ELSEVIER

European Journal of Pharmacology 438 (2002) 1–14

ejp

www.elsevier.com/locate/ejphar

Review

The role of angiotensin II in cognition and behaviour

Paul R. Gard *

School of Pharmacy and Biomolecular Sciences, University of Brighton, Brighton BN2 4GJ, UK

Received 9 January 2002; accepted 15 January 2002

Abstract

Polymorphisms of the renin–angiotensin system are associated with cardiovascular disorders, possibly as a consequence of increased brain angiotensin II activity. Within the brain, angiotensin controls blood pressure, fluid balance and hormone secretion; it also influences behaviour: reduction of central angiotensin function has both antidepressant-like and axiolytic-like actions. Evidence concerning the role of the renin–angiotensin system in learning and memory is contradictory, although more studies support the proposal that angiotensin reduces cognitive function. Studies of renin–angiotensin system genotype and psychological status have suggested an association between the angiotensin-converting enzyme deletion allele and age related cognitive decline, but a greater prevalence of the insertion allele in Alzheimer's disease. The deletion allele has also been associated with depressive illness, as has the M allele of the angiotensinogen gene although other studies have failed to replicate these findings. The role of the brain renin–angiotensin system in human psychopathology remains to be fully explored.

Keywords: Renin–angiotensin system; Affective disorder; Cognition; Memory

1. The renin–angiotensin system

The octapeptide angiotensin II is associated predominantly with the cardiovascular system where it acts to maintain blood pressure by vasoconstriction and stimulation of aldosterone secretion. Angiotensin II is synthesized from angiotensin I by the action of angiotensin-converting enzyme, which is present within the endothelium of most blood vessels but has highest concentrations within the pulmonary vasculature. Angiotensin I, in turn, is derived from angiotensinogen, a circulating peptide from the liver, by the action of renin which is released from the juxtaglomerular apparatus of the kidney in response to decreased pressure within the renal arterioles (Fig. 1). Angiotensin II produces its effects via a number of specific receptors, after which it is metabolised to angiotensin-(2–8) (Angiotensin III), angiotensin-(1–7), angiotensin-(3–7) or angiotensin-(3–8) (Angiotensin IV, Table 1). All of the angiotensins are pharmacologically active, with markedly different potencies, although different rank order of potency in different tissues has indicated the existence if multiple angiotensin receptors.

The most prevalent angiotensin receptor is the angiotensin type 1 receptor (AT_1) which is a seven transmembrane domain, G-protein coupled receptor comprised of 359 amino acids. In humans the gene coding for the receptor is on chromosome 3q. In rats and mice there are two subtypes of angiotensin AT_1 receptor, type 1_A and type 1_B which seem to be pharmacologically identical, but are coded by separate genes. The angiotensin type 2 receptor (AT_2) is similarly a G-protein coupled receptor with 363 amino acids and 34% homology with the AT_1 receptor, its gene is located on the X chromosome. The existence of an angiotensin type 3 receptor, which is selective for angiotensin III has been proposed, but is, as yet, unproven, although angiotensin III is known to be active at the AT_1 receptor and may even be the endogenous agonist for that receptor in the brain (Harding et al., 1986). Angiotensin type 4 receptors (AT_4) have been clearly identified in the brain, the endogenous agonist being angiotensin IV. The amino acid sequence of this receptor has yet to be determined, as is the location of the gene (see de Gasparo et al., 2000 for review).

Most of the physiological actions of angiotensin II are mediated via AT_1 receptors which have been identified in the gut, heart and vascular tissue, kidney, liver, uterus, ovaries, testes, adrenal gland and brain. In most cases, the transduction process involves generation of inositol trisphosphate (IP_3) and the mobilisation of Ca^+ ions, although other

* Tel.: +44-1273-642084; fax: +44-1273-679333.
E-mail address: p.r.gard@brighton.ac.uk (P.R. Gard).

0014-2999/02/$ - see front matter
PII: S0014-2999(02)01283-9

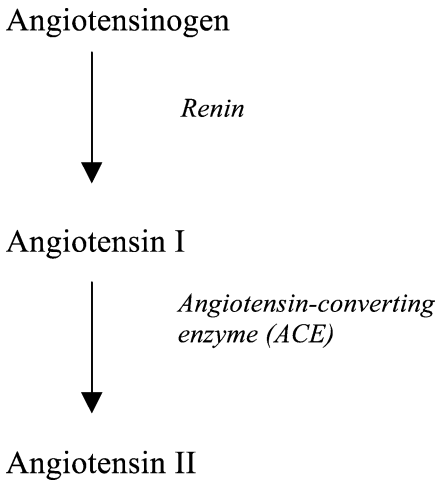

Fig. 1. Synthetic pathway for angiotensin II.

processes have also been identified. The AT_2 receptor is expressed ubiquitously in the foetus but densities decline rapidly after birth. AT_2 receptor expression, however, is maintained in the heart, non-pregnant uterus, adrenal glands, ovaries and brain. The signal transduction mechanism varies, but commonly involves K^+ and Ca^+ ion channels and growth factor stimulation. The AT_4 receptor is found predominantly in the brain in areas distinct from those possessing AT_1 and AT_2 receptors, and is also found in the adrenal gland, heart, thymus, kidney, bladder and aorta. The signal transduction process is, as yet, unclear, although it is unlikely to involve a G-protein (de Gasparo et al., 2000).

2. Polymorphisms of the renin–angiotensin system

The primary physiological function of the renin–angiotensin system is the control of blood pressure. There exist several strains of spontaneously hypertensive rat (SHR), the most commonly used of which were originally developed by selective breeding of hypertensive offspring of Wistar-Kyoto animals. Because this strain became available before it was fully inbred, however, the spontaneously hypertensive rat colonies currently used are considered to be a relatively genetically heterogeneous. The aetiology of the hypertension in spontaneously hypertensive rats is not fully determined, but it is recognized that they develop increased vascular resistance and left ventricular hypertrophy early in life, and that these symptoms respond to treatment with angiotensin-converting enzyme inhibitors, drugs commonly used in humans for the treatment of hypertension. It is therefore possible that the cardiovascular disorders in spontaneously hypertensive rats are a consequence of some renin–angiotensin system abnormality.

Working with the Okamoto strain of spontaneously hypertensive rat, Di Nicolantonio and colleagues (Wang et al., 1994) reported that the tandem repeat element of the first intron of the renin gene was 600 base pairs shorter than that of the normotensive Wistar-Kyoto control. It was speculated that this polymorphism may be partially responsible for the renin gene over-expression seen in spontaneously hypertensive rats. Further investigations revealed, however, that plasma renin concentrations were no different in hypertensive Okamata strain rats than in normotensive Wistar-Kyoto controls, and that renal renin mRNA was actually decreased in spontaneously hypertensive rats compared to Wistar-Kyoto although brain and adrenal mRNA were increased (Yu and Di Nicolantonio, 1996). It was finally concluded that the hypertension in Okamata rats was due to two G–A mutations at positions +502 and +934 of the first intron of the renin gene, that it was non-renal tissues that were responsible for the hypertension, and that there was a compensatory reduction in renal renin expression (Yu and Di Nicolantonio, 1998).

Other workers have reported that spontaneously hypertensive rats have normal or suppressed plasma concentrations of renin and angiotensin peptides (for example, Nakamura and Johns, 1995). These findings are not wholly consistent with the work of Di Nicolantonio, although the report of lower renal angiotensinogen mRNA and lower renin mRNA in spontaneously hypertensive rats, which does not increase in response to decreased renal blood supply (Nakamura and Johns, 1995) is consistent. Attempts to explain the hypertension in the absence of increased plasma concentrations of the renin–angiotensin peptides by investigating tissue concentrations revealed that kidney, adrenal, heart, aorta, adipose and lung tissue concentrations of angiotensin-(1–7), angiotensin II and angiotensin I were all lower in spontaneously hypertensive rats than in normotensive controls, although brain concentrations of angiotensin II were higher in spontaneously hypertensive rats during the first 6 weeks of life (Campbell et al., 1995). It is thus

Table 1
Amino acid sequences of the angiotensin family

	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Angiotensinogen	Asp	Arg	Val	Tyr	Ile	His	Pro	Phe	His	Leu	Leu	Val	Tyr	Ser
Angiotensin I	Asp	Arg	Val	Tyr	Ile	His	Pro	Phe	His	Leu				
Angiotensin II	Asp	Arg	Val	Tyr	Ile	His	Pro	Phe						
Angiotensin-(2–8) (AIII)		Arg	Val	Tyr	Ile	His	Pro	Phe						
Angiotensin-(1–7)	Asp	Arg	Val	Tyr	Ile	His	Pro							
Angiotensin-(3–7)			Val	Tyr	Ile	His	Pro	Phe						
Angiotensin-(3–8) (AIV)	Asp	Arg	Val	Tyr	Ile	His	Pro							

possible that the development of hypertension in spontaneously hypertensive rats involves increased brain angiotensin II activity early in life. Other possible contributory factors to the spontaneous hypertension in these rats include a recessive polymorphism of the angiotensin-converting enzyme gene (Zhang et al., 1996); increased expression of cardiovascular angiotensin-converting enzyme mRNA and angiotensin AT_1 receptor mRNA and increased density of cardiac angiotensin receptors (Makino et al., 1997).

These studies all demonstrate that there are naturally occurring genetic variations within the renin–angiotensin system in animals and that some of them impinge upon the cardiovascular system. A range of polymorphisms has also been identified in humans (Table 2). To date, 78 polymorphisms have been reported in the gene encoding for angiotensin-converting enzyme (Rieder et al., 1999) and several polymorphisms exist in angiotensinogen and AT_1 receptor genes (e.g., Inoue et al., 1997; Zhang et al., 2000). Research investigating the relationship between cardiovascular disorders and renin–angiotensin system-related genes has concentrated on just a few of the more common polymorphisms.

The most studied polymorphism is the insertion/deletion polymorphism of the angiotensin-converting enzyme gene. This polymorphism is defined as either the presence (insertion, I) or absence (deletion, D), of a 287 base pair insert in intron 16 of the angiotensin-converting enzyme gene on chromosome 17q23 (Rieder et al., 1999). The insertion appears to reduce angiotensin-converting enzyme expression, thus DD homozygotes have 65% more, and ID heterozygotes 31% more angiotensin-converting enzyme than II homozygotes (Rigat et al., 1990). A meta-analysis of prevalence studies indicates that the overall frequency of the D allele is 54%, being unrelated to gender but 49.9% lower in Asians (Staessen et al., 1997a,b). It might be expected that increased angiotensin-converting enzyme would be associated with increased incidence of cardiovascular disease, but reviews of the many studies undertaken indicate that the D allele may be associated with coronary artery disease, although there is contradictory evidence; has only a weak association with hypertension, in males only and is not associated with left ventricular hypertrophy (Padmanahhan et al., 2000; Wang and Staessen, 2000). A possible explanation for the lack of association lies in the fact that despite the increase in plasma and tissue angiotensin-converting enzyme associated with the D allele, there is only limited evidence that there is a resultant increase in angiotensin II synthesis (Danser and Schunkert, 2000).

Another gene that has been studied in relation to the cardiovascular system is the angiotensinogen gene, a gene of 13,000 base pairs, 5 exons, 4 introns, located on chromosome lq42-43. Over 10 variants have been identified (Jeunemaitre et al., 1997), but the most studied is that which encodes for threonine instead of methionine at position 235 (M235T). The overall prevalence of the TT genotype is 30.6%, with the TM and MM having 42.9% and 26.5%, respectively. The T allele is less common in whites (42.2%) than in blacks or Asians (77.0% and 78%, respectively) (Wang and Staessen, 2000). Some, but not all, studies have indicated that the T allele is associated with hypertension, but not cardiomyopathy or coronary vascular disease (see Padmanahhan et al., 2000; Wang and Staessen, 2000 for reviews). The hypertension may be related to the raised plasma angiotensinogen associated with the T allele, although plasma angiotensin II concentrations appear to be unaffected (Danser and Schunkert, 2000).

There is also a common polymorphism in the gene encoding for the angiotensin AT_1 receptor, an A-to-C transversion at position 1166 (Bonnardeaux et al., 1994). The C allele has a frequency of 25.7%, and is 77.4% lower in Asians (Staessen et al., 1997a,b). An association between hypertension and the A1166C polymorphism has been reported, although some studies failed to find a correlation (Wang and Staessen, 2000; Padmanahhan et al., 2000). Similar contradictory evidence exists for an association of the C allele with coronary artery disease and cardiomyopathies (ibid.). The clinical importance of this gene polymorphism is unclear as the presence of the C allele appears to be unrelated to AT_1 receptor density or affinity (Paillard et al., 1999) nor responses to angiotensin II (Hilgers et al., 1999; Miller et al., 1999).

3. Angiotensin II and the brain

In addition to its vascular effects, angiotensin II is also known to influence neuronal function. Radioligand binding using ^{125}I-angiotensin II, displaced with $Asn^1–Val^2$–angiotensin II has demonstrated that rat brain has high concentrations of angiotensin receptors in the septum with concen-

Table 2
Common polymorphisms of the renin–angiotensin system

Gene	Polymorphism	Prevalence	Consequence
Angiotensin-converting enzyme	Insertion/Deletion	Insertion = 46%	• Reduced expression of angiotensin converting enzyme • Insertion associated with decreased cognitive decline in elderly • Insertion associated with Alzheimer's Disease
Angiotensinogen	M235T	TT = 30.6%	• Raised plasma angiotensinogen • Hypertension • Association of M allele with Bipolar Depression
AT_1 receptor	A1166C	C = 25.7%	• No effect on receptor density, affinity or efficacy • Possible association with hypertension

trations decreasing, in order, in the thalamus, midbrain, area postrema, medulla, hypothalamus, striatum, cerebellum, hippocampus and cortex. Septal concentrations are approximately 14 times higher than those of the cortex, but are half those found in the anterior pituitary gland and 12% of those of the adrenal glands, the highest concentration of angiotensin receptors (Sirett et al., 1977). Systemic injection of ^{125}I-angiotensin II demonstrated that the receptors of the circumventricular organs (organum vasculosum of the lamina terminalis, the subfornical organ, the median eminence and the area postrema), which are not protected by the blood–brain barrier, are accessible to blood-borne angiotensin II (van Houten et al., 1980). More detailed investigations of angiotensin receptor subtype distribution have shown that there is good inter-species consistency, the species studied being rat, mouse, hamster, dog, monkey and human (Wright and Harding, 1997). Studies in adult human brain revealed that within the forebrain high concentrations of receptors were present in circumventricular organs; all receptors being of the AT_1 subtype (Barnes et al., 1993; MacGregor et al., 1995). In the substantia nigra Barnes et al. (1993) reported that 90% of receptors were AT_1 and that the remainder were AT_2, but MacGregor et al. reported that the receptors were purely AT_1. Lower concentrations of receptors were found within the putamen and caudate nucleus, where the AT_1/AT_2 ratio was 70:30. Within the cerebellum the angiotensin II receptor subtype distribution was found to be approximately 50% AT_1 and 50% AT_2 subtype (Barnes et al., 1993; MacGregor et al., 1995). AT_4 receptors have been found in high concentrations in the cortex, cerebellum, thalamus and hippocampus (Wright and Harding, 1997). A summary of the regional distribution of angiotensin receptor subtypes in the mammalian brain is presented in Table 3.

That the brain angiotensin II receptors are associated with endogenous, brain-derived, angiotensin II is now well established. Brain concentrations of angiotensin II in the rat are approximately 50 fmol/g of brain tissue (range 590 fmol/g in hypothalamus–15 fmol/g in cortex), compared with plasma concentrations of 17 fmol/ml (Hermann et al., 1984). Angiotensinogen, and its mRNA have been identified in the brain and found to be identical to those of the liver and renin and its mRNA are also present in the brain. The distribution of angiotensinogen within the brain generally correlates with the distribution of the angiotensin II receptors but there are also high concentrations within the choroid plexus and astrocytes. Immunohistochemical studies of renin, however, suggest that its distribution is not closely associated with angiotensin II-containing neurones, nor angiotensin II receptors. This finding may reflect an immunological difference between renal and brain renin or may indicate that renin is not the only enzyme involved in the conversion of angiotensinogen to angiotensin I in the brain. Angiotensin-converting enzyme is also widely distributed throughout the brain, it is found associated with the cerebral blood vessels, especially the choroid plexus, with astrocytes of the circumventricular organs, in brain areas with high concentrations of angiotensin II receptors and, paradoxically, in areas such as the basal ganglia where there are low concentrations of angiotensin II receptors. Angiotensin II itself is found within synaptic vesicles in nerve terminals in those areas with high angiotensin II receptor concentrations. These nerve terminals either have synaptic contacts with other neurones or are associated with the fenestrated blood vessels of the circumventricular organs (see Mendelsohn et al., 1990 for review).

Angiotensin II appears to have several roles as a neurotransmitter (for reviews see Ganong, 1984; Phillips, 1987; Phillips and Sumners, 1998), it is involved with thirst, drinking and antidiuretic hormone (ADH, arginine vasopressin) secretion; it has central pressor effects; it facilitates secretion of adrenocorticotrophic hormone (ACTH) and it influences secretion of luteinizing hormone (LH), the nature of the influence being dependent upon the presence or

Table 3
Regional distribution of angiotensin receptors in the mammalian brain

Structure	AT_1	AT_2	AT_4	Structure	AT_1	AT_2	AT_4
Amygdala	✓	✓		Locus Coeruleus	✓	✓	
Anterior Pituitary	✓		✓	Medial Preoptic Nucleus	✓		
Area Postrema	✓			Nucleus Accumbens			✓
Caudate–Putamen	✓	✓	✓	Nucleus of Lateral Olfactory Tract	✓		
Cerebellum	✓	✓	✓	Nucleus of Solitary Tract	✓		
Cerebral Cortex			✓	Organum Vasculosum of the Lateral Terminalis	✓		✓
Geniculate, Lateral	✓		✓	Paraventricular Nucleus of the Hypothalamus	✓		
Geniculate, Medial		✓	✓	Periaqueductal Gray			✓
Globus Pallidus		✓	✓	Piriform Cortex	✓		✓
Habenula, Lateral	✓	✓	✓	Septum		✓	
Habenula, Medial	✓	✓	✓	Subfornical Organ	✓		
Hippocampus			✓	Superior Colliculus	✓		✓
Hypoglossal Nucleus		✓		Supraoptic Nucleus	✓		
Inferior Colliculus		✓		Thalamus		✓	✓
Inferior Olivary Nucleus	✓	✓	✓	Ventral Tegmental Area		✓	✓
Lateral Olfactory Tract			✓				

absence of oestrogens and progesterone. There are also documented interactions between brain angiotensin II and other neurotransmitters such as noradrenaline and 5-hydroxytryptamine (5-HT) (Phillips, 1987). In the brain, angiotensin II potentiates the release of noradrenaline evoked by electrical stimulation or by application of K^+ and in cell culture angiotensin II increases neuronal concentrations of noradrenaline. Conversely, noradrenaline inhibits angiotensin II release and decreases the number of angiotensin II receptors. It therefore appears that there is a form of negative feedback relationship between noradrenaline and angiotensin II. It is also known that angiotensin II activates vasopressinergic neurones (Kisley et al., 2000), which are known not only to synthesise dopamine and noradrenaline (Chernigovskaya et al., 2001) but are also implicated in a range of behavioural processes including cognition (Bohus and de Wied, 1998). Angiotensin II also increases synthesis of 5-HT, an action that may be important in the dipsogenic effects of angiotensin II as 5-HT antagonists reduce the drinking response to angiotensin II in rats.

Angiotensin II, either acting directly, or by modulation of the activity of other transmitters, has been implicated in a range of cognitive and behavioural processes: in animals and humans pharmacological interruption of central angiotensin II activity has been shown to have both antidepressant-like and anxiolytic-like effects. Angiotensin II has also been seen to enhance learning and memory in rats although in humans it is inhibition of angiotensin II activity that has been associated with improved cognition. The aim of the remainder of this review is to describe the evidence that suggests that angiotensin II is important in behaviour and cognition, to explore the possible implications of the known polymorphisms of renin–angiotensin system-related genes in the aetiology of affective and cognitive disorders and to discuss the possible therapeutic potential of pharmacological manipulation of the renin–angiotensin system in the treatment of cognitive and psychological disorders.

3.1. Angiotensin and depression

Evidence exists to implicate angiotensin II in the aetiology and treatment of depressive illness. Repeated administration of antidepressant drugs to rats, with or without an α_2-adrenoceptor antagonist reduces the fluid intake elicited by subcutaneous (s.c.) and introcerebroventricular (i.c.v.) isoprenaline (Goldstein et al., 1985; Przegalinski et al., 1988). These results were initial taken to indicate an antidepressant-induced down-regulation of the central β-adrenoceptors, probably β_2-adrenoceptors (Katovich and Fregley, 1977) although it was recognised that s.c. isoprenaline induces the drinking response by stimulation of the renin–angiotensin system culminating in the production of angiotensin II (Gutman et al., 1971; Houpt and Epstein, 1971; Tang and Falk, 1974). It has subsequently be demonstrated that the antidepressant drugs desipramine, fluoxetine and tranylcypromine are all able to reduce angiotensin II-induced drinking in rats and to antagonize the contractile effects of angiotensin II in isolated smooth muscle (Gard and Mycroft, 1991; Gard et al., 1994). This suggests that the reduction of isoprenaline-induced drinking is achieved by antagonism of angiotensin II. The antagonistic effect, however, is probably non-competitive: the antidepressant drugs do not displace radiolabelled angiotensin II from its receptors nor are they selective antagonists for angiotensin II, raising the possibility that they act on the post-receptor signal transduction processes (Gard and Barnes, 1994; Gard et al., 1999).

The conclusion that antidepressant drugs of differing classes may block the actions of angiotensin II was of particular interest in the light of earlier case reports that angiotensin-converting enzyme inhibitors have antidepressant-like effects. In hypertensive patients who also suffered from depression it was noted that, unlike other antihypertensive therapies, the angiotensin-converting enzyme inhibitor captopril elicited a significant improvement in mental state (Zubenko and Nixon, 1984; Deicken, 1986; Germain and Chouinard, 1988, 1989). Similar results were reported in learned helplessness, an animal model of antidepressant activity. The most commonly used method for the assessment of learned helplessness is the forced swim test. The method involves placing mice or rats into water from which they cannot escape. Initially the animals swim around, but eventually they become immobile as a result of despair rather than exhaustion. If the animals are placed into the water again 1 day later, they adopt immobility much sooner than during the initial trial and subsequently swim much less than previously; administration of antidepressant drugs prior to the second trial reduces the extent of immobility. In mice, a single i.p. dose of captopril 10 or 30 mg/kg reduced immobility to the same extent as the reduction produced by the proven antidepressants imipramine 30 mg/kg and mianserin 3 mg/kg (Giardina and Ebert, 1989). In another assessment of learned helplessness in which rats become refractory to escape from footshock, 5 days treatment with captopril 16 and 32 mg/kg/day i.p. reduced escape to the same degree as imipramine 32 mg/kg/day i.p. (Martin et al., 1990). In both of these studies the effects of captopril could be reversed by naloxone, suggesting that the antidepressant-like effect of the angiotensin-converting enzyme inhibitor involved opioid mediation. It is probable, however, that the antidepressant-like effects of captopril involve reduced angiotensin II function, as opposed to inhibition of any other actions of angiotensin-converting enzyme, as the AT_1 receptor antagonist losartan has also been shown to give positive antidepressant-like results in a modification of the mouse forced swim test in which there is no prior conditioning (Gard et al., 1999).

Overall the experimental and clinical results suggest that antidepressant drugs reduce angiotensin II function, possible via a post-receptor action, and that drugs which decrease angiotensin II function, i.e. angiotensin-converting enzyme inhibitors or angiotensin II antagonists, exhibit antidepres-

sant-like properties. In an attempt to investigate the possible role of angiotensin II in the aetiology of depression, platelet AT_1 receptors were studied in a population prone to depressive symptomatology. Platelets were harvested from women in late pregnancy and again at times during the first 6 months post-partum, which correlated with the peak prevalences of purperal 'blues' and post-partum depression. No relationship was found between the number of receptors and the severity of the depressive symptoms (Gard et al., 1999). Such results suggest that there is no correlation between angiotensin receptor density and mood although the results may have been confounded by the profound endocrine changes that occur post-partum (it is known that angiotensin II function is influenced by oestrogens and progesterone, Nakamura et al., 1988; Ghazi et al., 1994); by the very low numbers of angiotensin receptors expressed in platelets and by the assumption that platelet receptor expression reflects changes in brain receptor expression.

3.2. Angiotensin and anxiety

Georgiev et al. (1987) reported that angiotensin II influenced rat behaviour in an open field. The dose response relationship was non-linear and time-dependent, thus 1 and 10 μg angiotensin II i.c.v. reduced locomotion and rearing 5 min after administration, but 5 μg had no significant effect. The effect was short-lived as 15 min after drug administration none of the doses had any significant effect on locomotion, but 1 and 5 μg angiotensin II now significantly increased rearing and grooming, evidence of a possible rebound effect. These latter effects of angiotensin II could be antagonized by co-administration of saralasin, a non-selective angiotensin receptor antagonist; 15 min pretreatment with the antagonist alone gave effects opposite to those of angiotensin II, significantly reducing locomotion, rearing and grooming and suggesting possible antagonism of endogenous angiotensin II. The later (15 min) behavioural effects of angiotensin II were reported to be prevented by the dopamine antagonist haloperidol and potentiated by the dopamine agonist apomorphine and the dopamine reuptake inhibitor/receptor agonist nomifensin. These results could be taken to indicate that angiotensin II initially increases anxiety-related behaviour but that there is a rebound reduction. The studies with dopamine antagonists, etc., suggest that the 'rebound anxiolysis' may involve increased dopaminergic activity although re-examination of the data suggests that the effects may be dependent on the effects of haloperidol, apomorphine and nomifensin on the open field behaviour rather than any pharmacological interaction.

Administration of captopril, ceronapril (another angiotensin-converting enzyme inhibitor) and losartan to rats and mice reduces behaviour normally susceptible to reduction by proven anxiolytics drugs. Using the light–dark aversion test, in which mice are placed into an environment in which 40% is black and illuminated by a red light and the remainder is white and illuminated by a bright light, mice have a natural aversion to the light and thus move to the dark area. Anxiolytic drugs increase the proportion of time that the mice spend in the aversive, bright area. Captopril, ceronapril and losartan have been shown to exhibit anxiolytic properties commensurate with the positive control diazepam (Costall et al., 1990; Barnes et al., 1990b). Similar results have been obtained in the elevated plus-maze in rats (Costall et al., 1990; Kaiser et al., 1992) and, for losartan, in mice (Cambursano et al., 1997), where the anxiolytic drugs increase the amount of time spent on the aversive open arms of the elevated cross-shaped maze in preference to the less aversive enclosed arms. Shepherd et al. (1996), however, were unable to replicate the anxiolytic-like effects of losartan in either rats or mice, possibly due to differences in the strain of animals tested (see later). Captopril and ceronapril also elicit anxiolytic-like responses in marmosets (Costall et al., 1990).

The initial studies of Georgiev described above suggested that angiotensin II caused an initial decrease in exploratory behaviour, which may reflect increased anxiety followed by a second period of increased exploration, saralasin produced the opposite effects. The second body of evidence suggested that decreasing angiotensin II function reduced behaviours associated with anxiety. In another measure of behaviour associated with anxiety in rats, defensive burying of an aversive stimulus, 10-min pretreatment with angiotensin II or saralasin had anxiolytic-like effects (Tsuda et al., 1992), which gives confusing messages about the role of angiotensin II in anxiety-like behaviours. In a more recent study combining elevated plus-maze and defensive burying in mice, however, it was revealed that i.p. losartan produced anxiolytic-like, and i.p. angiotensin II anxiogenic-like, responses 15 and 30 min after administration but opposite responses during the first 15 min with losartan causing anxiogenic-like burying and angiotensin II suppressing burying (Cresswell and Gard, 1998). The early anxiogenic-like effect of losartan was blocked by prior administration of the selective AT_2 receptor antagonist *S*(+)-1-[[4-(Dimethylamino)-3-methylphenyl] methyl]-5-(diphenylacetyl)-4,5,6,7-tetrahydro-1*H*-imidazo [4,5-*c*] pyridine-6-carboxylic acid ditrifluoroacetate (PD123319) (ibid.) suggesting that AT_1 receptor activity initially unmasked a previously unreported, short-lived, AT_2 receptor-mediated anxiogenic-like response, but eventually resulted in reduced anxiety-related behaviours.

In summary the results suggest that central administration of angiotensin II causes an early (5 min) increase in behaviours associated with anxiety, and a later (15 min) decrease in such behaviours. Peripheral administration of angiotensin II, however, causes early decreases in anxiety-like behaviours and later increases. Peripheral administration of drugs which decrease angiotensin II function causes early anxiety-like behaviour, possible AT_2 receptor-mediated, and later anxiolytic-like effects. A summary of these results is presented in Table 4.

Overall, it is apparent that angiotensin influences anxiety-like behaviour but that the nature of that influence depends

Table 4
Time dependency of the effects of alterations of central renin–angiotensin system activity on anxiety-related behaviour in rats and mice

Refs.	Route	Treatment	Species	Early Effect	Late effect
Georgiev et al. (1987)	i.c.v.	Angiotensin II	Rat	Increased anxiety-related behaviour (5 min)	Decreased anxiety-related behaviour (15 min)
Costall et al. (1990), Barnes et al. (1990b)	i.p.	Angiotensin-converting enzyme inhibitors	Rat	–	Decreased anxiety-related behaviour (Chronic dosing)
Cambursano et al. (1997)	i.p.	Losartan	Mouse	–	Decreased anxiety-related behaviour (30 min)
Tsuda et al. (1992)	i.c.v.	Angiotensin II	Mouse	Decreased anxiety-related behaviour (10 min)	–
		Saralasin		Increased anxiety-related behaviour (15 min)	–
Cresswell and Gard (1998)	i.p.	Angiotensin II	Mouse	Decreased anxiety-related behaviour (5 min)	Increased anxiety-related behaviour (15 min)
		Losartan		Increased anxiety-related behaviour (5 min)	Decreased anxiety-related behaviour (15 min)

on the route of drug administration, the time of testing after drug administration and possibly the relative predominance of AT_1 and AT_2- receptor-mediated responses. The mechanism of action of angiotensin II in its effects on anxiety-like behaviour is also still unknown. It has been suggested that dopaminergic pathways play an important role (see above), but it has also been suggested that γ-amino butyric acid (GABA) may be involved. The latter suggestion arises from the demonstrations that angiotensin II potentiates the actions of GABA (Georgiev et al., 1995), and that captopril suppresses the anxiety-like behaviour elicited by diazepam withdrawal (Costall et al., 1990). Whether both dopamine and GABA are equally important or whether one is more important than the other remains to be clarified.

3.3. Angiotensin and cognition

Learning and memory is assessed in animals using a variety of methods such as mazes, passive or conditioned avoidance and object recognition. Passive and conditioned avoidance tasks are commonly used measures of cognitive function, specifically associative learning, whilst mazes and object recognition are seen to assess spatial memory. Administration of a drug prior to the training sessions provides insight into the drug effects on acquisition, retention (storage) and recall, whereas drug administration post-training assesses drug effects on retention and recall only.

In a conditioned (active) avoidance task, an animal must learn to exhibit a behaviour that it normally would not exhibit, in order to avoid receiving an aversive stimulus. An example of an active avoidance task would be to place an animal into a cage that is partitioned into a light and dark chamber. Rodents prefer dark, enclosed spaces, so when placed into the dark chamber, the animal will typically only slowly move into the light chamber. If, when the rat or mouse is placed into the preferred dark chamber, it receives a mild electric shock (the learning trial), on subsequent tests it will remember to actively move to the light chamber within seconds of being placed in the apparatus in order to avoid receiving additional shocks. Memory and learning is assessed by the number of training sessions required prior to acquiring the task and by a decrease in the latency to enter the light chamber on subsequent tests. Both pre- and post-trial i.c.v. injection of angiotensin II facilitated learning and retention in such a conditioned avoidance test in rats (Georgiev and Yonkov, 1985). The pre-training effects of angiotensin II were antagonised by co-administration of the non-selective AT_1/AT_2 receptor antagonist saralasin although saralasin alone had no significant effects. Saralasin, when administered alone or in combination with angiotensin II immediately after training significantly improved memory but antagonised the facilitating effect of angiotensin II (ibid.). These results suggest that angiotensin II acts directly on brain angiotensin receptors to enhance associative memory and learning and that there are differential effects of angiotensin II on acquisition and on storage and recall.

These results were then extended by the work of Braszko and colleagues who reported that losartan was able to abolish the ability of angiotensin II to improve object recognition in rats, although it had no significant effect on angiotensin II-enhanced conditioned avoidance (Kulakowska et al., 1996). Object recognition is an assessment of spatial memory in which rats are placed individually into an arena containing two identical objects made of porcelain or glass. Twenty-four hours after initial habituation the rats are exposed to one familiar and one novel object, the amount of time spent exploring the novel object is taken as a measure of memory. The results were taken to highlight the involvement of AT_1 receptors in spatial memory.

Further work utilized object recognition, conditioned avoidance and passive avoidance to assess the differential roles of the angiotensin receptor subtypes in cognition using angiotensin-(3–7), a naturally occurring metabolite of angiotensin II. In a passive avoidance task, the animal is trained to suppress an action that it would normally exhibit. Thus, for example, a rat may be trained to avoid a dark area, in which it will receive an electric shock, in preference for a bright area. Memory and learning is again assessed by the

number of training sessions required prior to acquiring the task and by the display of increased latencies to enter the dark 'shock' chamber on subsequent tests. Pretreatment with angiotensin-(3–7) was found to mimic angiotensin II in its ability to enhance passive avoidance, conditioned avoidance and object recognition in rats (Karwowska-Polecka et al., 1997). Angiotensin-(3–7) is a low-affinity agonist at AT_1 receptors but binds with much higher affinity to AT_4 receptors; its effects on passive avoidance and object recognition were antagonized by losartan, suggesting the involvement of AT_1 receptors, but there was no significant reduction of the enhanced conditioned avoidance, suggesting the involvement of AT_4 receptors (ibid.).

Paradoxically, a conflicting body of evidence also exists concerning the role of angiotensin II in cognition. The above mentioned studies suggest that angiotensin II enhances animal memory and learning, but other studies suggest that angiotensin II decreases cognition. Barnes et al. (1989) reported enhanced learning in mice receiving angiotensin-converting enzyme inhibitors. Using a light–dark aversion paradigm similar to that used for the assessment of anxiety-related behaviour (see above), it was shown that repeated exposure to the apparatus decreased the latency of movement of the mouse through the partition from the aversive bright area to the dark area. Twice daily i.p. administration of angiotensin-converting enzyme inhibitors at low doses, for example 50 μg/kg captopril, enhanced the rate of the learning. Furthermore, learning deficits in aged mice or those induced by scopolamine or lesion of the nucleus basalis were also reversed by angiotensin-converting enzyme inhibitors.

The same authors also investigated the effects of angiotensin-converting enzyme inhibitors on rat learning using a T-maze in which food deprived rats were placed onto one arm of the elevated maze, and food was placed into a dish at the end of one of the other two arms. The rat is required to explore the maze and to learn which arm normally contains the food reward. Subsequent baiting of alternate arms meant that the rats had to learn that reward in one arm was followed by reward in the alternate arm. Learning and memory is assessed as the number of correct choices made by the rat in entering the arms of the maze; ceronapril (50 μg/kg), but not captopril (1.0 mg/kg), was able to reverse scopolamine-induced deficits in learning. Techniques such as this are perceived to involve both reference memory and working memory, reference memory being the longer term, day-to-day, memory; remembering that a reward is present at the end of an arm, working memory being which arm contained the reward on the previous trial.

Ceronapril was also effective in a water maze task in which the animal is placed into a tank filled with opaque water and trained to swim to a hidden platform that is located just beneath the surface of the water. The animals find the immersion aversive and thus are highly motivated to find the platform to get out of the water. Animals are introduced into the water at different locations around the tank and thus because the platform is not visible, the animals must depend on their spatial memory and use extra-maze visual cues to locate the platform. Ceronapril (5 μg/kg) again reversed scopolamine-induced deficits in the learning task; captopril was not tested (ibid.). A summary of the effects of increased and decreased angiotensin II function in animal models of learning and memory is presented in Table 5.

The findings of Barnes and colleagues are contradictory to those of Georgiev and Braszko. The suggested mechanism of the memory-enhancing effects of the angiotensin-converting enzyme inhibitors was proposed to involve reduction of the demonstrated ability of angiotensin II to inhibit acetylcholine release from brain slices (Barnes et al., 1990a), although the differences in the responses to the two inhibitors remains unexplained. This proposal, however, is confounded by the work of Chen and Mendelsohn (1992) which showed that ceronapril, at the high oral dose of 100 mg/kg twice daily

Table 5
Conflicting evidence of the role of angiotensin II in memory and learning as assessed by animal behavioural models

Drug	Route	Method	Species	Conclusion	Receptor subtype	Refs.
Ang II	i.c.v.	Conditioned avoidance	Rat	Ang II facilitates learning and memory	–	Georgiev and Yonkov (1985)
Ang II/Losartan	i.c.v.	Conditioned avoidance Object recognition	Rat	Ang II facilitates associative nd spatial memory	Associative memory: non-AT_1 Spatial memory: AT_1	Kulakowska et al. (1996)
Ang-(3–7)/Losartan	i.c.v.	Conditioned avoidance Passive avoidance Object recognition	Rat	Ang II facilitates associative and spatial memory	Conditioned avoidance: AT_4 Passive avoidance: AT_1 Object recognition: AT_1	Karwowska-Polecka et al. (1997)
Captopril	i.p.	Conditioned avoidance	Mouse	ACE inhibition facilitates learning	–	Barnes et al. (1989)
Ceronapril	i.p.	T maze Water maze	Rat	ACE inhibition facilitates learning	–	Barnes et al. (1989)
Losartan	i.p.	Passive avoidance Elevated-plus maze	Mouse	AT_1 antagonist facilitates learning	AT_1	Raghavendra et al. (1998)

Ang II: angiotensin II, ACE: angiotensin converting enzyme.

in rats, inhibited angiotensin-converting enzyme in the circumventricular organs, but not within structures protected by the blood–brain barrier. The consequences of a failure of a converting enzyme inhibitor to cross the blood–brain barrier are unclear, but in preliminary, unpublished, studies we have shown that Captopril (2 mg/kg, i.p.) enhanced salbutamol-induced drinking in rats. The proposed mechanism involves peripheral inhibition of converting enzyme resulting in increased availability of the substrate angiotensin I for the uninhibited enzyme within the brain. Whether such an effect could reconcile the conflicting results of Barnes and Georgiev/Braszko and explain the demonstrated cognitive-enhancing effects of angiotensin-converting enzyme inhibitors is unknown. In relation to the two bodies of evidence, however, it is important to note that the cognitive-enhancing effects of angiotensin II have been observed following i.c.v. administration whilst the effects of angiotensin-converting enzyme inhibitors were observed following peripheral administration.

Raghavendra et al. (1998) reported that losartan was able to enhance memory in mice, as assessed by a passive avoidance task and by the elevated plus-maze. Furthermore, losartan reversed the cognitive deficits induced by scopolamine and itself was potentiated by co-administration of a cholinesterase inhibitor. Losartan being an AT_1 receptor antagonist, these results support the initial hypothesis of Barnes and suggest the cognitive-enhancing effect of angiotensin II suppression and indicate a mediating role of acetylcholine.

The contradiction of the results of the studies of the renin–angiotensin system and cognition is further compounded by the fact that passive and conditioned avoidance tasks are based upon avoidance of or escape from aversive stimuli; they therefore depend upon or involve an element of fear or anxiety, the same is true of the water maze. As described earlier, in tests of anxiolytic activity, angiotensin-converting enzyme inhibitors and losartan have been shown to cause decreased anxiety-associated behaviour, although there may be an initial, short-lived, AT_2 receptor-mediated, increase in anxiety-related behaviour. Anxiolytic drugs increase the time spent on the open arms of the elevated plus-maze or in the bright area of the light aversion test, and thus such effects might be expected to be manifested as a reduction in cognition. The interplay of anxiety and cognition could possible explain some of the findings of Georgiev and Braszko in their independent studies of conditioned avoidance, but it is interesting to note that Barnes has reported both an anxiolytic effect of captopril, which reduces avoidance of an aversive stimulus (Barnes et al., 1990b) and a nootropic effect, which potentiates the avoidance of an aversive stimulus (Barnes et al., 1989).

Measurement of long-term potentiation in specific neurones is another method of studying memory and learning, independent of the behavioural consequences of ‘anxiety’ although the relevance of long-term potentiation as a measure of memory and its correlation with behavioural measures of memory has been questioned (Hilscher, 1997). Denny et al. (1991) reported that angiotensin II injected above the hippocampus in the intact rat blocked the induction of long-term potentiation in perforant path-stimulated dentate granule cells. That the effect was mediated by AT_1 receptors was later demonstrated by its antagonism by losartan (Wayner et al., 1993), although angiotensin II binding in the hippocampus is predominantly to AT_4 receptors (Wright and Harding, 1995). Angiotensin II also suppresses long-term potentiation in the lateral nucleus of the amygdala (von Bohlen und Halbach et al., 1998); receptors of the amygdala are of the AT_1 and AT_2 subtypes, with little AT_4 receptor binding (Wright and Harding, 1995). The effects of angiotensin II on long-term potentiation in the amygdala were antagonised by losartan but not by PD123,319, the selective AT_2 receptor antagonist (von Bohlen und Halbach et al., 1998). These results suggest that angiotensin II acts on AT_1 receptors to suppress memory, and thus support the proposals of Barnes and colleagues. The apparent involvement of AT_4 receptors in memory and learning, however, is re-emphasised by the recent biochemical evidence that angiotensin IV and LVV-hemorphin-7, both agonists of the AT_4 receptor, potentiate the release of acetylcholine from rat hippocampal brain slices (Lee et al., 2001). Table 6 summarises the findings of electrophysiological and biochemical studies investigating the role of angiotensin II in learning and memory.

The precise involvement of angiotensin II in cognition is thus unclear. The work of Georgiev and Braszko indicate that angiotensin II enhances memory and learning, effects that may involve both AT_1 and AT_4 angiotensin receptors. The work of Barnes and others, however, suggests that memory is enhanced by administration of angiotensin-converting enzyme inhibitors, at doses which may not be able to

Table 6
Evidence of the role of angiotensin II in memory and learning as assessed by electrophysiological and biochemical studies

Drug	Site of administration	Method	Species	Conclusion	Receptor subtype	Refs.
Ang II/Losartan	Hippocampus	Electrophysiology	Rat	Ang II inhibits of long-term potentiation	AT_1	Denny et al. (1991), Wayner et al. (1993)
Ang II/Losartan	Amygdala	Electrophysiology	Rat	Ang II inhibits of long-term potentiation	AT_1	von Bohlen und Halbach et al. (1998)
Ang IV/LVV-hemorphin-7	Hippocampus	Acetylcholine release	Rat	Potentiation of acetylcholine release	AT_4	Lee et al. (2001)

Ang II: angiotensin II.

penetrate the brain beyond the circumventricular organs; is enhanced by losartan; and that angiotensin II suppresses long-term potentiation.

The clinical evidence tends to support the findings of Barnes and colleagues: captopril treatment of hypertension has been associated with a perceived improvement in quality of life in several studies (e.g., Croog et al., 1986) although whether this improvement reflects improved cognition or other parameters is unclear. Another angiotensin-converting enzyme inhibitor, enalapril, however, does not appear to induce the same psychological effects as captopril, despite being equivalent in its antihypertensive effects (Testa et al., 1993). Losartan has also been shown to improve cognitive function in hypertensive patients, an effect that was not apparent in patients treated with the diuretic hydrochlorthiazide (Tedesco et al., 1999).

Attempts to relate cognition, the renin–angiotensin system and Alzheimer's disease have been unsuccessful. Ge and Barnes (1996) reported a lack of association between Alzheimer's disease and brain AT_1 receptors although there was a substantial increase in AT_2 receptor density in the temporal cortices of such patients, which may indicate the involvement of angiotensin II in the degenerative process. Savaskan et al. (2001), however, reported increased angiotensin-converting enzyme, angiotensin II and AT_1 receptor immunoreactivity in the cortices of Alzheimer's patients, particularly in association with the microvasculature. Angiotensin-converting enzyme inhibitors appear to be ineffective in improving cognitive function in Alzheimer's patients (Sudilovsky et al., 1993).

4. Renin–angiotensin system polymorphisms and behavioural differences

In animals, angiotensin II has been implicated in learning and memory, the mechanism of action of antidepressant drugs and in anxiety-related behaviour. In the light of the known polymorphisms of genes associated with the renin–angiotensin system, there is thus the potential for genetic differences in cognition and behaviour in humans dependent upon variations in activity of the brain renin–angiotensin system. In animals evidence of such differences are already extant in the identified species and strain differences in the behavioural effects of modification of the renin–angiotensin system.

Using Wistar strain rats, Georgiev and Braszko independently studied the effect of angiotensin II and found that it increased memory and learning (Georgiev and Yonkov, 1985; Kulakowska et al., 1996) whilst in hooded Lister rats, Barnes and colleagues implied that angiotensin II decreased memory and learning (Barnes et al., 1989). Whether the differences are solely due to rat strain is unknown but a study of object recognition in different strains of rat has indicated that Long–Evans rats have significantly greater object recognition than Wistar-Kyoto, BB or Lewis rats; Lewis rats being significantly poorer than the other three strains. It was also found that there were significant differences in the brain angiotensin II binding between the strains and that there was a positive correlation between performance in the object recognition test and brain angiotensin II binding (Karwowska-Polecka et al., 2000). These results indicate a relationship between endogenous AT_1 receptor expression in the brain and cognitive behaviour.

Strain differences have also been demonstrated in the behavioural role of angiotensin II in the mouse. Using the light–dark box with BKW strain mice, Costall, Barnes and colleagues (Costall et al., 1989; Barnes et al., 1990b) found that reduction in angiotensin II activity decreased the latency in movement from the light area to the dark, these results were used to indicate both increased cognition and decreased anxiety-like behaviour, respectively. Shepherd et al. (1996), using losartan in TO strain mice, however, was unable to replicate the results. In a study of strain differences in murine responses to losartan, Costall et al. (1989) and Gard et al. (2001) have demonstrated that BKW mice exhibit a high degree of anxiety-like behaviour, more than the other strains studied; BKW strain was the only strain to respond to the anxiolytic effects of losartan (Gard et al., 2001). In the same study it was also reported that the contractile responses of the isolated colon to angiotensin II were significantly smaller in BKW mice than in the other two strains studied, suggesting a generalized deficit in angiotensin II function in BKW mice, which may explain the increased response to the AT_1 receptor antagonist.

Behavioural differences have also been studied in rats and mice with known polymorphisms of renin–angiotensin system-related genes. Transgenic (mREN2)27 hypertensive rats with an altered brain renin–angiotensin system, for example, show greater anxiety-like behaviour than Sprague–Dawley rats (Wilson et al., 1996). Similarly, targeted disruption of the AT_2 receptor gene in mice (knockout) results in the production of an animal which displays anxiety-like behaviour which can be reversed by diazepam, captopril and an α_1-adrenoceptor antagonist (Okuyama et al., 1999), a result disparate with the earlier suggestion of an anxiogenic response to AT_2 receptor stimulation. In other studies, the Wistar-Kyoto rat has been proposed as a model of refractory depression as it not only exhibits greater depression-like behaviour than Sprague–Dawley rats but also shows a lesser response to antidepressant drugs (Lahmame et al., 1997); Wistar-Kyoto differ from Sprague–Dawley in the first intron of the renin gene. Finally, spontaneously hypertensive rats, which have a known abnormality of the renin–angiotensin system (see above) have been used as a model of attention deficit hyperactivity disorder (Sagvolden and Xu, 2000).

A small number of studies have investigated renin–angiotensin system-related gene polymorphisms in relation psychological disorders in humans. Richard et al. (2000) studied cognitive decline over 4 years in 1168 subjects aged 59–71. At the outset of the study there was a significant relationship between angiotensin-converting enzyme I/D

genotype and scores on the Mini Mental State Examination (MMSE), with DD scoring lowest, ID intermediate and II highest. At the 4-year follow up the DD also showed significantly greater cognitive decline than the other two groups, although the differences were small and not indicative of gross changes such as dementia. Similarly Bartres-Faz et al. (2000) reported that there was a greater prevalence of the D allele and reduced prevalence of the I allele in patients with age-associated memory impairment. In contrast no relationship was found between angiotensin-converting enzyme I/D genotype and dementia (Tysoe et al., 1997).

A greater number of studies have investigated polymorphisms and Alzheimer's disease. In a study of 350 Alzheimer's patients, it was found that there was a 28% increase in the frequency of the angiotensin-converting enzyme I allele compared to healthy controls (Alvarez et al., 1999). Similar results were also found in a study of 80 patients with Alzheimer's disease alone and in 34 patients with Alzheimer's disease with concomitant Parkinsonism (Matlia et al., 2000), although a study in a Turkish population found no association between angiotensin-converting enzyme genotype and either Alzheimer's disease or Parkinson's disease (Agachan et al., 2000). In a Han Chinese population, the frequency of the I allele amongst cases of Alzheimer's disease presenting after the age of 70 was twice that of the control group (Yang et al., 2000). Conversely, no association was found between angiotensin-converting enzyme genotype and Alzheimer's pathology in 113 patients diagnosed clinically and 121 patients diagnosed neuropathologically (Myllykangas et al., 2000), nor in a study of 204 patients compared to 186 controls (Prince et al., 2001). One study has found a greater association of Alzheimer's disease with homozygote II and DD patients in comparison with heterozygote ID patients (Narain et al., 2000).

Angiotensin-related polymorphisms have also been investigated in patients with affective disorders and psychoses. The angiotensin-converting enzyme D allele has been seen to be more frequent in Japanese patients with affective disorders, but there was no association with schizophrenia (Arinami et al., 1996). The D allele has also been associated with a more rapid response to antidepressant therapy (Baghai et al., 2001). Three studies have failed to replicate the association between angiotensin-converting enzyme genotype and either unipolar or bipolar depression (Furlong et al., 2000; Miera-Lima et al., 2000; Pauls et al., 2000), although one study found an increased frequency of the M allele of the M235T angiotensinogen gene amongst bipolar depressive patients (Miera-Lima et al., 2000).

5. Therapeutic implications of manipulation of the renin–angiotensin system

The evidence from both animal and human studies indicate that the brain renin–angiotensin system influences mood and cognition, although as yet no firm links have been determined between renin–angiotensin system activity and human psychopathology. Therapeutic use of agents to modulate angiotensin II and AT_1 receptor activity in cardiovascular medicine has provided insight into potential, alternative uses for these agents, for example in the treatment of anxiety and depression, but the effects of AT_2 and AT_4 receptor agonists and antagonists remain unexplored. With studies of renin–angiotenin system-associated polymorphisms still in progress and with AT_4 receptor relatively uninvestigated there is a possibility that angiotensin-related subtypes of depression, anxiety or dementias may be identified which, in turn, would permit development and use of more specific pharmacological agents. The role of the brain renin–angiotensin system in human psychopathology remains to be fully explored.

References

Agachan, B., Yilmaz, H., Aydin, M., Isbir, T., 2000. Is there any association between apolipoprotein E and angiotensin converting enzyme gene polymorphism in patients with Parkinson's disease and dementia in Turkish Population? Neurosci. Res. Commun. 27, 165–173.

Alvarez, R., Alvarez, V., Lahoz, C.H., Martinez, C., Pena, J., Sanchez, J.M., Guisasola, L.M., Salas-Puig, J., Moris, G., Vidal, J.A., Ribacoba, R., Menes, B.B., Uria, D., Coto, E., 1999. Angiotensin converting enzyme and endothelial nitric oxide synthase DNA polymorphisms and late onset Alzheimer's disease. J. Neurol. Neurosurg. Psychiatry 67, 733–736.

Arinami, T., Li, L.M., Mitsushio, H., Itokawa, M., Hamaguchi, H., Toru, M., 1996. An insertion/deletion polymorphism in the angiotensin converting enzyme gene is associated with both brain substance P contents and affective disorders. Biol. Psychiatry 40, 1122–1127.

Baghai, T.C., Minov, C., Schüle, C., Zwanger, P., Schwarz, M.J., de Jonge, S., Rupprecht, R., Bondy, B., 2001. The angiotesin-converting enzyme gene polymorphism is associated with the onset of antidepressant efficacy in major depressive patients. Biol. Psychiatry 49, 107S.

Barnes, J.M., Barnes, N.M., Costall, B., Coughlan, J., Horovitz, Z.P., Kelly, M.E., Naylor, R.J., Tomkins, D.M., 1989. ACE inhibition and cognition. In: MacGregor, G.A., Sever, P.S. (Eds.), Current Advances in ACE Inhibition, Proceedings of an International Symposium. Churchill Livingstone, Edinburgh, pp. 159–171.

Barnes, J.M., Barnes, N.M., Costall, B., Horovitz, Z.P., Ironside, J.W., Naylor, R.J., Williams, T.J., 1990a. Angiotensin-II inhibits acetylcholine-release from human temporal cortex—implications for cognition. Brain Res. 507, 341–343.

Barnes, N.M., Costall, B., Kelly, M.E., Murphy, D.A., Naylor, R.J., 1990b. Anxiolytic-like action of DuP753, a non-peptide angiotensin II receptor antagonist. NeuroReport 1, 15–16.

Barnes, J.M., Steward, L.J., Barber, P.C., Barnes, N.M., 1993. Identification and characterisation of angiotensin II receptor subtypes in human brain. Eur. J. Pharmacol. 230, 251–258.

Batres-Faz, D., Junque, C., Clemente, I.C., Lopez-Alomar, A., Valveny, N., Lopez-Guillan, A., Lopez, T., Cubells, M.J., Moral, P., 2000. Angiotensin I converting enzyme polymorphisms in humans with age-associated memory impairment: relationship with cognitive performance. Neurosci. Lett. 290, 177–180.

Bohus, B., de Wied, D., 1998. The vasopressin deficient Brattleboro rats: a natural knockout model used in the search for CNS effects of vasopressin. Adv. Brain Res. 119, 555–573.

Bonnardeaux, A., Davies, E., Jeunemaitre, X., Fery, I., Charru, A., Clauser, E., Tiret, L., Cambien, F., Corvol, P., Soubrier, F., 1994. Angiotensin type-1 receptor gene polymorphisms in human essential hypertension. Hypertension 24, 63–69.

Cambursano, P.T., Haigh, S.J., Keightley, J., Sutcliffe, M.A., Gard, P.R., 1997. Positive effects of losartan in laboratory tests indicative of anxiolytic-like activity and the importance of animal strain. J. Pharm. Pharmacol. 49 (suppl. 4), 64.

Campbell, D.J., Duncan, A.M., Kladis, A.M., Harrap, S.B., 1995. Angiotensin peptides in spontaneously hypertensive and normotensive Donryu rats. Hypertension 25, 928–934.

Chen, B.Z., Mendelsohn, F.A.O., 1992. Effect of acute and chronic administration of ceronapril on angiotensin converting enzyme in plasma, kidney, lung, brain-regions and cerebrospinal-fluid of rats. Neuropharmacology 31, 929–935.

Chernigovskaya, E.V., Glazova, M.V., Yamova, L.A., Yevteeva, S.E., Krasnovskaya, I.A., 2001. Role of catecholamines in regulation of the functional state of vasopressinergic cells of the rat hypothalamus. J. Evol. Biochem. Physiol. 37, 192–199.

Costall, B., Jones, B.J., Kelly, M.E., Naylor, R.J., Tomkins, D.M., 1989. Exploration of mice in a black and white test box: validation as a model of anxiety. Pharmacol. Biochem. Behav. 32, 777–785.

Costall, B., Domeney, A.M., Gerrard, P.A., Horovitz, Z.P., Kelly, M.E., Naylor, R.J., Tomkins, D.M., 1990. Effects of captopril and SQ29,852 on anxiety-related behaviours in rodent and marmoset. Pharmacol., Biochem. Behav. 36, 13–20.

Cresswell, A.G., Gard, P.R., 1998. Behavioural evidence of a paradoxical anxiogenic effect of an angiotensin II (AT1) receptor antagonist. J. Pharm. Pharmacol. 50, 215 (suppl.).

Croog, S.H., Levine, S., Testa, M.A., Brown, B., Bulpitt, C.J., Jenkins, C.D., Klerman, G.L., Williams, G.H., 1986. The effects of antihypertensive therapy on the quality-of-life. New Engl. J. Med. 314, 1657–1664.

Danser, A.H.J., Schunkert, H., 2000. Renin–angiotensin system gene polymorphisms: potential mechanisms for their association with cardiovascular diseases. Eur. J. Pharmacol. 410, 303–316.

de Gasparo, M., Catt, K.J., Inagami, T., Wright, J.W., Unger, T., 2000. The angiotensin II receptors. Pharmacol. Rev. 52, 415–472.

Deicken, R.F., 1986. Captopril treatment of depression. Biol. Psychiatry 21, 1425–1428.

Denny, J.B., Polancurtain, J., Wayner, M., Armstrong, D.L., 1991. Angiotensin-II blocks hippocampal long-term potentiation. Brain Res. 567, 321–324.

Furlong, R.A., Keramatipour, M., Ho, L.W., Rubinsztein, J.S., Michael, A., Walsh, C., Paykel, E.S., Rubinsztein, D.C., 2000. No association of an insertion/deletion polymorphism in the angiotensin I converting enzyme gene with bipolar or unipolar affective disorders. Am. J. Med. Genet. 96, 733–735.

Ganong, W.F., 1984. The brain renin–angiotensin system. Annu. Rev. Physiol. 46, 17–31.

Gard, P.R., Barnes, N.M., 1994. The effects of desipramine and fluoxetine on responses to angiotensin and angiotensin receptors. Can. J. Physiol. Pharmacol. 72 (Suppl. 1), 439.

Gard, P.R., Mycroft, N., 1991. Reduction of angiotensin II-induced drinking in rats by 21 hour pretreatment with desipramine. J. Pharm. Pharmacol. 43, 1 (suppl.).

Gard, P.R., Mandy, A., Whiting, J.M., Nickels, D.P.D., Meakin, A.J.L.S., 1994. Reduction of responses to angiotensin II by antidepressant drugs. Eur. J. Pharmacol. 264, 295–300.

Gard, P.R., Mandy, A., Sutcliffe, M.A., 1999. Evidence of a possible role of altered angiotensin function in the treatment, but not aetiology, of depression. Biol. Psychiatry 45, 1030–1034.

Gard, P.R., Haigh, S.J., Cambursano, P.T., Warrington, C.A., 2001. Strain differences in the anxiolytic effects of losartan in the mouse. Pharmacol., Biochem. Behav. 69, 35–40.

Ge, J.A., Barnes, N.M., 1996. Alterations in angiotensin AT_1 and AT_2 receptor subtype levels in brain regions from patients with neurodegenerative disorders. Eur. J. Pharmacol. 297, 299–306.

Georgiev, V., Yonkov, D., 1985. Participation of angiotensin II in learning and memory: I. Interaction of angiotensin II with saralasin. Meth. Find. Exp. Clin. Pharmacol. 7, 415–418.

Georgiev, V., Getova, D., Opitz, M., 1987. Mechanisms of the angiotensin II effects on the exploratory behaviour of rats in open field: 1. Interaction of angiotensin II with saralasin and catecholamine drugs. Find. Exp. Clin. Pharmacol. 9, 297–301.

Georgiev, V.P., Lazarova, M.B., Kambourova, T.S., 1995. Further evidence for the interactions between angiotensin II and GABAergic transmission in pentylenetetrazol kindling seizures in mice. Neuropeptides 28, 29–34.

Germain, L., Chouinard, G., 1988. Treatment of recurrent unipolar major depression with captopril. Biol. Psychiatry 23, 637–641.

Germain, L., Chouinard, G., 1989. Captopril treatment of major depression with serial measurements of blood cortisol concentrations. Biol. Psychiatry 25, 489–493.

Ghazi, N., Grove, K.L., Wright, J.W., Phillips, M.I., Speth, R.C., 1994. Variations in angiotensin-II release from the rat brain during the oestrous cycle. Endocrinology 135, 1945–1950.

Giardina, W.J., Ebert, D.M., 1989. Positive effects of captopril in the behavioural despair swim test. Biol. Psychiatry 25, 697–702.

Goldstein, J.M., Knobloch-Litwin, L.C., Malick, J.B., 1985. Behavioural evidence for β-adrenoceptor subsensitivity after subacute antidepressant/α_2-adrenoceptor antagonist treatment. Naunyn-Schmiedeberg's Arch. Pharmacol. 329, 355–358.

Gutman, Y., Benzakein, F., Livneh, P., 1971. Polydipsia induced by isoprenaline and by lithium: relation to kidneys and renin. Eur. J. Pharmacol. 16, 380–384.

Harding, J.W., Imboden, H., Felix, D., 1986. Is angiotensin III the centrally active form of angiotensin? Experientia 42, 706–709.

Hermann, K., Lang, R.E., Unger, T., Bayer, C., Ganten, D., 1984. Combined high-performance liquid chromatography—radioimmunoassay for the characterization and quantitative measurement or neuropeptides. J. Chromatogr. 312, 273–284.

Hilgers, K.F., Langenfeld, M.R.W., Schlaich, M., Veelken, R., Schmieder, R.E., 1999. 1166 A/C polymorphism of the angiotensin II type 1 receptor gene and the response to short-term infusion of angiotensin II. Circulation 100, 1394–1399.

Hilscher, C., 1997. Long-term potentiation: a good model for learning and memory? Prog. Neuropsychopharmacol. Biol. Psychiatry 21, 47–68.

Houpt, K.A., Epstein, A.N., 1971. The complete dependence of beta-adrenergic drinking on the renal dipsogen. Physiol. Behav. 7, 897–902.

Inoue, I., Nakajima, T., Williams, C.S., Quackenbush, J., Puryear, R., Powers, M., Cheng, T., Ludwig, E.H., Sharma, A.M., Hata, A., Jeunemaître, X., Lalouel, J.-M., 1997. A nucleotide substitution in the promoter of human angiotensinogen is associated with essential hypertension and affects basal transcription in vitro. J. Clin. Invest. 99, 1786–1797.

Jeunemaitre, X., Inoue, I., William, C., Charru, A., Tichet, J., Powers, M., Sharma, A.M., Gimenez-Roqueplo, A.P., Hata, A., Corvol, P., Lalouel, J.M., 1997. Haplotypes of angiotensinogen in essential hypertension. Am. J. Hum. Genet. 60, 1448–1460.

Kaiser, F.C., Palmer, G.C., Wallace, A.V., Carr, R.D., Fraserrae, L., Hallam, C., 1992. Antianxiety properties of the angiotensin-II antagonist, DuP753, in the rat using the elevated plus-maze. NeuroReport 3, 922–924.

Karwowska-Polecka, W., Kulakowska, K., Wisniewski, K., Braszko, J.J., 1997. Losartan influences behavioural effects of angiotensin II (3–7) in rats. Pharmacol. Res. 36, 275–283.

Karwowska-Polecka, W., Gard, P.R., Braszko, J.J., 2000. Strain differences in cognitive function in rats and the relationship to brain angiotensin receptor binding. Eur. J. Neurosci. 12 (suppl. 11), 254.

Katovich, M.J., Fregley, M.J., 1977. Mediation of isoproterenol-induced thirst in rats by β_2-adrenergic receptors. Can. J. Physiol. Pharmacol. 56, 465–470.

Kisley, L.R., Sakai, R.R., Flanagan-Cato, L.M., Fluharty, S.J., 2000. Estrogen increases angiotensin II-induced c-Fos expression in the vasopressinergic neurons of the paraventricular nucleus in the female rat. Neuroendocrinology 72, 306–317.

Kulakowska, A., Karwowska, W., Wisnieski, K., Braszko, J.J., 1996. Los-

artan influences behavioural effects of angiotensin II in rats. Pharmacol. Res. 34, 109–115.
Lahmame, A., del Arco, C., Pazos, A., Yritia, M., Armario, A., 1997. Are Wistar-Kyoto rats a genetic animal model of depression resistant to antidepressants? Eur. J. Pharmacol. 337, 115–123.
Lee, J., Chai, S.-Y., Mendelsohn, F.A.O., Morris, M.J., Allen, A.M., 2001. Potentiation of cholinergic transmission in the rat hippocampus by angiotensin IV and LVV-hemorphin-7. Neuropharmacology 40, 618–623.
MacGregor, D.P., Murone, C., Song, K., Allen, A.M., Paxinos, G., Mendelsohn, F.A.O., 1995. Angiotensin II receptor subtypes in the human central nervous system. Brain Res. 675, 231–240.
Makino, N., Sugano, M., Otsuka, S., Hata, T., 1997. Molecular mechanism of angiotensin II type I and type II receptors in cardiac hypertrophy in spontaneously hypertensive rats. Hypertension 30, 796–802.
Martin, P., Massol, J., Puech, A.J., 1990. Captopril as an antidepressant? Effects on the learned helplessness paradigm in rats. Biol. Psychiatry 27, 968–974.
Matilla, K.M., Rinne, J.O., Roytta, M., Laippala, P., Pietila, T., Kalimo, H., Koivula, T., Frey, H., Lehtimaki, T., 2000. Dipeptidylcarboxypeptidase 1 (DCP1) and butyrylcholinesterase (BCHE) gene interactions with the apolipoprotein E epsilon 4 allele as risk factors in Alzheimer's disease and in Parkinson's disease with coexisting Alzheimer's pathology. J. Med. Genet. 37, 766–770.
Mendelsohn, F.A.O., Allen, A.M., Chai, S.-Y., McKinley, M.J., Oldfield, B.J., Paxinos, G., 1990. The brain angiotensin system—insights from mapping its components. Trends Endocrinol. Metab. 1, 189–198.
Miera-Lima, I.V., Pereira, A.C., Mota, G.F.A., Krieger, J.E., Vallada, H., 2000. Angiotensinogen and angiotensin converting enzyme gene polymorphisms and the risk of bipolar affective disorders in humans. Neurosci. Lett. 293, 103–106.
Miller, J.A., Thai, K., Scholey, J.W., 1999. Angiotensin II type 1 receptor gene polymorphism predicts response to losartan and angiotensin II. Kidney Int. 56, 2173–2180.
Myllykangas, L., Polvikoski, T., Sulkava, R., Verkkoniemi, A., Tiernari, P., Niinisto, L., Kontula, K., Hardy, J., Haltia, M., Perez-Tur, J., 2000. Cardiovascular risk factors and Alzheimer's disease: a genetic association study in a population aged 85 or over. Neurosci. Lett. 292, 195–198.
Nakamura, A., Johns, E.J., 1995. Renal nerves, renin, and angiotensinogen-gene expression in spontaneously hypertensive rats. Hypertension 25, 581–586.
Nakamura, T., Matsui, K., Ito, M., Yoshimura, T., Kawasaki, N., Fujisaki, S., Okamura, H., 1988. Effects of pregnancy and hormone treatments on pressor response to angiotensin II in conscious rats. Am. J. Obstet. Gynecol. 159, 989–994.
Narain, Y., Yip, A., Murphy, T., Brayne, C., Easton, D., Evans, J.G., Xuereb, J., Cairns, N., Esiri, M.M., Furlong, R.A., Rubinsztein, D.C., 2000. The ACE gene and Alzheimer's disease susceptibility. J. Med. Genet. 37, 695–697.
Okuyama, S., Sakagawa, T., Chaki, S., Imagawa, Y., Ichiki, T., Inagami, T., 1999. Anxiety-like behaviour in mice lacking the angiotensin II type-2 receptor. Brain Res. 821, 150–159.
Padmanahhan, N., Padmanahhan, S., Connell, J.M.C., 2000. Genetic basis of cardiovascular disease—the renin–angiotensin–aldosterone system as a paradigm. J. Renin–Angiotensin–Aldosterone System 1, 316–324.
Paillard, F., Chansel, D., Brand, E., Benetos, A., Thomas, F., Czekalski, S., Ardaillou, R., Soubrier, F., 1999. Genotype–phenotype relationships for the renin–angiotensin–aldosterone system in a normal population. Hypertension 34, 423–429.
Pauls, J., Bandelow, B., Ruther, E., Kornhuber, J., 2000. Polymorphism of the gene of angiotensin converting enzyme: lack of association with mood disorder. J. Neural Transm. 107, 1361–1366.
Phillips, M.I., 1987. Functions of angiotensin in the central nervous system. Annu. Rev. Physiol. 49, 413–435.
Phillips, M.I., Sumners, C., 1998. Angiotensin II in central nervous system physiology. Regul. Pept. 78, 1–11.
Prince, J.A., Feuk, L., Sawyer, S.L., Gottfries, J., Ricksten, A., Nagga, K., Bogdanovic, N., Blennow, K., Brookes, A.J., 2001. Lack of replication of association findings in complex disease: an analysis of 15 polymorphisms in prior candidate genes for sporadic Alzheimer's disease. Eur. J. Hum. Genet. 9, 437–444.
Przegalinski, E., Siwanowicz, J., Baran, L., 1988. Effect of repeated administration of antidepressant drugs on the isoprenaline-induced drinking in rats. Pol. J. Pharmacol. 40, 251–258.
Raghavendra, V., Chopra, K., Kulkarni, S.K., 1998. Involvement of cholinergic system in losartan-induced facilitation of spatial and short-term working memory. Neuropeptides 32, 417–421.
Richard, F., Berr, C., Amant, C., Helbecque, N., Amouyel, P., Alperovitch, A., 2000. Effect of angiotensin I-converting enzyme I/D polymorphism on cognitive decline. Neurobiol. Aging 21, 75–80.
Rieder, M.J., Taylor, S.L., Clark, A.G., Nickerson, D.A., 1999. Sequence variation in the human angiotensin converting enzyme. Nat. Genet. 22, 59–62.
Rigat, B., Hubert, C., Alhenc-Gelas, F., Cambien, F., Corvol, P., Soubrier, F., 1990. An insertion/deletion polymorphism of the angiotensin I-converting enzyme gene accounting for half the variance of serum enzyme levels. J. Clin. Invest. 86, 1343–1346.
Sagvolden, T., Xu, T., 2000. Medication effects depend on gender and behavior in spontaneously hypertensive rat (SHR), an animal model of attention-deficit/hyperactivity disorder (ADHD). Eur. J. Neurosci. 12 (suppl. 11), 111.05.
Savaskan, E., Hock, C., Olivieri, G., Bruttel, S., Rosenberg, C., Hulette, C., Muller-Spahn, F., 2001. Cortical alterations of Angiotensin converting enzyme, angiotensin II and AT1 receptor in Alzheimer's dementia. Neurobiol. Aging 22, 541–546.
Shepherd, J., Bill, D.J., Dourish, C.Y., Grewal, S.S., McLenachan, A., Stanhope, K.J., 1996. Effects of the selective angiotensin II receptor antagonists losartan and PD123177 in animal models of anxiety and memory. Psychopharmacology 126, 206–218.
Sirett, N.E., McLean, A.S., Bray, J.J., Hubbard, J.I., 1977. Distribution of angiotensin II receptors ion the rat brain. Brain Res. 122, 299–312.
Staessen, J.A., Ginocchio, G., Wang, J.G., Saavedra, A.P., Soubrier, F., Vlietinck, R., Fagard, R., 1997a. Genetic variability in the renin–angiotensin system: prevalence of alleles and genotypes. J. Cardiovasc. Risk 4, 401–422.
Staessen, J.A., Wang, J.G., Ginocchio, G., Petrov, V., Saavedra, A.P., Soubrier, F., Vlietinck, R., Fagard, R., 1997b. The deletion/insertion polymorphism of the converting-enzyme and cardiovascular–renal risk. J. Hypertens. 15, 1579–1592.
Sudilovsky, A., Cutler, N.R., Sramek, J.J., Wardle, T., Veroff, A.E., Mickelson, W., Markowitz, J., Repetti, S., 1993. A pilot clinical-trial of the angiotensin-converting enzyme-inhibitor ceranapril in Alzheimer-disease. Alzheimer Dis. Assoc. Disord. 7, 105–111.
Tang, M.m., Falk, J.L., 1974. Sar^1–Ala^8 Angiotensin II blocks renin–angiotensin but not beta-adrenergic dipsogenesis. Pharmacol. Biochem. Behav. 2, 401–408.
Tedesco, M.A., Ratti, G., Mennella, S., Manzo, G., Grieco, M., Rainone, A.C., Iarussi, D., Iacono, A., 1999. Comparison of losartan and hydrochlorthiazide on cognitive function and quality of life in hypertensive patients. Am. J. Hypertens. 12, 1130–1134.
Testa, M.A., Anderson, R.B., Nackley, J.F., Hollenberg, N.K., 1993. Quality of life and antihypertensive therapy in men. New Engl. J. Med. 328, 907–913.
Tsuda, A., Tanaka, M., Georgiev, V., Emoto, H., 1992. Effects of angiotensin II on behavioral responses of defensive burying paradigm in rats. Pharmacol., Biochem. Behav. 43, 729–732.
Tysoe, C., Galinsky, D., Robinson, D., Brayne, C.E., Easton, D.F., Huppert, F.A., Dening, T., Paykel, E.S., Rubinsztein, D.C., 1997. Analysis of alpha-1 antichymotrypsin, presenilin-1, angiotensin-converting enzyme, and methylenetetrahydrofolate reductase loci as candidates for dementia. Am. J. Med. Genet. 74, 207–212.
van Houten, M., Schiffrin, E.L., Mann, J.F.E., Posner, B.I., Boucher, R., 1980. Radioautographic localization of specific binding sites for blood-borne angiotensin II in the rat brain. Brain Res. 186, 480–485.

von Bohlen und Halbach, O., Albrecht, D., Halbach, O.V.U., 1998. Angiotensin II inhibits long-term potentiation within the lateral nucleus of the amygdala through AT(1) receptors. Peptides 19, 1031–1036.

Wang, J.-G., Staessen, J.A., 2000. Genetic polymorphisms in the renin–angiotensin system: relevance for susceptibility to cardiovascular disease. Eur. J. Pharmacol. 410, 289–302.

Wang, D.Z.M., Wilks, A., Morgan, T.O., Di Nicolantonio, R., 1994. A new restriction-fragment-length-polymorphism in the first intron of the spontaneously hypertensive rat renin gene. Clin. Exp. Pharmacol. Physiol. 21, 339–341.

Wayner, M.J., Armstrong, D.L., Polancurtain, J.L., Denny, J.B., 1993. Role of angiotensin-II and AT1 receptors in hippocampal LTP. Pharmacol., Biochem. Behav. 45, 455–464.

Wilson, W., Voight, P., Bader, M., Marsden, C.A., Fink, H., 1996. Behaviour of the transgenic (mREN2) 27 rat. Brain Res. 729, 1–9.

Wright, J.W., Harding, J.W., 1995. Brain angiotensin receptor subtypes AT_1, AT_2 and AT_4 and their functions. Regul. Pept. 59, 269–295.

Wright, J.W., Harding, J.W., 1997. Important roles for angiotensin III and IV in the brain renin–angiotensin system. Brain Res. Rev. 25, 96–124.

Yang, J.D., Feng, G.Y., Zhang, J., Lin, Z.X., Shen, T., Breen, G., St. Clair, D., He, L., 2000. Association between angiotensin-converting enzyme gene and late onset Alzheimer's disease in Han Chinese. Neurosci. Lett. 295, 41–44.

Yu, H., Di Nicolantonio, R., 1996. Altered age-dependent modulation of tissue messenger RNA levels in the spontaneously hypertensive rat. J. Hypertens. 14, 871–880.

Yu, H., Di Nicolantonio, R., 1998. Altered nuclear protein binding to the first intron of the renin gene of the spontaneously hypertensive rat. Clin. Exp. Hypertens. 20, 817–832.

Zhang, L., Summers, K.M., West, M.J., 1996. Angiotensin I converting enzyme cosegregates with blood pressure and heart weight in F2 progeny derived from spontaneously hypertensive and normotensive Wistar-Kyoto rats. Clin. Exp. Hypertens. 18, 753–771.

Zhang, X., Erdmann, J., Regitz-Zagrosek, V., Hense, H.-W., Schunkert, H., 2000. Evaluation of three polymorphisms in the promoter region of the angiotensin II type I receptor gene. J. Hypertens. 18, 267–272.

Zubenko, G.S., Nixon, R.A., 1984. Mood-elevating effect of captopril in depressed patients. Am. J. Psychiatry 141, 110–111.