BJP BRITISH JOURNAL OF PHARMACOLOGY

BPS BRITISH PHARMACOLOGICAL SOCIETY

British Journal of Pharmacology (2010), 159, 1392–1401

0007-1188/10
www.brjpharmacol.org

REVIEW

Physiological and pathophysiological functions of different angiotensins in the brain

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The renin–angiotensin system (RAS) is better known for its role in the control of blood pressure, but evidence obtained from animal experiments and clinical trials suggests that it is involved in complex brain functions. It is now well accepted that neuronal AT_1 receptors mediate the stimulatory actions of angiotensin II regarding blood pressure and the intake of water and salt. In contrast, neuronal AT_2 receptors have been implicated in the stimulation of apoptosis and as being antagonistic AT_1 receptors. Angiotensin-(1-7) [Ang-(1-7)] mediates its antihypertensive effects by stimulating synthesis and release of vasodilator prostaglandins and nitric oxide. New data concerning the receptor types binding angiotensin IV or Ang-(1-7) also support the existence of complex site-specific interactions between multiple angiotensins and multiple receptors in the mediation of important central functions of the RAS. Different angiotensin receptors (AT_1, AT_2, AT_4, Mas) are also present in memory-relevant structures. The effects of different angiotensins on cognition initiated the search for their mechanisms of action. Studies looking for a possible link between the RAS and brain disorders (stress, anxiety, depression, alcohol abuse, epilepsy, Alzheimer's disease) either inherited or acquired have been reviewed. The therapeutic potential of different angiotensins, as well as the potential use of agents known to influence the RAS, will be considered.
British Journal of Pharmacology (2010) **159,** 1392–1401; doi:10.1111/j.1476-5381.2010.00648.x; published online 5 March 2010

Keywords: angiotensin II; angiotensin IV; angiotensin-(1-7); receptors; learning; long-term potentiation; depression; degenerative diseases; polymorphism

Abbreviations: ACE, angiotensin-converting enzyme; ACEI, angiotensin-converting enzyme inhibitor; AD, Alzheimer's disease; AMP, aminopeptidase; Ang I, angiotensin I; Ang II, angiotensin II; Ang III, angiotensin III; Ang IV, angiotensin IV; Ang-(1-7), angiotensin-(1-7); CNS, central nervous system; HFS, high-frequency stimulation; HPA, hypothalamic–pituitary–adrenocortical; IRAP, insulin-regulated aminopeptidase; LTD, long-term depression; LTP, long-term potentiation; LVV-H7, leucine–valine–valine–hemorphin-7; NEP, neutral endopeptidase (neprilysin); NMDA, *N*-methyl-D-aspartate; NO, nitric oxide; (P)RR, (pro)renin receptor; RAS, renin–angiotensin system; TLE, temporal lobe epilepsy

Formation of active angiotensins in the brain

It is now well known that a complete brain renin–angiotensin system (RAS) exists, which is distinctly separated from the peripheral system and comprises all necessary precursors and enzymes required for the formation and metabolism of the biologically active forms of angiotensin. Although typically assumed to function entirely in the interstitium, there is evidence that various components of the RAS are formed intracellularly (Grobe *et al.*, 2008). As shown in Figure 1, angiotensinogen is the precursor of the decapeptide angiotensin I (Ang I), which is cleaved by renin. The presence of the (pro)renin receptor [(P)RR] has been identified in the brain (Shan *et al.*, 2008; Contrepas *et al.*, 2009), and it is able to bind both renin and prorenin, resulting in an activity increase for both enzymes, thus leading to enhanced formation of Ang I. Through the activity of the angiotensin-converting enzyme (ACE), Ang I is hydrolysed at its carboxy terminus, leading to the generation of the octapeptide angiotensin II (Ang II). Other functions of ACE comprise degradation of bradykinin and substance P. Ang II is not only generated in the brain via this classical pathway, using renin and ACE, but can also be produced directly from angiotensinogen by cathepsin G or tonin (Lippoldt *et al.*, 1995). Aminopeptidase A converts Ang II into a 2–8 fragment, named angiotensin III (Ang III). This peptide is cleaved by aminopeptidase N to form the neuroactive 3–8 hexapeptide fragment of Ang II, named angiotensin IV (Ang IV), with the amino acid sequence Val-Tyr-Ile-His-Pro-Phe (Lavoie and Sigmund, 2003). Alternatively, Ang IV may also be formed by aminopeptidases acting on Ang I prior to the conversion to Ang II by ACE (Ardaillou and Chansel,

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Received 6 July 2009; revised 30 October 2009; accepted 4 November 2009

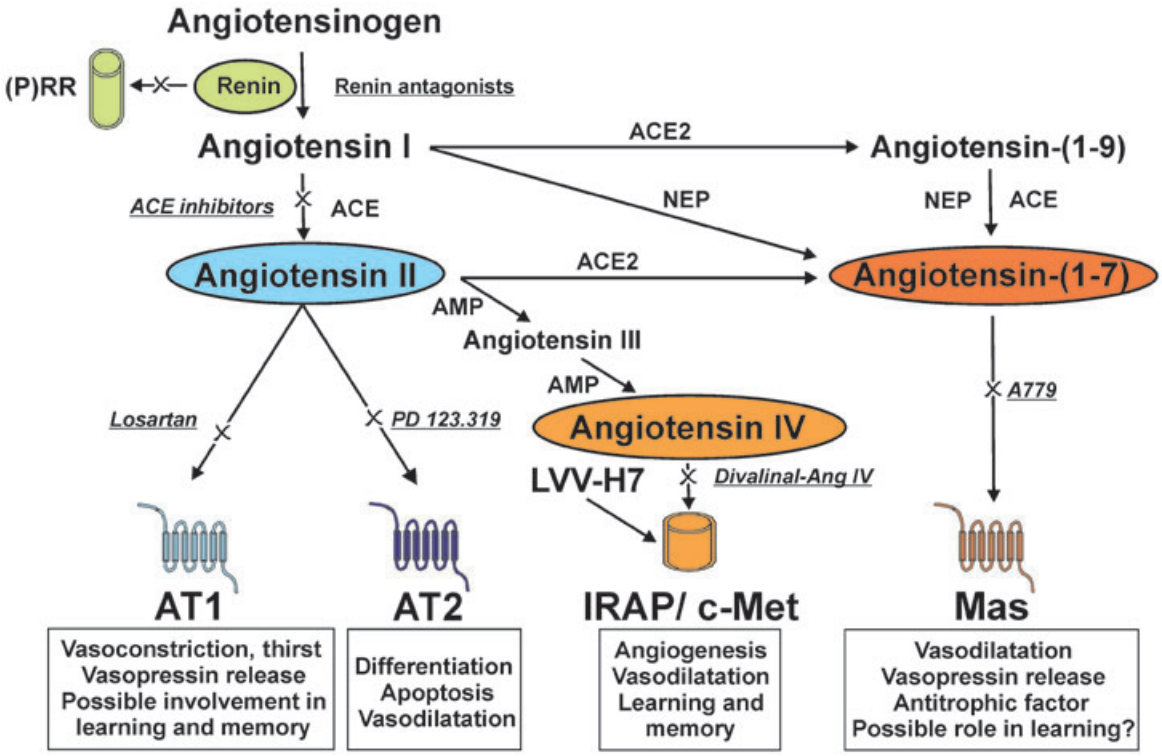

Figure 1 RAS in the brain: simplified schematic illustration showing the formation of functionally active components of RAS and involved receptors. Not shown that Ang III acts on AT1 and AT2 receptors. LVV-H7, leucine–valine–valine–hemorphin-7; underlined: examples of receptor antagonists. Essential functions in the brain are also mentioned.

1997) or may be generated by the activity of aminopeptidase A and N directly from Ang II (Lavoie and Sigmund, 2003). Angiotensin-(1-7) [Ang-(1-7)] can either be formed by cleavage of Ang I via prolyl endopeptidases (Chappell *et al.*, 1990; Hallberg and Nyberg, 2003) or by cleavage of the phenylalanine residue of Ang II via carboxypeptidase P. At the start of the new century came the discovery of a new homologue of ACE, called ACE2, and studies suggest that ACE2 is more active in the brain than ACE (Elased *et al.*, 2008). ACE2 metabolizes Ang II to Ang-(1-7), while neprilysin [neutral endopeptidase (NEP)] generates Ang-(1-7) from Ang I. ACE2 seems not essential for baseline blood pressure regulation, but becomes important in pathophysiological situations, when it protects tissue from the actions of Ang II by locally degrading this peptide and generating Ang-(1-7) (Alenina *et al.*, 2008). Thus, ACE2 may play a pivotal role in the RAS by controlling the balance between the vasoconstrictor effects of Ang II and the vasodilatory properties of the Ang (1-7) (Lazartigues *et al.*, 2007). Further details of enzymatic pathways and their role in the formation and degradation of the growing number of active angiotensins in the brain are described elsewhere (Karamyan and Speth, 2007). It has become clear that the simplified view of the RAS shown in Figure 1 cannot fully explain the physiological complexity of the system in health and disease.

However, the literature strongly suggests the idea that not only Ang II may act as a neurotransmitter in the brain, but Ang IV and Ang-(1-7) as well (Ferrario *et al.*, 1990; Pickel and Chan, 1995; Bai and Renaud, 1998; Allen *et al.*, 2009).

Angiotensin receptor subtypes (AT_1, AT_2, AT_4, Mas) are involved in different functions

Ang I is considered inactive, while Ang II and Ang III are full agonists at the AT_1 and AT_2 receptor subtypes in accordance with the nomenclature (*Guide to Receptors and Channels*, Alexander *et al.*, 2008). The brain contains high densities of AT_1 receptors, localized mainly to specific nuclei within the hypothalamus and brainstem regions. AT_1 receptors are further subgrouped in the rodent brain into AT_{1A} and AT_{1B} receptors. Centrally administered AT_1 receptor antagonists or angiotensinogen antisense oligonucleotides inhibit sympathetic activity and reduce arterial blood pressure, as well as disrupt water drinking and sodium appetite, vasopressin secretion, sodium excretion, renin release and thermoregulation (McKinley *et al.*, 2003; Saavedra, 2005). These different functions of the G-protein-coupled AT_1 receptor occur by wide variety of signalling pathways (reviewed in Sayeski *et al.*, 1998; Sumners *et al.*, 2002). Brain angiotensins seem to be not essential for the adequate functioning of neural pathways mediating osmoregulatory thirst. However, Ang II of either peripheral or central origin is probably necessary for thirst and salt appetite that results from hypovolemia (McKinley *et al.*, 2008). In addition, brain-selective over-expression of AT_1 receptors results in an enhanced salt appetite and altered water intake (Lazartigues *et al.*, 2008). Studies in knock-out mice also indicate that the central effect of Ang II on alcohol consumption is mediated by AT_1 receptors, whereas AT_2 receptors and the bradykinin B_2 receptors were not involved (Maul *et al.*, 2005).

These data support earlier reports that the AT_1 receptor antagonist losartan can effectively block some of the intoxicating effects of low doses of ethanol in rats (Wayner *et al.*, 1994). Recently, it has been shown that while expression of angiotensin AT_1 receptors on striatal neurons of mice has no impact upon basal alcohol consumption or preference, AT_1 receptors do modulate the sensitivity of dopamine D_2 receptors to regulation by alcohol and the ability of a D_2 receptor antagonist to reduce consumption (Moore *et al.*, 2007).

Besides the abundant representation of AT_1 receptors in the adult brain, AT_2 receptors are expressed in high density mainly in the neonate brain (Reagan *et al.*, 1994), and stimulation of AT_2 receptors by Ang II provokes apoptosis (Shenoy *et al.*, 1999). Therefore, most reports concerning this receptor subtype suggest a role in differentiation and development. Some of the actions of the AT_2 receptor are even directly opposed to those of the AT_1 receptor, especially concerning the growth- and differentiation-modulating actions of Ang II (von Bohlen und Halbach *et al.*, 2001). Recent results encompassing different studies underline the crucial role of AT_2 in normal brain function, and that dysfunction of the receptor has impact on brain development and ultrastructural morphology with distinct consequences on learning and memory (Maul *et al.*, 2008; Abdalla *et al.*, 2009b).

There is convincing evidence that subsequent to binding at the AT_1 receptor, Ang II undergoes endocytosis and is degraded to Ang IV (Wright and Harding, 2008). The distribution of AT_4 receptors with a significant association with cholinergic neurons, motor and sensory nuclei in the brain suggests that Ang IV may modulate central motor and sensory activities, as well as memory (Vauquelin *et al.*, 2002; Albiston *et al.*, 2004; De Bundel *et al.*, 2008; Wright *et al.*, 2008). It is a well-known fact that, in addition to the effects of Ang IV on blood pressure, Ang IV enhances acquisition, consolidation and recall in animal learning and memory models (for review, see Gard, 2008; Wright and Harding, 2008). The stimulation of AT_4 receptors can potentiate depolarization-induced release of acetylcholine from hippocampal slices (Lee *et al.*, 2001). These memory-improving effects of Ang IV are not only dependent on the cholinergic system (Wilson *et al.*, 2009), but also on the functional integrity of dopamine receptors (Braszko, 2009). Now, it is also clear that the facilitation of learning and improvement of memory observed after an intracerebroventricular injection of Ang II is, in fact, caused by its derivative Ang IV (Braszko *et al.*, 2006).

In 2001 it was discovered that the AT_4 receptor seems to be an insulin-regulated aminopeptidase (IRAP) (Albiston *et al.*, 2001) that co-distributes with the GLUT4 transporter. IRAP is known to cleave oxytocin, vasopressin and other biologically active peptides such as Ang III. The endogenous peptide LVV-hemorphin-7, which is structurally unrelated to Ang IV, but known to bind to AT_4 receptors (Moeller *et al.*, 1997), inhibits the enzymatic activity of IRAP *in vitro*, similar to Ang IV (Albiston *et al.*, 2004). There is presently a dispute over the identity of Ang IV receptor either as IRAP or the growth factor receptor c-Met (Stragier *et al.*, 2008; Wright *et al.*, 2008; Vanderheyden, 2009). This type I tyrosine kinase receptor has attracted considerable attention because of its ability to blunt neurodegenerative changes, and its potential involvement in learning and memory mechanisms.

Several studies have shaped the hypothesis that Ang-(1-7) acts through a specific receptor. Recently, a G-protein-coupled receptor, Mas, encoded by the *Mas* protooncogene, has been identified as possible receptor for Ang-(1-7) (Santos *et al.*, 2003). It has been demonstrated that the receptor for Ang-(1-7), Mas is predominantly present in neurons in many regions of the brain. An abundant labeling was found in the hippocampus, amygdala, anterodorsal thalamic nucleus and cortex (Becker *et al.*, 2007). The function of Ang-(1-7) includes release of vasopressin, nitric oxide (NO), prostaglandin and the facilitation of baroreceptor reflex sensitivity (Santos *et al.*, 2000). Considering Mas as one of the receptors for Ang-(1-7), it is important to note that Mas can hetero-oligomerize with the AT_1 receptor, and, by doing so, inhibits the actions of Ang II (Kostenis *et al.*, 2005). This is a novel demonstration of a G-protein-coupled receptor acting as a physiological antagonist of a previously characterized receptor. These data also support our results obtained from the amygdala. We analysed whether field potentials are altered by Ang II in brain slices. Opposite actions of Ang II were obtained in mice lacking the *Mas* protooncogene, in comparison to wild-type mice. The use of different angiotensin receptor antagonists provided the *in vitro* evidence for a functional interaction between Mas and the AT_1 receptor (von Bohlen und Halbach *et al.*, 2000). Santos *et al.* (2007) reported that these two receptors are co-localized and therefore might form dimers. The authors also showed how Mas receptor expression uncouples the wild-type AT_1 receptor from the G-protein. Consequently, the AT_1–Mas complex could be of great importance as a target for pharmacological intervention in cardiovascular diseases. Besides the functional coupling between the AT_1 receptor and Mas, other seven transmembrane receptor heterodimers were described in the RAS. A detailed description of the current data on RAS receptor heterodimerization (AT_1/AT_2, AT_1/Mas, AT_1/dopamine D1-D3-D5 and endothelin B receptors) has been reviewed by Lyngso *et al.* (2009).

Whereas Ang II, Ang IV and Ang-(1-7) mainly cause an increase in discharge rates of neurons (Ferrario *et al.*, 1990; Albrecht *et al.*, 1997a,b, 2000; Albrecht, 2007), discharge rate is inhibited by renin acting on (P)RR (Shan *et al.*, 2008).

It still remains to be established if there is a non-AT_1, non-AT_2 receptor as suggested recently (Karamyan *et al.*, 2008), and if Ang III is the real ligand for the AT_1 receptor in the brain. Recent data (Kokje *et al.*, 2007) do not support the Ang III hypothesis, and suggest that conversion of exogenously applied Ang II to Ang III is not necessary to cause brain-mediated pressor or dipsogenic responses.

Neuronal plasticity – long-term potentiation (LTP) and depression (LTD)

Synaptic plasticity is a fundamental process underlying learning and memory formation. LTP and LTD are the predominant experimental models used for studying the mechanisms of synaptic plasticity. The hippocampus is known to be involved in a variety of learning tasks, especially spatial learning, whereas the lateral nucleus of the amygdala is considered as a putative locus associated with conditioned and

unconditioned stimuli during fear conditioning. The hippocampus and the amygdala receive angiotensinergic synaptic inputs, which have the capacity to either promote or restrict the induction and/or expression of long-term plasticity. Besides central pathways controlling thirst and blood pressure (Lenkei *et al.*, 1997), Ang II immunoreactive nerve fibres have been also identified in memory relevant brain structures (von Bohlen und Halbach and Albrecht, 1998). We were also able to demonstrate specific Ang IV binding sites in the forebrain of mice, in particular in the cortex, hippocampus and amygdala (von Bohlen und Halbach and Albrecht, 2000).

While much literature exists describing the effects of different angiotensins on LTP, as well as the underlying mechanisms and implications for animal behavior, publications describing the role of angiotensins in LTD remain scarce. Injection of Ang II just above the CA1 field in intact anaesthetized rats has been shown to block the induction of LTP in perforant path-stimulated dentate granule cells (Denny *et al.*, 1991). Further experiments demonstrated that this inhibition can be blocked by the administration of AT_1 receptor antagonists (Wayner *et al.*, 1993). These results have been confirmed in hippocampal brain slices (Armstrong *et al.*, 1996). Similarly, we have shown that Ang II induces an AT_1-mediated inhibition of high-frequency stimulation (HFS)-induced LTP in the lateral nucleus of the amygdala (von Bohlen und Halbach and Albrecht, 1998). In addition, the suppressive effect of Ang II could not be shown in AT_1-deficient mice. Because NMDA receptors are involved in the mediation of LTP in the CA1 region of the hippocampus and the lateral amygdala, and because we could demonstrate an inhibitory action of Ang II on NMDA-induced neuronal excitation in the lateral nucleus of the amygdala (von Bohlen und Halbach and Albrecht, 2006), an interaction of Ang II with NMDA receptors might be supposed. In contrast to LTP, Ang II suppresses LTD in the amygdala through the involvement of L-type calcium channels (Tchekalarova and Albrecht, 2007).

The Ang IV and Ang-(1-7)-induced plasticity changes in limbic structures seem not to be mediated by the involvement of NMDA receptors. Ang IV induces facilitation of hippocampal CA1-LTP *in vitro* (Kramar *et al.*, 2001), whereas perfusion with an AT_4 antagonist, disrupts LTP stabilization in area CA1 (Davis *et al.*, 2006). Given the short half-life of native Ang IV, several laboratories have tested the high-affinity and metabolically more stable Ang IV analog Norleucine^1–Ang IV. It was demonstrated that increased calcium influx through postsynaptic calcium channels contributes to Norleucine^1–Ang IV-induced enhancement of LTP. In rat dentate gyrus, both Ang IV and Norleucine^1–Ang IV were shown to cause an enhancement of LTP *in vivo* (Wayner *et al.*, 2001). Moreover, ethanol-induced suppression of CA1-LTP could be attenuated with Norleucine^1–Ang IV (Wright *et al.*, 2003). Taken together, these experimental data strongly support an inhibitory influence of Ang II and a facilitative role of Ang IV on LTP in memory relevant structures.

We demonstrated for the first time that Ang-(1-7) reliably enhances hippocampal CA1-LTP and LTP in the amygdala. In Mas-deficient mice, Ang-(1-7) did not provoke an enhancement of hippocampal LTP (Hellner *et al.*, 2005). In contrast to Ang II and Ang IV, the effects of Ang-(1-7) on behaviour have not been examined in detail until now. Given that Mas encodes an Ang-(1-7) receptor, Ang-(1-7) may play a role in emotional behaviour. Mas-deficient mice displayed higher levels of anxiety (Walther *et al.*, 1998). In addition, we have shown that cell numbers are not changed in the hippocampus of *Mas*-knock-out mice compared to their wild-type littermates. In contrast, the cell number was reduced in AT_1- and AT_2-deficient mice (von Bohlen und Halbach *et al.*, 2001). Therefore, the more robust LTP in the dentate gyrus (Walther *et al.*, 1998) and in the CA1 region of the hippocampus in Mas-knock-out mice is unlikely to be due to morphological alterations. Our experiments showed that both NO and cyclooxygenase 2 are involved in the mediation of Ang-(1-7)-induced effect on LTP in the amygdala (Albrecht, 2007).

Cognition, Parkinson's and Alzheimer's disease (AD)

Cognitive enhancing action for the ACE inhibitors (ACEIs) has been demonstrated in a number of animal models for memory function (Costall *et al.*, 1989; Domeney, 1994; Nikolova *et al.*, 2000). For example, in active avoidance tasks, an ACEI improved learning in the second trial of the acquisition test and enhanced retention of memory when administered prior to training in mice (Raghavendra *et al.*, 2001). It was also reported that ACE inhibition can improve both basal and impaired performance in animal models of learning (Barnes *et al.*, 1992). Moreover, it has been shown that ACEIs improve cognition and depressed mood in hypertensive patients. Untreated hypertensive patients scored lower than normotensive controls in cognitive tests and significantly worse in cumulative recall and paired words association. When compared with normotensive subjects, untreated hypertensive patients also scored significantly higher on depression with anxiety. ACEIs reversed these deficits and blockade by losartan improved cognitive function, in particular immediate and delayed memory (Fogari *et al.*, 2003). The AT_1 receptor antagonist losartan also reverses the effects of ethanol on learning and memory (Tracy *et al.*, 1997). Moreover, blocking the RAS may reduce the risk of developing type 2 diabetes mellitus (Scheen, 2004; Leiter and Lewanczuk, 2005). These experiments have led to the hypothesis that the ability of ACE inhibitors to facilitate cognitive processes may be related to reduced availability of Ang II (Domeney, 1994), although a higher availability of Ang-(1-7) (Tom *et al.*, 2003) may also be a reason for the improvement of cognition in ACEI-treated patients. It has been concluded that although no class of antihypertensive agents presents a clearly superior effect over the others in terms of quality of life, the current impression is that ACEIs and Ang II receptor antagonists may offer some advantage, at least in regard to effects on cognitive function and sexual activity (Fogari and Zoppi, 2004). It is suggested that the continuous activation of the RAS impairs cognitive function via stimulation of the AT1 receptor with a decrease in cerebral surface blood flow and an increase in oxidative stress (Inaba *et al.*, 2009). In addition, previous results have shown that Ang II inhibits the potassium-stimulated release of acetylcholine from slices of the human temporal cortex (Barnes *et al.*, 1990). Besides the action of

Ang II on cognitive processes, it has been shown that activation of hippocampal AT_4 receptors can overcome the disruption of spatial memory accompanying treatment with the muscarinic receptor antagonist scopolamine (Pederson *et al.*, 2001). Thus, the interplay between the angiotensin receptor subtypes in influencing cognition and the mechanisms underlying the observed effects of ACE inhibition still need to be characterized.

In addition to the effects of RAS on cognition, treatment with ACEIs causes an improvement of the clinical features of moderately severe Parkinson's disease. The patients had a faster onset in their motor response to L-DOPA and a reduction in 'on phase' peak dyskinesia (Reardon *et al.*, 2000). The co-localization of ACE and AT_1 receptors in the substantia nigra, the caudate nucleus and putamen of human and rat brain, which contain the dopamine-synthesizing neurons, suggests that the central RAS might modulate central dopamine release (Zhuo *et al.*, 1998). In Parkinson's disease, there is a marked reduction of these receptors associated with the nigrostriatal dopaminergic neuron loss. It has been established that Ang II activates (via AT_1 receptors) NADPH-dependent oxidases, which are a major source of superoxide. ACEIs, commonly used in the treatment of hypertension, have shown antioxidant properties in several tissues (Lopez-Real *et al.*, 2005). Oxidative stress is a key contributor to the pathogenesis and progression of Parkinson's disease. In rat mesencephalic cultures, Ang II increased 6-hydroxydopamine-induced dopaminergic cell death, generation of superoxide in these neurons and microglial cells, the expression of NADPH-oxidase mRNA and the number of reactive microglial cells (Rodriguez-Pallares *et al.*, 2008). The authors concluded that Ang II, via AT_1 receptors, increases the dopaminergic degeneration process by amplifying the inflammatory response. In an *in vivo* study, rats were subjected to intraventricular injection of 6-hydroxydopamine which resulted in a bilateral reduction in the number of dopaminergic neurons and terminals. Injection of Ang II alone did not induce any significant effect. However, Ang II increased the toxic effect of 6-hydroxydopamine. Rats treated with an AT_1 receptor antagonist before injection of 6-hydroxydopamine (with or without exogenous administration of Ang II) showed a significant reduction in 6-hydroxydopamine-induced oxidative stress (lipid peroxidation and protein oxidation) and degeneration (Rey *et al.*, 2007). When compared to Ang II, Ang IV was only moderately effective in models of Parkinson's disease (Grammatopoulos *et al.*, 2007). Therefore, animal and human studies support the suggestion that the treatment with AT_1 antagonists or ACEIs may reduce the progression of Parkinson's disease. However, the hypothesis that the D allele of the *ACE* gene confers a protective effect with respect to Parkinson's disease could not be confirmed (Mellick *et al.*, 1999).

AD is also a neurodegenerative disorder characterized by severe memory and learning impairments. The loss of cholinergic neurons is believed to be a major contributory cause of the cognitive symptoms characteristic of AD. In AD patients, an up-regulation of different components of the RAS in the cortex has been found (Savaskan *et al.*, 2001).

ACE can also degrade beta-amyloid (Aβ) (Hemming and Selkoe, 2005), the pathological hallmark of AD, thereby inhibiting its aggregation. However, at least in mice, ACE deficiency did not alter steady-state Aβ concentration (Eckman *et al.*, 2006), whereas Aβ levels are significantly elevated in NEP knock-out mice. We found that while endogenous Aβ concentrations were elevated in the brains of NEP-knock-out mice, immunohistochemical analysis using monoclonal antibodies did not detect any Aβ deposits even in old NEP knock-out mice (24 months). Surprisingly, tests of learning and memory revealed that the ability to learn was not reduced in old NEP-deficient mice, but instead had significantly improved. Sustained learning and memory in the aged mice was congruent with improved LTP in brain slices of the hippocampus and amygdala. Our data suggest a beneficial effect of pharmacological inhibition of cerebral NEP on learning and memory in mice due to the accumulation of peptides other than Aβ degradable by NEP. By conducting degradation studies and peptide measurements in the brain of both genotypes, we identified two neuropeptide candidates, glucagon-like peptide 1 and galanin, as first potential candidates to be involved in the improved learning of aged NEP-deficient mice (Walther *et al.*, 2009). Data from different AD models suggest that ACE inhibitors do not cause Aβ accumulation *in vivo* (Hemming *et al.*, 2007). In contrast, it is known that ACEIs improve learning and memory in AD rats, which correlates with decreased ACE activity and delayed AD pathogenesis (Hou *et al.*, 2008). Analysis of the nitric oxide and antioxidant enzyme systems suggested that the protective effect is also related to an antioxidant action of the RAS inhibitors and a reduced formation of reactive oxygen species. Ang II inhibition might produce changes in the mechanisms of oxidative stress especially at the mitochondrial level. Prevention of mitochondrial decrease and/or damage would be related with the delay of the normal ageing process (Basso *et al.*, 2005). In addition, it has been also shown that AT2 receptor oligomers mediate G-protein dysfunction in an animal model of AD (Abdalla *et al.*, 2009a).

Several studies have documented that insertion/deletion (I/D) of DNA polymorphism at the intron 16 of *ACE* gene seems to be associated with late-onset AD (Crawford *et al.*, 2000; Yang *et al.*, 2000; Kehoe *et al.*, 2004; Tian *et al.*, 2004; Sleegers *et al.*, 2005). Other studies failed to replicate the positive association between the I allele and AD (Taylor *et al.*, 2001; Monastero *et al.*, 2002; Wakutani *et al.*, 2002). These heterogeneous results on the association of the *ACE* gene with AD, and clinical significance of using an ACE inhibitor in AD highlight the necessity of exploring detailed mechanisms from the *ACE* gene in the development of AD.

Stress and depression

It is now evident that chronic exposure to stress can create traumatic memories and even result in the development of mood and anxiety disorders, including major depressive illness. AT_1 receptors are present in all of those structures of the hypothalamic–pituitary axis (HPA) responsible for the stress response. Glucocorticoids are able to stimulate AT_1 receptor expression during stress. Renin secretion and consequently circulating levels of Ang II increase after stress exposures in rodents (Jindra and Kvetnansky, 1982). A variant of

learned helplessness, the forced swim test, provokes an enhancement of Ang II-positive cells in the brain (Pedreanez *et al.*, 2006). It has been shown that sustained pretreatment with AT_1 receptor antagonists prevents the sympathoadrenal and hormonal responses to 24 h isolation stress (Armando *et al.*, 2007). In addition, AT_1 receptor blocking agents reverse the cortical alterations of corticotrophin-releasing hormone and benzodiazepine receptors characteristic of isolation stress (Saavedra *et al.*, 2006). In a microarray-based gene expression analysis in the hypothalamic paraventricular nucleus after maternal separation, one of the prominently up-regulated genes was angiotensinogen (Liebl *et al.*, 2009). In addition, robust changes in ACTH release were also found after application of the AT_1 receptor antagonist candesartan in maternally separated mice. During stress, an increased Ang II level has also been demonstrated in humans (Yang *et al.*, 1996). Recent developments indicate that blockade of the brain AT_1 receptors not only contributes to a significant blood pressure decrease in hypertension, but also reduces the sympathoadrenal and hormonal responses to stress and prevents stress-induced gastric injury (Armando *et al.*, 2003; Saavedra *et al.*, 2006).

The high arterial blood pressure is not only significantly associated with an impairment of cognition (Vicario *et al.*, 2005), but also with the occurrence of depression with anxiety in humans. Case reports indicate that in hypertensive patients who also suffered from depression, ACEIs elicited an improvement in mental state (Germain and Chouinard, 1988; Michalsen *et al.*, 2001). ACE is assumed to influence the activity of the HPA system, which shows hyperactivity in the majority of patients with major depression. The AT_1 receptor antagonist losartan possesses antidepressant-like activity (Gard *et al.*, 1999), whereby the chronic infusion of the AT_1 receptor antagonist candesartan produces a significant increase in the levels of hippocampal noradrenaline and serotonin, and the latter's content in the frontal cortex (Jenkins, 2008). Thus, RAS seems to be part of the neurochemical dysregulation underlying negative affective states, anxiety disorders and ethanol dependence (Sommer and Saavedra, 2008). Thus, the blockade of AT_1 receptors could be proposed as a potentially useful therapy for stress-induced disorders (Saavedra and Benicky, 2007).

Variations in CNS expression of ACE might also influence the response to various antidepressant therapies (Baghai *et al.*, 2004). In addition, recent results support the hypothesis that increased RAS activity may increase relative risk of depression. It is suggested that RAS gene polymorphisms associated with increased RAS activity may also be associated with age of onset depression (Stewart *et al.*, 2009). Suicide involves genetic vulnerability factors, and is often associated with major depression. Different research teams have reported an association between the insertion allele of the *ACE* gene I/D polymorphism with completed suicide (Sparks *et al.*, 2009). However, other studies did not find a significant association with bipolar disorder type I or unipolar recurrent depression and the polymorphism of the *ACE* gene (Pauls *et al.*, 2000; Segman *et al.*, 2002). Genotypic and phenotypic misclassifications or the presence of interaction with other genes or environmental factors are possible explanations for the contradictory findings.

Epilepsy

In patients with temporal lobe epilepsy (TLE) related to mesial temporal sclerosis, an up-regulation AT_1 receptor, as well as its mRNA expression in the cortex and hippocampus, has been found. In addition, an increased immunoexpression of Ang II AT_2 receptors was found only in the hippocampus of these patients with no changes in its mRNA levels (Arganaraz *et al.*, 2008). TLE is associated with impaired hippocampal glucose metabolism. It is discussed whether Ang IV ligands may ameliorate the neuronal metabolic dysfunction by facilitation of neuronal glucose uptake through the glucose transporter GLUT4 (De Bundel *et al.*, 2008). The pilocarpine model is one of the best animal models to investigate drug resistance in TLE. It has been shown that the intracerebroventricular infusion of either Ang IV or somatostatin-14 in rats produced an elevation in hippocampal dopamine and serotonin levels, and protected against pilocarpine-induced seizures. Such neural protective effects could be blocked by simultaneous treatment with a somatostatin receptor antagonist (Stragier *et al.*, 2006). The authors concluded that the Ang IV-induced anticonvulsive effect was mediated via somatostatin receptor-2 activation. It is well known that somatostatin receptors have anticonvulsant and anti-epileptic properties. In addition, it has been shown in other experimental seizure models that Ang IV and Ang III decrease the pentylenetetrazol seizure susceptibility by involving adenosine A1 receptors (Tchekalarova and Georgiev, 1999; Tchekalarova *et al.*, 2001). Ang II also increases the threshold for bicuculline- and picrotoxin-induced seizures in mice (Tchekalarova and Georgiev, 2005). It is worth noting that the mutation of the (P)RR is associated not only with mental retardation, but also with epilepsy (Ramser *et al.*, 2005), pointing to an essential role of (P)RR in brain development (Nguyen and Contrepas, 2008). In summary, with regard to a role for angiotensins in the development and/or suppression of epileptic seizures, there are as yet insufficient data in humans to confirm positive indicators reported in the animal literature.

Conclusion

Since the first description of a brain RAS (Ganten *et al.*, 1971), it has been the subject of controversy and debate. Aside from the classical functions of the RAS in salt and water homeostasis, and in the regulation of blood pressure, angiotensins are also involved in the regulation of multiple functions in the brain, including processes of sensory information, learning and memory, as well as regulation of emotional responses. Moreover, there is growing evidence that the RAS is also involved in several neurodegenerative diseases. Drugs known to interfere with the RAS have been shown to have beneficial cognitive effects in humans. The use of transgenic rats and mice either over-expressing or ablating the synthesis of RAS components has resulted in a wealth of new detailed information on the role of the RAS in brain functions (Morimoto and Sigmund, 2002; von Bohlen und Halbach and Albrecht, 2006; Bader and Ganten, 2008; Phillips and de Oliveira, 2008). However, it should be considered that global pharmacological inhibition of RAS components or traditional gene

targeting cannot differentiate systemic from local actions of the RAS. Further studies that determine the role of the different angiotensins and their receptors in many neuropathological states are required. The use of antihypertensive drugs, particularly ACE inhibitors and angiotensin receptor blockers, may be associated with a lower rate of cognitive decline in older adults, including those with Parkinson's and AD (Reardon *et al.*, 2000; Gard and Rusted, 2004; Hajjar *et al.*, 2005).

Acknowledgements

The Deutsche Forschungsgemeinschaft supported the work of the author. I thank Andreas Patzak, Michael Bader and David Betances for critical reading of the manuscript.

Conflict of interest

The author has declared that no conflict of interest exists.

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