Acta Neurol. Belg., 2009, **109**, 171-180

Brain renin-angiotensin system in cognitive function: pre-clinical findings and implications for prevention and treatment of dementia

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Abstract

Biochemical, physiological and functional studies suggest that the brain renin-angiotensin system (RAS) is regulated independently of the peripheral RAS. Also, all enzymes and peptides necessary for the biosynthesis of various angiotensins have been recognized within the central nervous system. There are divergent opinions concerning the localization of the different components of this system which is not fully understood. It is believed that central actions of angiotensins are not exclusively associated with their traditional roles, many studies showing that central angiotensins are also involved in learning and memory processes. Moreover, clinical trials and studies on animal models suggest that pharmacological manipulation of angiotensin ligands may be of clinical importance in slowing or even stopping the cognitive deterioration seen in vascular dementia and Alzheimer's disease.

Key words: Brain renin-angiotensin system; angiotensin II; angiotensin III; angiotensin IV; angiotensin-(3-7); angiotensin 1-7; cognitive functions; neurodegenerative disorders.

Introduction

The renin-angiotensin system (RAS) is one of the best-studied enzyme-neuropeptide systems in the brain and can serve as a model for the action of peptides on neuronal function in general. It is now well established that the brain has its own intrinsic RAS with all its components present in the central nervous system (CNS) (von Bohlen and Albrecht, 2006) (Fig. 1).

It is believed that the RAS of the brain is involved not only in the regulation of blood pressure, but also in the modulation of multiple additional functions in the brain, including processes of sensory information, learning and memory, and the regulation of emotional responses (Haulica *et al.*, 1999; Llorens and Mendelsohn, 2002). Also, our group was among the first to demonstrate the involvement of the brain RAS in pain perception (Haulica *et al.*, 1986).

The central RAS generates a family of bioactive angiotensin peptides with variable biological and neurobiological activities. These include angiotensin-(1-8) [Ang II], angiotensin-(2-8) [Ang III], angiotensin-(3-8) [Ang IV], angiotensin-(3-7) [Ang-(3-7)] and angiotensin-(1-7) [Ang-(1-7)] (Table 1). Data concerning the angiotensin ligands describes Ang I as inactive, while Ang II and Ang III are full agonists for the AT1 and AT2 receptor subtypes. Ang IV binds with low affinity at the AT1 and AT2 receptor subtypes, but with high affinity and specificity at the AT4 receptor subtype (that is an insulin-regulated aminopeptidase). A specific binding site for Ang-(1-7) has been reported (as the Mas protooncogene), but not fully elucidated (Santos *et al.*, 2003; von Bohlen and Albrecht, 2006; Haulica *et al.*, 2006).

These receptors have been identified in a variety of brain structures. However, high densities of angiotensin peptides binding sites can be found both in the cortex and in other brain areas associated with cognitive functions (hippocampus, amygdala, thalamus, substantia nigra, ventral tegmental area, locus coeruleus etc) (Fig. 2).

Although all the components of RAS have been found in the brain, the co-localisation of angiotensinogen, renin and Ang I within a single brain cell has failed. Since angiotensinogen is present in astrocytes, angiotensins could be also produced here (Stragier *et al.*, 2008). Also, since renin mRNA levels are low or undetectable in the brain, it has been proposed that other enzymes besides renin are producing angiotensin peptides from angiotensino-

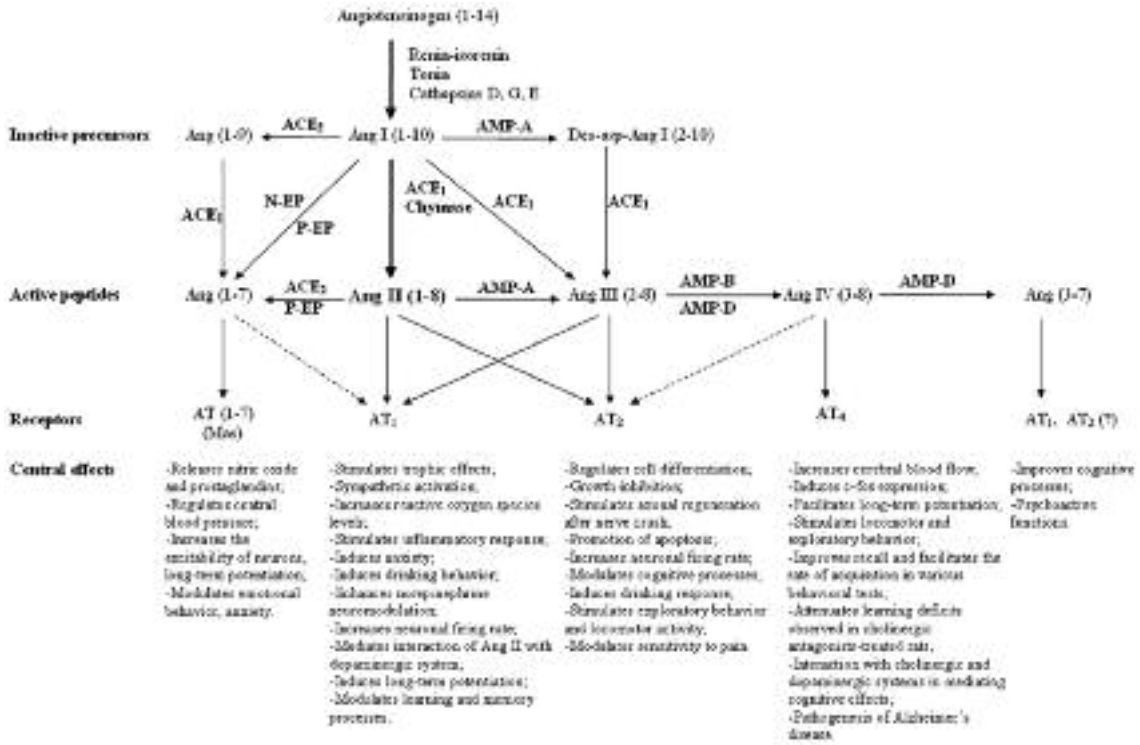

FIG. 1. — Synthesis and actions of bioactive angiotensins. ACE = Angiotensin-Converting Enzyme; AMP = Aminopeptidase; N-EP = Neutral endopeptidase; P-EP = Prolylendopeptidase (Braszko *et al*., 1998; Walther *et al*., 2000; Stol and Unger, 2001; Gendron *et al.*, 2003; Olson *et al*., 2004; Sun *et al*., 2005; Bonini *et al.*, 2006; von Bohlen and Albrecht, 2006; Alenina *et al.*, 2008; Chai, 2008).

Table 1

The members of the angiotensin family of peptides (Gard, 2008)

Angiotensin	Chemical structure									
	1	2	3	4	5	6	7	8	9	10
Ang I (Angiotensin I) (1-10)	Asp	Arg	Val	Tyr	Ile	His	Pro	Phe	His	Leu
Ang II (Angiotensin II) (1-8)	Asp	Arg	Val	Tyr	Ile	His	Pro	Phe		
Ang III (Angiotensin III) (2-8)		Arg	Val	Tyr	Ile	His	Pro	Phe		
Ang 1-7 (Angiotensin 1-7)	Asp	Arg	Val	Tyr	Ile	His	Pro			
Ang 3-7 (Angiotensin 3-7)			Val	Tyr	Ile	His	Pro			
Ang IV (Angiotensin IV) (3-8)			Val	Tyr	Ile	His	Pro	Phe		

Asp - Aspartic acid, Arg - Arginine , Val - Valine, Tyr - Tyrosine, Ile - Isoleucine, His - Histidine, Pro - Proline, Phe - Phenylalanine, Leu - Leucine.

gen inside the brain. These could include: tonin, cathepsin G or chymase (Baltatu *et al*., 1997, 1998; Stragier *et al*., 2008) (Fig. 1).

Angiotensin II

Angiotensin II is the main effector of the renin-angiotensin system (RAS). The actual role of Ang II on learning and memory processes has been difficult to comprehend. This is probably due to the fact that the cognitive effects of this peptide are highly dependent on different methodological issues, particularly time and via of administration, number and frequency of training sessions as well as the type of learned response evaluated. For example, it has been reported that centrally administered Ang II improves aversive memory (Braszko, 2002), but using similar learning tasks, others have shown that this peptide either impairs or has no action at all on memory retention (Kerr *et al.*, 2005; Bonini *et al.*, 2006). Similarly, when angiotensin II is injected directly into the dorsal neostriatum, retention of a step-down

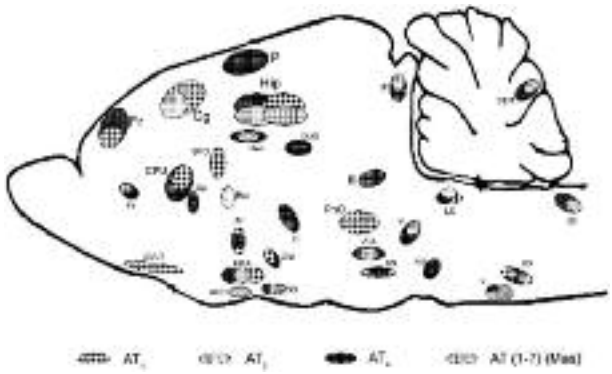

FIG. 2. — Distribution of angiotensin receptors in the rat brain. BAOT = Bed nucleus of the accessory olfactory tract; CER = Cerebellum; Cg = Cingulate cortex; CPU = Caudate putamen; DLG = Dorsolateral geniculate nucleus; DM = Dorsomedial hypothalamus; Fr = Frontal cortex; Gp = Globus pallidus; Hab = Habenula; Hip = Hippocampus; IF = Inferior colliculus; IO = Inferior olive; LC = Locus coeruleus; MEA = Medial nucleus of amygdala; OVLT = vascular organ of the lamina terminalis; P = Parietal cortex; Pir = Piriform cortex; PnO = Pontine reticular nucleus; Pr = Preoptic nucleus; Ret = Reticular nucleus; SFO = Subfornical organ; SN = Substantia nigra; SO = Supraoptic nucleus; VTA = Ventral tegmental area; Zi = Zona incerta; III = Oculomotor nucleus; V = Motor trigeminal nucleus; VII = Facial nucleus; X = Vagal nucleus; XII = Hypoglossal nucleus (Chai *et al*., 2000; Llorens and Mendelsohn, 2002; McKinley *et al*., 2003; Thomas and Mendelsohn, 2003; Silva *et al.*, 2005; von Bohlen and Albrecht, 2006; Bonini *et al*, 2006; Alenina *et al.*, 2008; Wright and Harding, 2008).

shock avoidance response is impaired, whereas retrieval in a similar passive avoidance conditioning task improves following intracerebroventricular administration of angiotensin II (von Bohlen and Albrecht, 2006). We previously reported both inhibitory and stimulatory effects of Ang II in 8-arm radial maze and Y maze tasks (Bild *et al*., 2009).

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 (Walther *et al.*, 1999).

However, in a recent paper Maul *et al.* (2008) demonstrated that mice lacking the AT2 receptor gene are significantly impaired in their performance in a spatial memory task and in a one-way active avoidance task. Also, authors noted that receptor knockout mice showed abnormal dendritic spine morphology and length, both features found to be associated with some cases of mental retardation.

Other studies showed that angiotensin II administered to the hippocampus affects memory by the activation of AT 1 (Bonini *et al*, 2006) or AT2 receptors (Kerr *et al*., 2005). There is also a possible role of hippocampal angiotensin II receptors in voluntary exercise-induced enhancement of learning and memory in rat (Akhavan *et al*, 2008).

Some authors indicate that data suggesting the facilitator effect of angiotensin II on learning and memory must be interpreted with care, since Ang II is also a precursor for neuroactive angiotensin fragments like Ang IV. Thus, different results might be obtained depending on the time intervals between the injection of Ang II and the tested behavioral paradigm (Braszko *et al*., 2006).

The Ang II receptor antagonists, losartan and PD123177, which are selective for the AT1 and AT2 receptor subtypes respectively, constitute important pharmacological tools for the assessment of behavioral consequences through the modulation of Ang II function (von Bohlen and Albrecht, 2006; Hritcu *et al.*, 2009). Several studies have shown that low doses of losartan and PD123177 improved scopolamine-impaired performance in a light/dark box habituation task. Similarly countering effect was observed in the case of captopril and ceranopril (Chalas and Convay, 1996).

Long-term potentiation (LTP), a specific form of synaptic plasticity, is thought to represent a correlation of processes attributable to learning and memory and has been extensively studied in terms of both its underlying mechanisms and its behavioral significance. Injection of angiotensin II just above the CA1 field in rats has been shown to block the induction of LTP (von Bohlen and Albrecht, 1998). Further experiments have demonstrated that this inhibition can be blocked by the administration of AT1-receptor antagonists (von Bohlen and Albrecht, 2006).

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 AT1 receptors, since losartan blocked the Ang II induced effect on LTD, whereas AT2 receptors seem not to be involved. Also, the importance of L-type calcium channels on this process was demonstrated (Tchekalarova *et al.*, 2007).

Some authors suggest an unexpected role of angiotensin II and the AT2 receptor in the regeneration processes following neuronal injury. In the *in vivo* optic nerve crush model, angiotensin II induced a concentration-dependent outgrowth of neurites. This effect is mediated by the AT2 receptor, since the regeneration process was paralleled by a time-dependent increase in AT2 receptor mRNA expression in the retina and the crushed optic nerve. Moreover, these data provide direct evidence that stimulation of AT2 receptors can promote axonal regeneration *in vivo* after neuronal lesions (Culman *et al*., 2002).

Angiotensin III

Some central actions of angiotensin III are hard to explain only on the basis of their interaction with AT1 and AT2 receptors (Vauquelin *et al*., 2002). Immunohistochemical and neuropharmacological studies suggest that angiotensinergic neuronal pathway use angiotensin III as a neurotransmitter or neuromodulator in regions like hypothalamic paraventricular and supraoptic nuclei, ventrolateral medulla and nucleus of the solitary tract (McKinley *et al*., 2003).

As we already mentioned, Ang II and the heptapeptide Ang III bind with similar affinity to the AT1-receptor and both peptides are equally potent agonists for this receptor. Still, Ang III was shown to be at times even more effective than Ang II. For example, Ang III appeared twice as effective as Ang II in stimulating the firing rate of certain neurons. To deal with such findings, the question was raised by some authors, to whether Ang III might be the predominant effector peptide in the brain rather than Ang II (Vauquelin *et al*., 2002).

Angiotensin IV

Angiotensin IV has been implicated in a number of physiological actions, including the regulation of blood flow, the modulation of exploratory behaviour and processes attributed to learning and memory. Since the AT1 and AT2 receptors bind angiotensin IV with low affinity only, a specific binding site for Ang IV has been described. It is believed that Ang IV bound specifically to the enzyme insulin-regulated aminopeptidase (IRAP), which is proposed to be the site in the brain that mediates the memory effects of these peptides. However, the mechanism of action is still unknown but may involve inhibition of the aminopeptidase activity of IRAP, since both angiotensin IV and LVV-hemorphin 7 are competitive inhibitors of the enzyme (Albiston *et al.*, 2004; Chai *et al.*, 2008; Vanderheyden, 2009). Recently, the hepatocyte growth factor receptor c-MET was also proposed as a receptor for AT(4) ligands (De Bundel *et al*., 2008).

Central administration of the Ang IV results in facilitation of memory and exploratory locomotor, as demonstrated in the conditioned and passive avoidance paradigm (Braszko, 2004), and enhanced performance in the spatial memory tasks, as in the swim and Barnes mazes (Lee *et al*., 2004). Also, the improvement in the recall of passive avoidance responses is dose-dependent (Gard, 2008).

In addition, stimulation of AT4 receptors has been shown to attenuate learning deficits observed for scopolamine-treated animals in the passive avoidance task and in spatial learning (Albiston *et al*., 2004). As we previously demonstrated, intracerebroventricular administration of the nicotinic acetylcholine receptor antagonist mecamylamine interferes with spatial memory performance in rats, similarly to the muscarinic acetylcholine receptor antagonist scopolamine (Hritcu *et al*., 2008). Interestingly, Norleucine-angiotensine IV attenuates mecamylamine-induced deficits in spatial memory, but could not, however, compensate for spatial learning impairments precipitated by both mecamylamine and scopolamine, suggesting that cognitive facilitation by angiotensin IV could be attributable to the potentiation of brain cholinergic neurotransmission (Olson *et al*., 2004; von Bohlen and Albiston 2006). Also, Braszko *et al.* (2004, 2006) showed that that D(1) and D(2) dopamine receptors are indispensable for the cognitive effects of angiotensin IV.

Other groups demonstrated that Ang IV attenuates memory deficits generated by chronic alcohol intake, different central lesions or ischemia (Wisniewski *et al*., 1993; Wright *et al.*, 1996; Chai, 2008).

At the cellular level, Ang IV has been shown to facilitate long-term potentiation in the dentate gyrus of rats *in vivo* and in the CA1 region of the hippocampus *in vitro* (Wayner *et al.*, 2001; Kramar *et al*., 2001). In view of the fact that long-term potentiation is considered to be a cellular marker for memory formation, these findings provide further evidence that Ang IV does indeed play a role in memory processing (Chai et al., 2008). Moreover, ethanol-induced suppression of CA1 LTP can be attenuated with Ang IV (Wright *et al.*, 2003). The AT 4 ability to facilitate LTP is separate from NMDA-dependent LTP, which suggests a non-glutamatergic signaling pathway (Yamin, 2009).

Gard described strain differences in the behavioural effects of peripherally administered angiotensin IV. Using the object recognition test, he showed that DBA2 mice are more responsive to the effects of angiotensin IV than the BKW mice. The interesting feature of these results is that the mice with best inherent cognition benefit least from angiotensin IV. This either indicates a "ceiling effect" of the behavioural method, that is, the inability to measure greater cognition, or the possibility that angiotensin IV replaces some deficit responsible for the inherent poor performance (Gard, 2008).

Infusion of Ang IV led to c-fos expression in the hippocampus and piriform cortices (Roberts *et al*., 1995). It has been shown that the densest brain distributions of the AT4 receptor subtype are in neocortex, hippocampus, amygdala, and the basal nucleus of Meynert, which are consistent with expectations concerning central locations for a

mediator of cognitive processing (Wright and Harding, 2008).

Considering that IRAP is also known as oxytocinase, some authors concentrate on the possible interaction of Ang IV, IRAP and oxytocin. Such studies showed that stimulatory effects of Ang IV on learning and memory could include the inhibition of oxytocinase, which would affect the dose-dependent actions of oxytocin on learning and memory (Gard *et al*., 2007).

As we mentioned before, it is believed that the facilitation of learning and improvement of memory observed in some studies after injection of angiotensin II (Ang II) is, in fact, caused by its derivative angiotensin IV (Ang IV). This was demonstrated in experiments in which rats received Ang II and Ang IV, given 5, 10 and 15 minutes before testing. Ang IV significantly increased step-through latencies in a passive avoidance paradigm in all groups regardless of the time of injection, while rats treated with Ang II demonstrated significant improvement of memory of aversive stimuli in the same tests only 15 minutes after its i.c.v. injection, with no effect in the groups injected five minutes before testing and slight efficacy in those injected 10 minutes before the test. It seems like the delay in the Ang II cognitive effects is caused by the necessity of processing the peptide to Ang IV which is well known for its cognition enhancing properties (Braszko *et al.*, 2006).

However, cognitive enhancers like Ang IV-peptides have some limitations in their use as clinically therapeutics, because they are rapidly degraded with short half-lives and they are too large and hydrophilic to penetrate the bloodbrain barrier. Current studies are working to overcome these limitations by designing and synthesizing Ang IV analogues with improved stability, smaller size and hydrophobicity characteristics compatible with blood-brain barrier permeability (Wright and Harding, 2008).

Angiotensin (3-7)

It has also been reported that angiotensin (3-7) exerts facilitatory effects on conditioned reflexes and enhances the associative memory in rat. Braszko demonstrated that angiotensin (3-7) given intracerebroventricularly at the dose of 1 nmol, significantly enhanced recall of the passive avoidance behaviour and learning of the conditioned avoidance responses (Braszko *et al*., 1998; Kuziema *et al*., 1998, 1999). Also, the number of rearings and bar approaches in the open field was increased, suggesting that Ang-(3-7) could be responsible for the psychoactive properties of angiotensins (Braszko *et al*., 1991).

The same group reported that Ang-(3-7) given intracerebroventricularly, 15 min before the retention testing, significantly prolonged avoidance latencies by improving retrieval of memory for the electric footshock experienced during a specific learning trial (Winnicka *et al.*, 1998). Moreover, it seems like the facilitatory effect of angiotensin (3-7) on cognitive processes could be mediated by the glutamatergic and dopaminergic systems (Winnicka *et al.,* 1999).

Angiotensin (1-7)

Angiotensin (1-7) acts through a specific G-protein-coupled receptor, Mas, encoded by the Mas protooncogene. Although *in-vitro* studies confirmed that Ang-(1-7) is a Mas functional ligand, it cannot be excluded that Mas may have additional ligands and that Ang-(1-7) may have additional receptors (Santos *et al*., 2003; Hellner *et al.*, 2005; Alenina *et al.*, 2008). Recently, it was shown that Mas can heterooligomerize with the AT1 receptor and inhibit the actions of Ang II, thus being a physiological antagonist of the AT1 receptor (Kostenis *et al.* 2005).

Although the effects of angiotensin (1-7) on behavior have not been examined in detail, there are a few studies that demonstrated the enhancing effects of Ang-(1-7) on LTP in the hippocampus (Hellner *et al.*, 2005). Also, Ang-(1-7) antagonist A-779 blocked this LTP-enhancing effect of Ang-(1-7) in wild-type mice, while low concentrations of Ang-(1-7) did not change the magnitude of CA1 LTP in *Mas*-deficient mice (Alenina *et al.*, 2008).

These positive effects of Ang-(1-7) in LTP did not result in clear changes of spatial learning in water Maze, as showed by Walther in 1998 (Walther *et al.*, 1998). The same author reported that Mas-deficient animals display an increased anxiety as assessed in the elevated-plus maze, which could be expressed in a sex-specific manner (Walther *et al.*, 2000).

However, some authors affirm that a higher availability of Ang-(1-7) in patients treated with angiotensin-converting enzyme (ACE) inhibitors might underlie some improvement of cognitive processes (Tom *et al*. 2003; von Bohlen and Albrecht, 2006).

The connection between angiotensins and neurological disorders

In addition to the brain RAS role in neurogenic hypertension, evidence is accumulating that brain RAS is involved in Alzheimer's disease (AD), stroke, memory and learning, alcoholism, depression and emotional stress (Philips and de Oliveira, 2007).

An increase in the ACE activity and alteration in others components of brain RAS has been demon-

strated in AD (Ohrui *et al.*, 2004). Generally, ACE inhibitors and Ang II antagonists seem to be effective in preventing cognitive decline and even improving cognitive function in hypertensive patients (Fogari *et al.*, 2003).

Although the relationship between the level of cognitive function and blood pressure values has been the subject of numerous conflicts, it is generally believed that ACE inhibitors and Ang II antagonists are effective in maintaining, or even improving, cognitive function through other mechanisms than blood pressure control (Fogari and Zoppi, 2004). Still, in a recent study, Jennings et al. demonstrated that regional cerebral blood flow responses during memory processing, which are blunted among untreated hypertensive adults, are enhanced as a result of lisinopril (ACE blocker) treatment (Jennings *et al.*, 2008).

Therefore, 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 Alzheimer Disease (Hanon and Leys, 2002; Hou *et al.*, 2008).

This suggests that reducing brain RAS activity is important. There are many effects of decreased Ang II activity including reduced blood pressure, less acetylcholine release, and increase of substance P, a substrate which is reported to increase neprilysin activity, a recognized amyloid degrading enzyme (Philips and de Oliveira, 2007; Kehoe and Wilcock, 2007).

Some authors noted that captopril induces mood-elevating effects in depressed patients suggesting that elevated brain angiotensin levels may interfere with acetylcholine release, which in turn could interfere with cognitive processing. According to this hypothesis, ACE inhibitors could facilitate cognitive functioning by reducing the synthesis of Ang II, thus removing an inhibitory influence upon acetylcholine release (von Bohlen and Albrecht, 2006; Kumaran *et al.*, 2008). We also demonstrated that intraperitoneal and intracerebroventricular administration of captopril facilitates cognitive processes in radial 8 arms maze and Y maze paradigms (Bild *et al.*, 2009).

Concerning depression and anxiety, it has been reported that drugs blocking the RAS may be antidepressant or anxiolytic. For example, captopril induces mood elevating effect in depressed patients (von Bohlen and Albrecht, 2006). We also found that in elevated plus maze measuring anxiety, captopril, losartan and PD123319 diminished anxiety state in rats (Bild *et al.*, 2009). Moreover, we showed that angiotensin II can exert anxiolytic effects (unpublished observation).

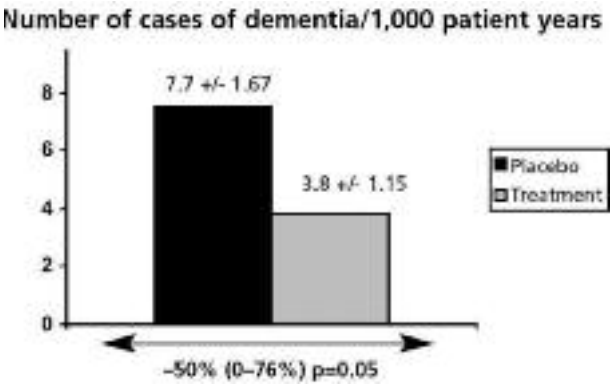

FIG. 3. — Reduction in the incidence of dementia with antihypertensive treatment in Syst-Eur study (Hanon and Leys, 2002; Forette *et al.*, 1999).

As a major player in vascular homeostasis, RAS proteins constitute an interesting source of candidate genes which may be involved in the pathogenesis of dementia. Among these, ACE presents in its sequence a deletion/insertion polymorphism which has been associated with variations of plasma ACE levels and with the risk of cognitive impairment and dementia in several epidemiological studies. Physiopathological hypotheses suggest a possible involvement of the RAS proteins in the occurrence and evolution of Alzheimer's disease. Moreover, although inconsistent, several case-control studies tend to suggest that this ACE genetic polymorphism may constitute a genetic susceptibility factor for dementia (Amouyel *et al.*, 2000).

It is believed that perturbation of the RAS improves basal cognition and reverses age-, scopolamine-, ethanol-, and diabetes-induced deficits (von Bohlen and Albrecht, 2006).

Moreover, studies like HOPE, SHEP, SYST-EUR or SCOPE showed that long-term blood pressure control by ACE inhibitors or AT1/AT2 antagonists may reverse cognitive impairment associated with preexisting hypertension (Starr *et al.*, 1996) (Fig. 3).

These types of trials reported that reduction of systolic blood pressure in hypertensives could protect against cognitive deterioration in later life (Cervilla *et al.,* 2000). More specific studies also demonstrated that losartan (Tedesco *et al.*, 1999), valsartan or telmisartan (Fogari *et al.*, 2003, 2006) improve the quality of life scores and have beneficial effects on cognition in old hypertensive patients.

This suggests that during chronic oral treatment with ACE inhibitors, some of these compounds are able to penetrate the blood-brain-barrier and to block the brain RAS. In this context, several studies in

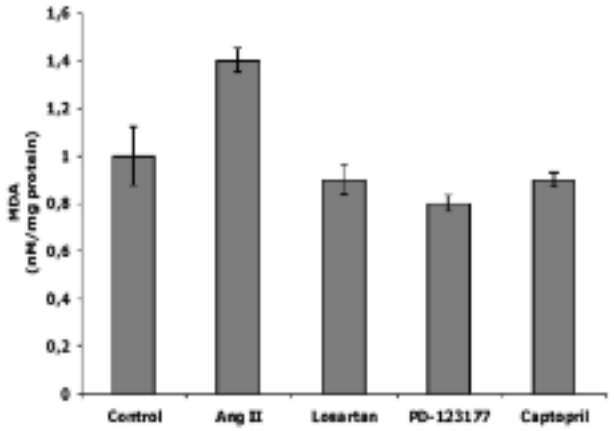

FIG. 4. —. Effects of angiotensin II, losartan (AT1 antagonist), PD-123177 (AT2 antagonist) and captopril (ACE inhibitor), 10 mg/kg b.w., i.p., on malondialdehyde levels (MAD) in rat temporal lobe homogenates. The values are mean ± S.E.M. (n = 12 per group) – unpublished data.

laboratory animals show that reduction in the activity of the brain RAS via the injection of ACE inhibitors or AT1/AT2 antagonists results in an improvement in cognitive performance (Llorens and Mendelsohn, 2002), possibly by reducing the levels of oxidative stress, another very important aspect of the degenerative neuropathology (unpublished observations) (Fig. 4).

Similarly to angiotensin IV, Gard demonstrated that not all strains of laboratory mice exhibit the same behavioral responses to losartan. So, it is possible for different individuals to show different cognitive responses (Gard, 2008).

Some authors also speculate that this kind of therapies may involve the perturbation of angiotensin IV (Chai *et al.*, 2008). Actually, a wide range of studies have made it clear that IRAP might become an important target for drug development against different pathologies such as Alzheimer's disease, epilepsy and ischemia (Stragier *et al.*, 2008).

Recently, central renin inhibitors (e.g. aliskiren) which could prevent the synthesis of all types of angiotensins have been tested (Tayal and Kalra, 2008; Sanoscki, 2009).

Concerning Parkinson's disease and a possible connection with RAS, the results are controversial. However, decreased angiotensin-binding sites in the substantia nigra of postmortem brains from patients with Parkinson's disease have been found. AT1 receptor levels are decreased by approximately 90% in the substantia nigra in patients with Parkinson's disease relative to matched controls. Changes in AT1 receptor levels have not only been observed in cases of Parkinson's disease, but also in Huntington's disease in which AT1 receptor levels are decreased by approximately 30% in the putamen (Lopez *et al.*, 2005). However, recent data suggest some adverse effects as a result of using losartan in Parkinson's disease patients (Sarma *et al.*, 2008). The issue is still in debate and there are many unknowns regarding the association between antihypertensive drug use and the risk of developing a first-time diagnosis of Parkinson disease (von Bohlen and Albrecht, 2006; Becker *et al.*, 2008).

Conclusions

Intensive research over the past years has delivered new insights into the role of RAS in neuronal tissue. Aside from the classical functions of the angiotensin system in salt and water homeostasis and the regulation of blood pressure, this central system is also involved in the regulation of multiple brain functions, including processes of sensory information, regulation of emotional responses, learning and memory. There is strong evidence for the involvement of the angiotensin system in several neurodegenerative diseases. Drugs known to interfere with the renin-angiotensin system have been shown to have beneficial cognitive effects in animals and humans. However, further studies are needed to precisely define the role of various angiotensins and angiotensin receptors in many neuropathological states. For this purpose, a better understanding of the complex interactions between the various angiotensins and synaptic transmission is necessary and may lead to targeted therapeutic intervention in the future.

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