angiotensin system (RAS) is mainly responsible for the regulation of fluid homeostasis and blood pressure. In addition to the peripheral RAS, a locally acting RAS including all components such as angiotensinogen, angiotensin-converting enzyme (ACE), angiotensin (Ang) peptides I–IV, and angiotensin receptors has been identified in the brain. The brain RAS, especially Ang II acting as a neuromodulator, effects hormone secretion, drinking behaviour and neurotransmitter release, especially noradrenaline and acetylcholine. Ang II and IV, as well as Ang IV receptor agonists, have distinct cognitive effects, and brain RAS alterations in Alzheimer's disease (AD) and other neurodegenerative diseases suggest a role for the brain RAS in the pathology and clinical symptoms of these maladies. In the present review the role of ACE inhibitors and angiotensin receptor-based therapeutic strategies are discussed to evaluate the cognitive enhancing effects of RAS components.

Key words: renin-angiotensin system; angiotensin-converting enzyme; angiotensin; cognition; Alzheimer's disease

The renin-angiotensin system (RAS) is a complex enzymatic pathway generating several active peptides which control fluid homeostasis, blood pressure and hormone secretion, as well as behavioural and cognitive responses [1]. Renin, a proteolytic enzyme released from the juxtaglomerular apparatus of the kidney when arterial blood pressure decreases, acts on the inactive precursor angiotensinogen to form the decapeptide angiotensin (Ang) I. Ang I, in turn, is hydrolysed by the action of angiotensin-converting enzyme (ACE), a zinc metalloproteinase, at the carboxy terminal to form the active octapeptide Ang II. ACE, which is present in the endothelial cells of the blood vessels, has an additional effect of degrading bradykinin, an active vasodilator. In further steps of angiotensin metabolism Ang II is converted to the heptapeptide Ang III by the enzymatic action of aminopeptidase A. Ang III, on the other hand, is cleaved by aminopeptidase B to form Ang IV. Finally, Ang IV is degraded by aminopeptidase N and dipeptidylaminopeptidase.

Ang II is a potent vasoconstrictor peptide with different physiological actions. It has not only peripheral effects, but also induces a centrally mediated hypertensive response [2]. Today it is well established that Ang II exerts a number of central actions modulating autonomic nervous system activity, the hypothalamic-pituitary-adrenal axis, vasopressin secretion, stimulation of thirst and baroreflex control, and thus has antidepressant, anxiolytic and cognitive effects with impact on learning and memory [3, 4]. Also Ang IV has been implicated in the modulation of exploratory behaviour and processes attributed to learning and memory [5].

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Angiotensin peptides exert their functions through specific receptors, namely AT_1 (AT_{1A} and AT_{1B}), AT_2, AT_3 and AT_4 [1, 6]. The AT_{1A} receptor subtype is a G-protein-coupled receptor with signalling via phospholipase-C and calcium. It is also coupled to intracellular signalling cascades which regulate gene transcription and the expression of proteins that mediate cellular proliferation and growth [6]. The recently discovered AT_{1B} subtype is approximately 92–95% homologous with AT_{1A}. The AT_{1A} subtype appears to be chiefly responsible for the classic functions of the RAS. It has been suggested that AT_2, probably also a G-protein-coupled receptor, is involved in brain development, apoptosis, vascular growth, blood flow control and NMDA receptor modulation [1]. An AT_3 angiotensin-binding site is also identified which causes marked cGMP stimulation, but so far it has not been possible to attribute a physiological function to it. Finally, a separate and distinct binding site for Ang IV was identified and classified as the AT_4 subtype [6]. The identity and signalling mechanism of AT_4 has yet to be determined.

The brain renin-angiotensin system

Active components of the RAS, such as Ang II, do not cross the blood–brain barrier and can exert their actions only in brain regions, such as circumventricular areas, that lack the blood–brain barrier [1]. The peripheral Ang II acts on subfornical organ and area postrema regulating salt appetite, thirst, vasopressin secretion and blood pressure increase.

Beyond their peripheric effects all components of the RAS exist in the brain acting locally. Renin, angiotensinogen, Ang I, Ang II, ACE and angiotensin-binding sites have been identified in the brain. Ang II is localised in the basal ganglia, cortex, hypothalamus, thalamus, brainstem, ocular tissues and cerebellum, and Ang-binding sites are present in the forebrain, substantia nigra, basal ganglia, cerebellum, cortex, thalamus and hippocampus [1, 7–10]. Thus it has been suggested that Ang II in the brain acts as a neuromodulator regulating thirst, drinking behaviour, antidiuretic hormone secretion, facilitating vasopressor effects and secretion of adrenocorticotrophic and luteinising hormones as well as regulating noradrenaline and acetylcholine release. The heaviest brain distributions of the AT_4 receptor subtype, on the other hand, are in neocortex, hippocampus, amygdala and nucleus basalis of Meynert [6], all regions with high impact for cognitive processes.

Cognitive and behavioural effects of renin-angiotensin system components

The cognitive effects of Ang II are well recognised. Ang II inhibits acetylcholine release in fresh tissue slices of human temporal cortex [11] and rodent amygdala [12]. In addition, it suppresses long-term potentiation (LTP) in the hippocampus and amygdala of rats, which is mediated by the AT_1 receptor [12]. Ang II has also been found to interfere with memory acquisition in research animals [6]. Ang II administered in the brain disrupted an operant task in rabbits. Since AT_1 receptor is a major target for antihypertensive drugs, ACE inhibitors, which reduce the conversion of Ang I to Ang II, facilitate cognitive functioning, probably by decreasing Ang II and thus removing inhibitory influence upon acetylcholine release [6, 13]. ACE inhibitors in particular, such as captopril and perindopril, which effect 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 [14].

Also, the activation of AT_4 receptor by native Ang IV or AT_4 agonists improves learning and memory [6]. Central administration of Ang IV in rodents stimulates exploratory locomotor behaviour, enhances recall in passive avoidance situations and facilitates memory retention [1]. 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 [1].

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 [1, 15]. 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.

The brain renin-angiotensin system in Alzheimer's disease and other neurodegenerative diseases

An increase in ACE activity was reported in the cortex and caudate nucleus of patients with Alzheimer's disease (AD) [8, 16]. ACE immunoreactivity was found to be increased not only in neuronal locations but also in perivascular tissue, probably because of the severe amyloid angiopathy found in cerebral vessels. In addition, AT receptors and Ang II were increased in AD striatum, parietal cortex and hippocampus, these being typically affected in AD patients [7–9], suggesting augmented brain RAS activity during the disease process. The increased perivascular Ang II activity may again point to an underlying vascular pathology.

RAS receptor alterations have been identified in different neurodegenerative disorders, especially in Parkinson's disease (PD) and Huntington's chorea (HC) [17]. AT_1 receptor was found to be reduced in the basal ganglia and substantia nigra of PD patients and in the putamen of HC patients. AT_2, on the other hand, was decreased in the caudate nucleus of PD patients and increased in HC patients. It has been suggested that RAS receptors are principally localised on basal ganglia neurons which undergo degeneration during the disease process, and these neurons are probably dopaminergic [17]. The brain RAS seems to contribute to the pathology of the dopaminergic nigrostriatal pathway in these patients.

Renin-angiotensin system genes in Alzheimer's disease

Most studies on RAS-gene and AD association have focussed on ACE1, the gene that encodes ACE [18]. A common Alu (indel) insertion(I)/deletion(D) polymorphism (rs1799752) in intron 16 of ACE1 studied in the context of hypertension research was found to be associated with plasma ACE level, whereas the homozygosity for the D allele was associated with the highest plasma ACE levels. In the CSF, on the other hand, ACE protein levels were found to be significantly decreased in AD cases, especially in individuals with the genotype I/I [19]. Although initial studies showed no clear association between ACE1 indel polymorphism and increased risk of AD, later a large study demonstrated significant consistent evidence across three independent case-control cohorts [20]. Recent meta-analyses support the hypothesis of a modest contribution by ACE1 variation to the risk of developing AD [18]. ACE1 variants have been found to be associated with Aβ1-42 concentration, earlier onset of AD and smaller hippocampal and amygdalar volumes. But there are also studies showing no relationship between ACE genotype and either Aβ load or cerebral amyloid angiopathy [21]. Hence the relationship of ACE1 variants to AD risk remains unclear and it has been suggested that the ACE1 contributes to AD pathology indirectly through interaction with other genes. At the moment, none of the genome-wide associated studies of single nucleotide polymorphisms has found strong evidence to support direct ACE1 involvement in AD.

Can angiotensin-converting enzyme inhibitors affect the progression of dementia?

Since hypertension appears to contribute to the development of dementia, including both AD and vascular dementia (VaD), ACE inhibitors such as antihypertensive drugs (captopril, enalopril, lisinopril, perindopril) may alter the incidence and progression of the disease [22]. Indeed, the systematic review of randomised controlled trials suggested that ACE inhibitors reduce the progression of AD by slowing cognitive decline and the incidence of VaD and unspecified dementia [22]. In particular, brain-penetrating ACE inhibitors such as captopril and perindopril appeared to have neuroprotective activities beyond their antihypertensive properties. Stabilisation of cognitive function by ACE inhibitors has also been reported in patients with mild cognitive impairment, a clinical state which can precede AD [23].

As discussed above, reduction of Ang II synthesis by ACE inhibitors can facilitate cognitive functioning by removing the inhibitory action of Ang II on acetylcholine release. In addition, ACE inhibitors may improve cognitive

performance by reducing the occurrence of vascular pathology following haemorrhagic and ischaemic cerebrovascular accidents [24].

Today it is well known that ACE inhibitors can also directly affect AD pathology, since ACE has been found to regulate the generation of amyloid-β peptide (Aβ) [6, 25]. Extracellular deposition of Aβ to plaque formations is one of the most important pathological hallmarks of AD, and excessive formation of Aβ is mainly responsible for neurotoxicity. Whereas the 42 peptides-long Aβ (Aβ1-42) plays a causative role in the development of AD pathology, the 40 peptides-long Aβ (Aβ1-40), which is the predominant secreted form of Aβ, has been reported to have neuroprotective effects and to inhibit amyloid deposition [25]. ACE retards Aβ aggregation, fibril formation and deposition, and inhibits neurotoxicity [26]. These neuroprotective effects of ACE could be blocked by the application of ACE inhibitors. In addition, ACE facilitates the conversion of Aβ1-42 to Aβ1-40, and its inhibition with current ACE inhibitors enhances brain Aβ1-42 deposition [25]. It has recently been shown that ACE has two homologous domains, each having a functional active site, and whereas the N-domain is responsible for the Aβ1-42 to Aβ1-40 converting activity, the C-domain of ACE is associated with angiotensin-converting activity [25]. Novel ACE inhibitors developed as an antidementia therapeutic strategy may be designed to specifically target the angiotensin-converting C-domain, without inhibiting Aβ converting activity. In a recent study the ambiguous effect of ACE inhibitors in dementia prevention was related to the fact that brain ACE is not specific for Ang I [27]. Since brain ACE also catabolises cognition-enhancing brain peptides and amyloid peptides and converts toxic Aβ1-42 into less toxic Aβ1-40, it has been suggested that ACE inhibitors have short-term cognition-enhancing properties and may increase the Aβ1-42 burden and cognitive decline in the long term [27].

AT_1 and AT_4 receptor-based therapeutic strategies

Review of cohort studies and clinical trails evaluating antihypertensive drugs in the prevention of cognitive decline showed that two antihypertensive drug classes have greater protective effect: dihydropyridine calcium-channel blockers and AT_1 receptor blockers [27, 28]. It has been suggested that AT_1 receptor blockers have greater cognition protecting effects than ACE inhibitors, as they share with ACE inhibitors cognition-enhancing effects directly linked with a common AT_1-blunting effect [27]. In addition, they increase Ang II and Ang IV formation and therefore stimulate non-opposed AT_2 and AT_4 receptors, whose activation in cognitive processes is well established.

Recent studies indicate that many of the cognitive facilitating effects initially attributed to Ang II may be through Ang IV acting on AT_4 receptor [6]. According to this hypothesis ACE inhibitors improve cognitive processing in that increased Ang I levels are probably converted to other angiotensin peptides such as Ang(1-9) which then are converted to Ang II, III, IV and Ang (3-7). It has been assumed that several observations and research findings may be relevant to the interpretation of this model of how AT_4 activation may facilitate cognition: as mentioned above, the main localisations of AT_4 in the brain are in those regions highly relevant for cognitive processes. In addition, AT_4 has the ability to facilitate LTP, separate from NMDA-dependent LTP, which suggests a non-glutamatergic pathway, and AT_4 activation causes a rapid and salient cell signalling event by increased internalisation of calcium [6]. Thus, a neural plasticity function and controlling effects on dopamine release have been attributed to Ang IV analogues. All these effects make AT_4 receptor a novel therapeutic target in cognitive processing. Therefore the development of Ang IV analogues and AT_4 agonists may definitively establish RAS-generated compounds in cognitive therapy.

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