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Angiotensin receptor subtype mediated physiologies and behaviors: New discoveries and clinical targets

John W. Wright[a,b,c,*], **Brent J. Yamamoto**[b,c], and **Joseph W. Harding**[a,b,c]

a*Department of Psychology, Washington State University, P.O. Box 644820, Pullman, WA 99164-4820, USA*

b*Department of Veterinary and Comparative Anatomy, Pharmacology, and Physiology, Washington State University, P.O. Box 646520, Pullman, WA 99164-6520, USA*

c*Programs in Neuroscience and Biotechnology, Washington State University, P.O. Box 646520, Pullman, WA 99164-6520, USA*

Abstract

The renin–angiotensin system (RAS) mediates several classic physiologies including body water and electrolyte homeostasis, blood pressure, cyclicity of reproductive hormones and sexual behaviors, and the regulation of pituitary gland hormones. These functions appear to be mediated by the angiotensin II (AngII)/AT_1 receptor subtype system. More recently, the angiotensin IV (AngIV)/AT_4 receptor subtype system has been implicated in cognitive processing, cerebroprotection, local blood flow, stress, anxiety and depression. There is accumulating evidence to suggest an inhibitory influence by AngII acting at the AT_1 subtype, and a facilitory role by AngIV acting at the AT_4 subtype, on neuronal firing rate, long-term potentiation, associative and spatial learning, and memory. This review initially describes the biochemical pathways that permit synthesis and degradation of active angiotensin peptides and three receptor subtypes (AT_1, AT_2 and AT_4) thus far characterized. There is vigorous debate concerning the identity of the most recently discovered receptor subtype, AT_4. Descriptions of classic and novel physiologies and behaviors controlled by the RAS are presented. This review concludes with a consideration of the emerging therapeutic applications suggested by these newly discovered functions of the RAS.

Keywords

Renin–angiotensin system; Angiotensin receptor subtypes; Angiotensin II; Angiotensin III; Angiotensin IV; Angiotensin(1–7); Cardiovascular control; Thirst; Sodium appetite; Long-term potentiation; Learning and memory; Cerebroprotection; Seizure; Stress; Depression

1. Introduction

Well over 100 years ago Tiegerstedt and Bergman (1898) discovered a pressor agent extracted from the kidney that they called "renin". Some 40 years later this finding led to the isolation of a vasoconstrictor agent from the ischemic kidneys of Goldblatt hypertensive dogs (Braun-

* Corresponding author at: Department of Psychology, Washington State University, P.O. Box 644820, Pullman, WA 99164-4820, USA. Tel.: +1 509 335 2329; fax: +1 509 335 5043. *E-mail address:* wrightjw@wsu.edu (J.W. Wright).

Menendez et al., 1940). Page and Helmer (1940) independently isolated the same agent after injecting renin into intact animals and they also identified a "renin activator", later determined to be angiotensinogen (de Gasparo et al., 2000). The vasoconstrictor agent was determined to be an octapeptide and was variously called "renin substrate", "angiotonin", and "hypertensin" but was later termed angiotensin II (AngII; Bumpus et al., 1957, 1958; Elliott and Peart, 1956; Skeggs et al., 1957). From this beginning many additional findings have been made including the observation that intracerebroventricular (icv) AngII produced brain-mediated pressor (Bickerton and Buckley, 1961) and drinking responses (Epstein et al., 1970). Ganten et al. (1971a,b) isolated renin in the dog brain; while Fisher-Ferraro et al. (1971) identified both renin and AngII in the dog brain. Sirrett et al. (1977) developed a radio-receptor binding assay permitting the identification and localization of angiotensin receptors in the brain and throughout the body. Taken together these findings suggested the presence of an independent brain renin–angiotensin system (RAS). Confirmation of this hypothesis required several additional years of laboratory work utilizing a variety of techniques including radioimmunoassay, immunohistochemistry, radio-receptor binding assays, and Northern blots of renin and angiotensinogen mRNAs (Dzau et al., 1986; Ganten et al., 1983; Harding et al., 1981; Hermann et al., 1984; Lynch et al., 1986; Phillips et al., 1979).

Two recent discoveries have further extended our understanding of the RAS: (1) the angiotensin receptor proteins AT_1 and AT_2 were cloned and sequenced (Chiu et al., 1989; Whitebread et al., 1989; Iwai et al., 1991; Murphy et al., 1991; Kambayashi et al., 1993; Mukoyama et al., 1993). (2) A third angiotensin receptor subtype, AT_4, was discovered (Harding et al., 1992) that appears to mediate a number of novel functions including memory consolidation, blood flow, renal tubular reabsorption, and cellular proliferation (Llorens-Cortes and Mendelsohn, 2002; Wright and Harding, 1997, 2004). These discoveries have rekindled interest in the brain RAS and its role in additional physiologies and pathologies.

The present paper briefly describes the biochemistry of the RAS including the formation of active angiotensin ligands, and the three receptor subtypes thus far identified. Next, the controversy over the identity of the AT_4 receptor subtype is presented, followed by descriptions of classic and novel functions of the RAS. We conclude with a consideration of potential clinical targets resulting from these new discoveries.

2. Biochemistry of the renin–angiotensin system

The RAS mediates a number of classic physiologies and behaviors including blood pressure, sodium and body water balance, cyclicity of reproductive hormones and sexual behaviors, and pituitary gland hormones. These functions appear to be under the control of the AT_1 receptor subtype (Allen et al., 2000; de Gasparo et al., 2000; Gard, 2002; McKinley et al., 2003; Thomas and Mendelsohn, 2003). A second subtype, AT_2, has also been implicated in the regulation of blood pressure, renal function, and vascular growth (de Gasparo and Siragy, 1999; de Gasparo et al., 2000; Speth et al., 1995). AngII has traditionally been considered the end-product of the RAS and therefore the active ligand at these receptors subtypes. Accumulating evidence indicates that additional shorter chain angiotensins also serve as effector peptides in this system. These peptides include the heptapeptide des Asp^1-AngII, referred to as angiotensin III (AngIII) (Vauquelin et al., 2002; Wright and Harding, 1997), the hexapeptide des Asp^1, des Arg^2-AngII, referred to as AngIV (Albiston et al., 2003; de Gasparo et al., 2000; Thomas and Mendelsohn, 2003; Wright and Harding, 1994, 1997; Wright et al., 1995), and the heptapeptide des Phe^8-AngII, referred to as Ang(1–7) (Ferrario, 2003; Ferrario et al., 1997; Santos et al., 2000). The proposed functions mediated by AngIV include influences upon blood flow (Coleman et al., 1998; Kramár et al., 1997; Møeller et al., 1997; Slinker et al., 1999), kidney natriuresis (Hamilton et al., 2001; Handa et al., 1998), expression of plasminogen activator inhibitor (PAI-1) in endothelial cells (Kerins et al., 1995: Mehta et al., 2002) and in epithelial cells of

the kidney proximal tubule (Gesualdo et al., 1999), and memory facilitation (reviewed in Albiston et al., 2003; von Bohlen und Halbach, 2003; Wright et al., 2002a). The functions thus far identified for Ang(1–7) include vasopressin, nitric oxide (NO), and prostaglandin release, and facilitation of baroreceptor reflex sensitivity (Ferrario and Chappell, 2004; Kucharewicz et al., 2002; Santos et al., 2000).

2.1. Formation of angiotensin ligands

The protein angiotensinogen serves as a precursor to angiotensin peptides (Fig. 1). The decapeptide angiotensin I (AngI) is formed by renin (EC 3.4.23.15) acting upon the amino terminal of angiotensinogen. AngI is a substrate for angiotensin converting enzyme (ACE: EC 3.4.15.1), a zinc metalloprotease that hydrolyzes the carboxy terminal dipeptide His-Leu to form AngII (Johnston, 1990), and the chymotrypsin-like serine protease, chymase (Unger, 2004). AngII is converted to AngIII by glutamyl aminopeptidase A (AP-A: EC 3.4.11.7, or A-like activity) that cleaves the Asp residue at the N-terminal (Chauvel et al., 1994;Ramírez et al., 1990;Rich et al., 1984;Wilk and Healy, 1993). Membrane alanyl aminopeptidase N (AP-N: EC 3.4.11.2) cleaves Arg at the N-terminal of AngIII to form AngIV. AngIV can be further converted to Ang(3–7) by carboxypeptidase P (Carb-P) and propyl oligopeptidase (PO) cleavage of the Pro-Phe bond. Endopeptidases such as chymotrypsin are capable of cleaving the Val, Tyr, and Ile residues along with dipeptidyl carboxypeptidase that cleaves the His–Pro bond, reducing AngIV and Ang(3–7) to inactive peptide fragments and amino acid constituents (Banegas et al., 2006;Johnston, 1990;Reudelhuber, 2005;Saavedra, 1992;Speth et al., 2003;Unger et al., 1988).

AngII can also be converted to Ang(1–7) by Carb-P cleavage of Phe (Wright and Harding, 1997), by the newly discovered mono-peptidase ACE_2 (Ferrario and Chappell, 2004) or by ACE cleavage of the dipeptide Phe-His from Ang(1–9) (Vauquelin et al., 2002), and can be further converted to Ang(2–7) by AP-A acting at the Asp-Arg bond (Mentlein and Roos, 1996).

AngI is considered inactive while AngII and AngIII are full agonists at the AT_1 and AT_2 receptor subtypes (reviewed in de Gasparo et al., 2000). AngIV binds with low affinity at the AT_1 and AT_2 receptor subtypes (Bennett and Snyder, 1976; Glossmann et al., 1974; Harding et al., 1992; Swanson et al.,1992), but with high affinity and specificity at the AT_4 receptor subtype (Bernier et al., 1994; Harding et al., 1992; Jarvis et al., 1992; Swanson et al., 1992). A specific binding site for Ang(1–7) has been reported (Ferrario, 2003; Neves et al., 2003; Santos et al., 1994, 2000), but not fully elucidated.

2.2. Angiotensin receptor subtypes

As described above, at present there are three recognized angiotensin receptor subtypes (de Gasparo et al., 1995), two structurally similar, and a third that is different (Table 1). The AT_1 and AT_2 subtypes are G-protein coupled. In contrast the AT_4 subtype is a much larger protein insensitive to guanine nucleotides, suggesting that it is not G-protein-linked (de Gasparo et al., 2000). There is presently a dispute over the identy of this sybytpe as insulin-regulated aminopeptidase (IRAP) or the growth factor receptor c-Met (Yamamoto et al., submitted for publication). This controversy is further described below.

2.2.1. AT_1 and AT_2 receptor subtypes—The AT_1 receptor subtype is a G-protein coupled receptor with signaling via phospholipase-C and calcium. Thus, the angiotensin ligand binds to the AT_1 receptor and induces a conformational change in the receptor protein that activates G proteins, and in turn, mediate signal transduction. This transduction involves several plasma membrane mechanisms including phospholipase-C, -A_2, and -D-adenylate cyclase, plus L-type and T-type voltage sensitive calcium channels (de Gasparo et al., 2000; Sayeski et al., 1998).

This AT_1 receptor (now designated AT_{1A}) is also coupled to intracellular signaling cascades that regulate gene transcription and the expression of proteins that mediate cellular proliferation and growth in many target tissues. Expression cloning was used to isolate the cDNAs encoding this receptor protein (Murphy et al., 1991; Sasaki et al., 1991) and it was found to be a seven-transmembrane domain protein consisting of 359 amino acids with a mass of approximately 41 kDa (Sandberg et al., 1994). Subsequently, a second AT_1 subtype was discovered and designated AT_{1B} that was also cloned in the rat (Iwai and Inagami, 1992; Kakar et al., 1992), mouse (Sadamura et al., 1992), and human (Konoshi et al., 1994). This subtype is approximately 92–95% homologous with the amino acid sequence of the AT_{1A} subtype (Guo and Inagami, 1994; Speth et al., 1995). Of these two isoforms the AT_{1A} subtype appears to be responsible for the classic functions associated with the brain angiotensin system (reviewed in Saavedra, 1999; Thomas and Mendelsohn, 2003).

The AT_2 receptor subtype has also been cloned and sequenced using a rat fetus expression library (Bottari et al., 1991; Kambayashi et al., 1993). In common with the AT_1 subtype, this receptor protein also evidences a seven-transmembrane domain characteristic of G-protein coupled receptors, however, it shows only about 32–34% amino acid sequence identity with the rat AT_1 receptor. The AT_2 receptor protein includes a 363 amino acid sequence (40 kDa) with 99% sequence agreement between rat and mouse, and 72% homology with human (de Gasparo et al., 2000). Even though this AT_2 receptor possesses structural features in common with members of the 7-transmembrane family of receptors, it displays few if any functional similarities with this group, although it does appear to be G-protein coupled (Bottari et al., 1991; Kambayashi et al., 1993; Mukoyama et al., 1993).

2.2.2. AT_4 receptor subtype—Prior to 1988 angiotensins shorter than AngIII were considered biologically inactive and therefore of little physiological importance. This assumption was based on two facts: (1) AngIV reveals a very poor affinity for the AT_1 and AT_2 sites (Bennett and Snyder, 1976; Glossmann et al., 1974; Harding et al., 1992; Swanson et al., 1992). (2) AngIV and shorter fragments are considerably less potent than Ang II and AngIII in eliciting classic angiotensin-dependent functions (Blair-West et al., 1971; Fitzsimons, 1971; Tonnaer et al., 1982; Unger et al., 1988; Wright et al., 1989). Two discoveries changed this assumption. First, Braszko et al. (1988) reported that AngIV facilitated acquisition of a conditioned avoidance response in rats. Second, a separate and distinct binding site for AngIV was identified (Harding et al., 1992; Swanson et al., 1992) and subsequently classified as the AT_4 subtype (de Gasparo et al., 1995). This subtype was originally isolated using bovine adrenal membranes (Bernier et al., 1994; Harding et al., 1992; Jarvis et al., 1992; Swanson et al., 1992). These characterization studies indicated that the AT_4 receptor subtype is distinct from the AT_1 and AT_2 sites given that ligands known to bind to these sites do not bind at the AT_4 site (Harding et al., 1992; Swanson et al., 1992). It was determined that $[^{125}I]$AngIV binds at the AT_4 site reversibly, saturably, and with high affinity. This AT_4 site has been found in a variety of mammalian tissues including adrenal gland, bladder, colon, heart, kidney, prostate, brain, and spinal cord (Wright et al., 1995).

Given that a small peptide is capable of activating the AT_4 site, and that the vast majority of small peptide receptors are G protein-linked, it was logical to predict that the AT_4 receptor would be a serpentine G protein-linked receptor. However, this is not the case since binding to this site was found to be insensitive to guanine nucleotides. In addition, the AT_4 receptor subunit exhibited a molecular weight in the 100+ kDa range as determined by reduced SDS-polyacrylamide gel electrophoresis. An equivalent molecular weight has been reported for this receptor in other bovine tissues including heart, thymus, kidney, bladder, aorta, and hippocampus (Zhang et al., 1999). Further, Bernier et al. (1995, 1998) established a similar molecular weight for the binding subunit of the AT_4 receptor in bovine aortic endothelial cells. The lack of linkage to G proteins is also supported by the observation that GTPγS failed to

alter [^{125}I]AngIV binding in rabbit heart (Hanesworth et al., 1993), guinea pig brain (Miller-Wing et al., 1993), and rat vascular smooth muscle (Hall et al., 1993). A single report by Dulin et al. (1995) indicated that GTPγS inhibited AT_4 receptor binding in opossum kidney cells. Thus, to date there is little evidence linking the AT_4 receptor to G proteins, however, as experienced with the AT_2 receptor, a definitive conclusion must await sequencing of this receptor protein.

2.2.3. Is the AT4 receptor c-Met or insulin-regulated aminopeptidase (IRAP)?—

A potentially important advance in our understanding of the AT_4 receptor system was the identification of the AT_4 receptor as insulin-regulated aminopeptidase (Albiston et al., 2001), a membrane associated aminopeptidase that co-distributes with the $GLUT_4$ transporter (Kandror and Pilch, 1994; Keller et al.,1995). This initial identification was based on sequence homology between a tryptic fragment derived from the human brain AT_4 receptor and human IRAP, and the near identical masses of IRAP and the AT_4 receptor binding subunit protein. Subsequent expression of IRAP in HEK293T cells yielded an AT_4 receptor-like binding site with an affinity for AngIV that was similar to the native receptor (Lee et al., 2003). These investigators further proposed that the multiple physiological actions of AT_4 receptor ligands are due to their ability to competitively inhibit the peptidase activity of IRAP, thus potentiating the actions of endogenous peptides that are normally degraded by IRAP (Lew et al., 2003). This model predicts that the efficacy of all AT_4 receptor ligands should be qualitatively equivalent since their action is due to binding to IRAP and competitive interference with IRAP's ability to catabolize endogenous peptides.

There are several problems with this proposal. (1) This notion is difficult to reconcile with results from agonist and antagonist compounds that exhibit opposite physiological actions (Hamilton et al., 2001; Kramár et al., 1997, 2001; Wright et al., 1999). (2) The onset of physiological effects should be slow since this action requires an accumulation of endogenous AT_4 ligand. This prediction does not agree with the observation that AT_4 ligands have very rapid effects on signaling molecules (Chen et al., 2001; Handa, 2001; Li et al.,2002). For example, AT_4 receptor activation can lead to a 20-fold increase in ERK activation in C6 glioma cells within 30 s (Harding, Anderson and Meighan, unpublished). Similarly, *in vivo* studies indicate rapid AT_4-mediated changes in blood flow (Kramár et al., 1997), renal oxygen consumption (Handa et al., 1998), and long-term potentiation (LTP; Kramár et al., 2001; Wayner et al., 2001), typically manifesting in less than 1 min. It is unlikely that sufficient peptide accumulates to impact physiological responses in such a short period of time. More typical time frames for *in vivo* peptidase inhibitors are hours or days, not seconds. (3) The concentrations of AT_4 ligands required to effect changes in physiological function are subpicomolar or subnanomolar (Chen et al., 2001; Handa, 2001; Li et al., 2002); concentrations well below those reported for any known enzyme inhibitor. This concern is relevant for IRAP given that the reported K_i of Nle^1-AngIV for IRAP (>0.3 μM, Lew et al., 2003) is several orders of magnitude higher than the biologically effective doses of AT_4 ligands. (4) Also casting doubt on the hypothesis that AT_4 ligands function as competitive substrates is a study by Caron et al. (2003) indicating that AngIV ligands interact allosterically with IRAP at a site distinct from the active site. The precise characteristics concerning the structure of AngIV, its analogs, and other angiotensins such as AngIII, that render them nonsubstrates for IRAP, but still able to bind, are presently unclear (Lew et al., 2003). (5) This proposal is in opposition to earlier work by Tsujimoto et al. (1992) demonstrating that AngIII is an excellent substrate for human placental leucine aminopeptidase (homolog of rat IRAP, Keller et al., 1995).

The discordance between the IRAP inhibitor model and laboratory observations suggests two likely possibilities. First, IRAP is not the signal transducing AT_4 receptor but is instead involved with regulating the extracellular levels of endogenous AT_4 receptor ligands. Second, IRAP may be the signal transducing receptor but relies on activities beyond its abilities as an

aminopeptidase. If the second possibility is correct then IRAP should possess within its short 109-amino acid hydrophilic N-terminal segment the information required for signal transduction. Lending credibility to this possibility are prevous studies, one indicating that the N-terminus of IRAP contains two dileucine motifs and several acidic regions, that play important roles in vesicular trafficking (Keller et al., 1995; Waters et al., 1997). A peptide consisting of residues 55–82 of the N-terminus, containing one of the dileucine motifs and acidic clusters, was sufficient to cause $GLUT_4$ translocation (Waters et al., 1997). Correspondingly, Ryu et al. (2002) showed *in vitro* phosphorylation of IRAP Ser80, which is involved in the regulation of insulin stimulated $GLUT_4$ translocation. The poly (ADP-ribose) polymerase tankyrase was identified in a yeast two-hybrid system and interacted with 96–101 amino acids of IRAP (Chi and Lodish, 2000). Interestingly, acyl-coenzyme A dehydrogenases (ACDs), identified by glutathione-S-transferase (GST) fusion-IRAP (GST-IRAP55–82) is probably involved in retention of $GLUT_4$ vesicles to designated intracellular compartments (Katagiri et al., 2002). Similar mechanisms might exist for IRAP at the plasma membrane resulting in signal transduction given that several signaling events have been associated with activation of AT_4 receptor by AT_4 ligands (Handa, 2001; Li et al., 2002). No matter the exact role played by IRAP in AT_4 ligand signaling, the affinity of IRAP for AT_4 receptor ligands suggests that its function is in some way important.

The above considerations led members of our laboratory to the conclusion that the physiological actions of angiotensin IV-related ligands are not mediated by IRAP. Furthermore, we made the assumption that Ang IV, and related analogs, must have structural homology with one or more naturally occurring ligands that work through their cognate receptors to mediate physiological actions reminiscent of those initiated by the Ang IV analogs. Based on this thinking we carried out a homology search that yielded a partial match to the anti-angiogenic protein, angiostatin, and the related plasminogen family member hepatocyte growth factor (HGF). HGF is a powerful mitogenic, morphogenic, and motogenic growth factor that acts via the type I tyrosine kinase receptor, c-Met (Fig. 2; Ma et al., 2003). Classically, c-Met has been noted for its ability to direct stem cell proliferation and differentiation (Nakamura et al., 1989;Stoker et al., 1987), induce tubular morphogenesis in many organs including kidney, and support angiogenesis by activating vascular endothelial cells (Birchmeier et al., 2003;Liao et al., 2005). More recently, c-Met has attracted considerable attention because of its role in multiple cancers (Jiang et al., 2005;Shinomiya and Vande Woude, 2003), its ability to blunt neurodegenerative changes, and its potential involvement in learning and memory consolidation (Akimoto et al., 2004;Date et al., 2004;Shimamura et al., 2006;Tada et al., 2006). The known ability of AngIV analogs to alter cognitive function, augment neurite outgrowth, and activate vascular endothelial cells (Wright and Harding, 1997,2004), which direct the angiogenic process, encouraged us to investigate the possibility that Ang IV-like analogs exert their biological activity through the HGF/c-Met system. These studies demonstrated that the AT_4 receptor antagonist, norleual (Nle-Tyr-Leu-$(CH_2-NH_2)^{3-4}$-His-Pro-Phe), is capable of inhibiting HGF-dependent proliferation, invasion, and scattering in several cell lines at picomolar concentrations (Yamomoto et al., submitted). Moreover, norleual was shown to block [^{125}I]-HGF binding to c-Met with a K_i of 3 pM; while conversely HGF was found to effectively block [^{125}I]-norleual to HEK cell membranes. As anticipated from these results, norleual exhibits potent anti-angiogenic and anti-tumor activities. Specifically, norleual inhibited the *in vivo* growth of B-16 melanomas, a c-Met-dependent murine cancer, and induced apoptosis of the U-87 human glioblastoma cells, the survival of which is strictly dependent on an a active c-Met signaling system.

2.2.4. Angiotensin(1–7)—Ferrario et al. (1988; Schiavone et al., 1988) were the first to report biological activity by Ang(1–7) in the form of vasopressin release from the posterior pituitary gland. In the years since that discovery many investigators have confirmed the biological importance of this peptide (reviewed in Carey and Saragy, 2003; Kucharewicz et

al., 2002; Santos et al., 2000). Ang(1–7) opposes several actions of AngII and AngIII. Specifically, Ang(1–7) stimulates the release of NO and vasodilator prostaglandins (Brosnihan et al., 1996; Li et al., 1997; Meng and Busija, 1993; Osei et al., 1993; Paula et al., 1995). Ang (1–7) stimulated release of NO appears to be primarily from vascular endothelial and smooth muscle cells (Jaiswal et al., 1992; Muthalif et al., 1998) thus opposing AngII-induced vasoconstriction (Ueda et al., 2000). This peptide also appears to protect cardiac and endothelium function as well as coronary perfusion as demonstrated in a heart failure model (Loot et al., 2002). Further, Ang(1–7) has been shown to facilitate baroreceptor reflex sensitivity and modulate circadian rhythm influences on heart rate and blood pressure (Campagnole-Santos et al., 1992; Silva-Barcellos et al., 2001). Recent evidence suggests a role for this peptide in kidney diuresis and natriuresis associated with increased glomerular filtration rate, and protection against preeclampsia during pregnancy (Ferrario and Chappell, 2004).

It is well established that AngII promotes thrombosis primarily via expression of plasminogen activator inhibitor 1 (PAI-1) (Feener et al., 1995; Vaughan et al., 1995); although this effect could be via AngIV (Kerins et al., 1995). Kucharewicz et al. (2000, 2002) have shown that Ang(1–7) functions as an antithrombotic compound when administered to renal hypertensive rats that served as a venous thrombosis model. A putative binding site with high affinity for Ang(1–7) has been identified but not characterized (Santos et al., 1994). Tallant et al. (1997) reported that Ang(1–7) binding to this site cannot be inhibited by AT_1 or AT_2 receptor subtype antagonists, but can be blocked by sarile (Sar^1,Ile^8-AngII) in bovine aortic endothelial cells. On the other hand, Santos et al. (2000) have noted the action of Ang(1–7) to be inhibited by losartan and AT_2 receptor antagonists. The Mas oncogene has been suggested as the Ang(1–7) receptor (reviewed in Reudelhuber, 2005; Roks and Henning, 2003). The intracellular signaling mechanisms are presently undetermined (reviewed in Santos et al., 2000).

2.3. Cerebral distributions of angiotensin receptor subtypes

Circumventricular organs (CVOs) were initially investigated for the presence of angiotensin receptors because they possess a reduced blood–brain-barrier due to fenestrated capillaries. Binding sites for AngII were discovered within the CVOs, specifically in the subfornical organ (SFO), organum vasculosum of the lamina terminalis (OVLT), area postrema (AP), median eminence, and anterior pituitary gland (Landas et al., 1980; Phillips, 1987; Van Houten et al., 1980). Subsequent investigations localized AngII receptor sites in several brain structures within the blood–brain-barrier. The distribution of brain structures possessing receptor sites is reasonably consistent among the mammalian species examined using quantitative autoradiography and homogenate tissue preparations. These species include rat, mouse, hamster, dog, monkey, and human (reviewed in Chai et al., 2000; von Bohlen und Halbach, 2003; Wright and Harding, 1997, 2004). The above studies have now been extended and indicate that the AT_1 subtype is localized with especially high densities in the anterior pituitary, area postrema, median eminence, lateral geniculate, nucleus of the solitary tract (NTS), the anterior ventral third ventricle region (including OVLT), paraventricular (PVN), supraoptic (SON), and ventral medial nuclei (VMN), and the preoptic region of the hypothalamus, SFO, ventral tegmental area (VTA), and the inferior olivary nucleus of the medulla (Table 2).

The highest levels of the AT_2 site are found in the amygdala, medial geniculate, hypoglossal nucleus, inferior olivary nucleus, lateral habenula, caudate putamen, globus pallidus, locus coeruleus, thalamus, inferior colliculus, and VTA.

Structures with the greatest densities of the AT_4 subtype include anterior pituitary gland, caudate-putamen, cerebellum, cerebral and piriform cortices, claustrum, globus pallidus, habenula, hippocampus, inferior olivary nucleus, lateral geniculate, periaquaductal gray, superior colliculi, thalamus, and VTA. Lesser densities of the AT_4 subtype have been identified in the lateral olfactory tract and nucleus accumbens.

Comparing the distributions of AT_1, AT_2, and AT_4 receptors, the AT_4 site is expressed in reasonably high densities and rather uniquely in the cerebellum, cerebral and piriform cortices, claustrum, hippocampus, caudate putamen, nucleus accumbens, medial habenula, nucleus basalis of Meynert, and periaquaductal gray. Several of these brain structures are intimately involved in cognitive processing.

In summary, the functions mediated by the brain RAS have been assumed to include classic mechanisms concerned with body water balance, blood pressure maintenance, and cyclicity of reproductive hormones and behaviors. The discovery of the AT_4 receptor subtype and accumulating evidence concerning its role in neural plasticity, strongly indicate that angiotensin peptides are also involved in the mediation of learning and memory processes.

3. Classic angiotensin-mediated physiologies and behaviors

The RAS is well known as a mediator of systemic blood pressure and the maintenance of volume and electrolyte homeostasis (Table 3). These functions appear to be under the control of the $AngII/AT_1$ receptor subtype system. AngIII and Ang(1–7) also appear to contribute to the regulation of these physiologies. Angiotensins have been implicated in additional nonclassical functions including learning and memory, cerebroprotection, renal blood flow and natriuresis, stress and depression (von Bohlen und Halbach, 2003;Gard, 2002;Saavedra, 2005;Thomas and Mendelsohn, 2003;Wright and Harding, 1997,2004). This and the following section describe the well-established functions of this system and newly emerging novel physiologies and behaviors, respectively.

3.1. Cardiovascular control

The peripheral RAS contributes to cardiovascular functioning by direct inotropic influences upon the heart and via increased vascular resistance (reviewed in Johnston, 1990; Wright and Harding, 1997). The increase in vascular resistance occurs due to direct action on vascular smooth muscle and indirect action via the brain resulting in sympathetic nervous system arousal, the release of the powerful vasoconstrictor vasopressin, and inhibition of the baroreceptor reflex (Culman et al., 2002; Phillips and Sumners, 1998; Unger et al., 1988).

The discovery of RAS components in the brain led to the notion of a local and independent brain RAS. Considerable evidence now supports the existence of two primary brain angiotensinergic pathways (Llorens-Cortes and Mendelsohn, 2002). A forebrain pathway integrates CVOs with the PVN, SON and median preoptic nuclei. A second pathway links the hypothalamus and medulla (including AP, and NTS). Since CVOs possess fenestrated capillaries and are heavily distributed with angiotensin receptors, activation of these receptors by blood–borne angiotensins is thought to impact central cardiovascular circuits, thus permitting interaction between the peripheral and central RASs. Given that the AT_1 receptor subtype binds AngII and AngIII with approximately the same affinity, and similarly provoke changes in blood pressure, thirst, and vasopressin release, it has been postulated that either AngII and AngIII are equivalently potent at the AT_1 subtype, or AngII must be converted to AngIII in order to activate this receptor subtype (Llorens-Cortes and Mendelsohn, 2002; Stragier et al., 2004; Wright and Harding, 1997). Thus, there is continuing debate over the identity of the active ligand(s) at the AT_1 receptor subtype.

This section summarizes the influences of AngII and AngIII upon blood pressure and vasopressin release.

3.2. Angiotensin II

Intracerebroventricular (icv) injections of AngII produce reliable pressor responses via activation of AT_1 receptors located in the CVOs (SFO, OVLT, and AP) that directly or

indirectly project to the PVN and SON to induce vasopressin release (reviewed in Phillips and Sumners, 1998; Wright and Harding, 1992). The primary mechanism mediating vasopressin release from these nuclei appears to be norepinephrine activation of α-adrenergic receptors located on PVN and SON neurons (Culman et al., 1995). Microinjections of AngII into the SFO, OVLT, and PVN also elicit elevations in blood pressure (reviewed in Wright and Harding, 1992). The pressor response induced by circulating AngII appears to be mediated primarily by the SFO and AP. The absence of a blood–brain barrier at these CVO sites permits penetration by other circulating hormones. AngII also activates AT_1 receptors at cardiovascular centers in the medulla. Target structures include NTS, AP, and anterior ventrolateral medulla (Culman et al., 2002). In particular, the AP appears to detect blood–borne AngII; while AngII activation of the NTS influences the baroreceptor reflex. Thus, circulating levels of AngII impact the baroreceptor reflex via a pathway from the AP to the NTS (Muratami, 1996; Phillips, 1987). In addition, AngII activation of AT_1 receptors in the anterior ventralateral medulla increases blood pressure by facilitating the sympathetic nervous system, tachycardia, and catecholamine release from the adrenal medulla (Allen et al., 2001; Dampney et al., 1996; Head, 1996; Muratami, 1996; Unger et al., 1985).

3.3. Angiotensin III and shorter fragments

In the 1970s and 1980s Fitzsimons and colleagues investigated the pressor potency of centrally applied AngIII and found it to possess 50% or less the potency of AngII depending upon the infusion site (reviewed in Fitzsimons, 1998; Wright and Harding, 1992, 1997). Tonnaer et al. (1982) reported the greatest pressor activity to icv injected AngII followed by AngI and AngIII (picomol range), with less activity induced by AngII(3–8), (4–8), (5–8), and (6–8) (nmol range). The C-terminal dipeptide AngII(7–8) and other dipeptites were inactive. Studies by Fink and Bruner (1985) and Wright et al. (1985) reevaluated the potency of AngIII and corrected potential shortcomings by siliconizing all glassware to discourage adherence of peptides, reduced the doses in order to minimize the half-life advantage of AngII over AngIII, and utilized degradation resistant analogs in an effort to reduce the *in vivo* conversion of AngII to AngIII, and AngIII to AngIV. Under these conditions pressor responses induced by icv infused AngII, AngIII and successively shortened C-terminal fragments through AngII(5–8) were compared (Wright et al., 1985, 1989). The results indicated that AngII, AngIII, Sar^1-AngII, and Sar^1-AngIII were comparable with respect to pressor responses in the alert rat, while AngIV and Sar^1-AngIV revealed approximately 70% of the activity of the above compounds. The activity of the shorter C-terminal fragments dropped to below 35%.

Zini et al. (1996) took a different approach to this issue by developing selective inhibitors of AP-A and AP-N (Fig. 3). The AP-A inhibitor (3-amino-4-thio-butyl-sulfonate: EC33) has been shown to increase the half-life of AngII by 2.6-fold as measured in hypothalamic homogenates, and completely blocked the formation of AngIII. An AP-N inhibitor (2-amino-pentane-1,5-dithiol: EC27) increased the half-life of AngIII by 2.3-fold. When AngII was icv injected in mice, plasma vasopressin levels were increased by 2-fold, however, the co-application of EC33 inhibited this AngII-induced vasopressin response in a dose-dependent fashion. In contrast, the icv injection of EC27 alone increased plasma vasopressin levels in a dose-dependent fashion. This EC27 stimulation of vasopressin release could be blocked by the accompanying injection of the nonspecific angiotensin receptor antagonist saralasin (Sar^1, Ala^8-AngII). These results suggest that central angiotensin-induced vasopressin release is dependent upon the conversion of AngII to AngIII, and therefore AngIII may be the main effector peptide in the brain with respect to the mediation of vasopressin release. Consistent with these findings are results utilizing an antiserum with anti-catalytic activity against AP-A (Song et al., 1997). When icv infused this antiserum reduced both drinking and blood pressure responses to the subsequent icv delivery of AngII by 73 and 59%, respectively. This same antiserum had no effect on icv AngIII-induced drinking and blood pressure responses.

Our laboratory has utilized icv infused EC33 or PC18 (an AP-N inhibitor with similar structure to EC27) followed by the metabolically stable analogs $_D$-Asp^1-AngII and $_D$-Arg^1-AngIII in an attempt to sort out relative contributions by AngII and AngIII to pressor responding in rats (Wright et al., 2002b). Pretreatment icv infusion with EC33 blocked the pressor activity induced by the subsequent infusion of $_D$-Asp^1-AngII; while EC33 had no effect on the pressor response to subsequent infusion of $_D$-Arg^1-AngIII. In contrast, pretreatment infusion with PC18 extended the duration of the $_D$-Asp^1-AngII pressor effect by approximately two to three times, and the duration of $_D$-Arg^1-AngIII's effect by approximately 10–15 times. Pretreatment with the specific AT$_1$ receptor antagonist losartan blocked the pressor responses induced by the subsequent infusion of both analogs indicating that they act via the AT$_1$ receptor subtype. These results suggest that the brain AT$_1$ receptor may be designed to preferentially bind AngIII in mediating systemic blood pressure.

3.3.1. Thirst—One of the most dramatic behavioral phenomena associated with the central injection of angiotensin is its ability to produce robust drinking. Linazasoro et al. (1954) and Nairn et al. (1956) first demonstrated that peripherally infused renal extracts produced drinking in rats and postulated that this response was angiotensin-induced. Since then many investigators have confirmed and extended these initial observations.

3.4. Angiotensin II

Booth (1968) discovered that microinjections of AngII into the rostral hypothalamus produced drinking. Soon after Epstein et al. (1970) observed dose-response water intake to icv injected AngII. Simpson and Routtenberg (1973) showed that microinjection of AngII into the SFO produced drinking. Buggy et al. (1975) and Buggy and Fisher (1976) reported that AngII infused into the third ventricle in the proximity of the OVLT, but not permitted to reach the SFO, was also dipsogenic. Following additional efforts to establish the respective contributions of the SFO and OVLT it was generally agreed that the OVLT detects angiotensins in both the cerebrospinal fluid and blood, while drinking induced by elevations in blood–borne angiotensins is primarily mediated by the highly vascularized SFO (reviewed in Lind, 1988; Wright and Harding, 1992).

3.5. Angiotensin III and shorter fragments

AngIII was originally found to possess about 50% of the dipsogenic activity of AngII when delivered into the diencephalon of the rat; while AngIV, AngII(4–8) and Ang(5–8) produced only slight dipsogenic acivitity (Fitzsimons, 1971, 1980). With the removal of phenylalanine from the C-terminal [i.e., Ang(1–7)] a complete loss of drinking was noted. Tonnaer et al. (1982) examined AngI, AngII, and several C-terminal fragments for dipsogenic activity when injected icv in rats. The greatest intakes occurred to AngII, AngI, and AngIII (picomol range) in that order, followed by AngII(4–8), AngIV, AngII(5–8), and AngIII(6–8) (nmol range). The C-terminal dipeptide AngII(7–8), and other dipeptide fragments, were relatively ineffective. Pretreatment with the ACE inhibitor, captopril, greatly reduced the drinking induced by AngI suggesting that conversion of AngI to AngII and/or AngIII is necessary for biological activity in the brain. In addition, pretreatment with saralasin blocked drinking to AngI and AngII(4–8); while the other angiotensins and fragments were not similarly tested. More recent investigations have established reasonably equivalent drinking responses in rats to icv infusions of AngII and AngIII, particularly at low doses if precautions are taken to avoid peptide adherence to glass mixing and storage containers, adjustments are made for differences in the purities of the compounds, and the angiotensins are infused rather than bolus injected (Wright et al., 1985).

3.5.1. Sodium appetite—Central application of angiotensins also produces a sodium appetite that follows a slower time course to develop than the drinking response (reviewed in

Fitzsimons, 1998). Body sodium conservation is primarily controlled by the renin–angiotensin–aldosterone system and these hormones are elevated during sodium deficiency, and in turn, act directly or indirectly on the brain to stimulate a sodium appetite (Epstein, 1982; Richter, 1936). The salt appetite that develops in a sodium-depleted rat can be suppressed by central application of angiotensin receptor antagonists (Buggy and Jonklaas, 1984; Weiss et al., 1986) or ACE inhibitors (Moe et al., 1984). In fact, sodium appetite induced by adrenalectomy can be suppressed by interruption of the brain RAS (Sakai and Epstein, 1990). AngII-induced sodium intake appears to be a function of activation of forebrain angiotensin receptors, but is not dependent on the SFO. Microinfusion of AngII near the OVLT produced both water and sodium intake in rats, while injections into the SFO elicited only water consumption (Fitts and Masson, 1990).

Peripheral infusions of high doses of AngII are required to provoke a sodium appetite that results in increases in plasma aldosterone, thus facilitating central AngII-elicited sodium intake (Summy-Long et al., 1983). Peripheral aldosterone can penetrate the blood–brain-barrier and has been shown to elevate brain AngII receptor numbers (Wong et al., 1990). There have also been attempts to determine whether this sodium appetite is primary or secondary to an immediate and sustained natriuresis (reviewed in Fitzsimons, 1998; Unger et al., 1988). Intracerebroventricular injections of AngII produced an immediate increase in urinary sodium excretion in alert rats prepared with a chronic indwelling urethral catheter that lasted for at least 1 h (Unger et al., 1989). Thus, it appears that icv AngII-induced sodium loss stimulates sodium appetite as a compensatory response.

Little evidence exists concerning AngIII's potential involvement in sodium appetite, and what is available is conflicting. Peripheral administration of AngIII has been shown to be ineffective in eliciting a salt appetite in Fischer 344 and Sprague–Dawley rats; while AngII was capable of producing a sodium appetite (Caputo et al., 1992). Acute AngIII infusions into the preoptic area failed to increase sodium appetite in rats, whereas AngII stimulated the appetite (Avrith and Fitzsimons, 1980). However, icv infused AngIII is equipotent to AngII in stimulating sodium consumption in baboons (Blair-West et al., 2001). Our laboratory has utilized the AP-A and AP-N inhibitors, EC33 and PC18, respectively, to investigate the roles of AngII and AngIII in salt appetite (Wilson et al., 2005). Rats were sodium depleted with furosemide, followed by endogenous angiotensin blockade with the ACE inhibitor captopril. [$_D$-Asp^1,$_D$-Arg^2]AngII and [$_D$-Arg^1]AngIII were then icv infused in order to evaluate the relative roles of AngII and AngIII in provoking sodium appetite. Both forms were effective in eliciting water and sodium solution (0.3 M NaCl) intakes. AngII analog-induced intakes of water and NaCl were decreased following pretreatment with EC33. Use of PC18 produced increased intakes of both fluids following treatment with the AngIII analog. These findings support a role for both peptides in eliciting and mediating sodium appetite.

4. Novel angiotensin-mediated physiologies and behaviors

4.1. Long-term potentiation

The phenomenon of LTP was originally described in the rabbit hippocampal slice preparation by Bliss and colleagues (Bliss and Garner-Medwin, 1973; Bliss and Lomo, 1973). Excitatory postsynaptic potentials evoked in the dentate gyrus could be progressively enhanced by short bursts of electrical stimulation. LTP is now thought by many researchers to represent a basic physiological mechanism of memory storage (Eichenbaum and Oto, 1992; Lynch et al., 1991; Martinez and Derrick, 1996). Wayner's laboratory was the first to report a role for AngII inhibition of hippocampal and dentate LTP (Armstrong et al., 1996; Denny et al., 1991; Wayner et al., 1973, 1993, 1995). This AngII-induced blockade could be prevented by co-injection with saralasin or losartan suggesting that the effect was via activation of the AT_1 receptor subtype; while the AT_2 receptor antagonist, PD123319, had no effect (Wayner et al., 1993). AngIII was

found to be much less effective than AngII at inhibiting LTP (Denny et al., 1991). Activation of the AT_4 receptor by Nle^1-AngIV significantly increased hippocampal LTP (Kramár et al., 2001). The application of an AT_4 receptor antagonist prior to tetanization disrupted the maintenance phase of LTP. This Nle^1-AngIV facilitation of LTP was subsequently shown to be NMDA-independent; however, this effect was dependent upon increased intracellular calcium via altered voltage dependent calcium channels (Davis et al., 2006).

Recently, Ang(1–7) has been shown to enhance hippocampal LTP independent of the AT_1 and AT_4 receptor subtypes (Hellner et al., 2005). These authors present convincing evidence that the Ang(1–7) receptor is the G-protein-coupled Mas receptor, encoded by the mas protooncogene.

There is one paper that evaluated HGF interaction with the hippocampal c-Met receptor as related to LTP and long-term depression (LTD; Akimoto et al., 2004). These investigators first established the presence of the c-Met receptor and HGF in the brain of adult rats. HGF is processed by proteases, including tissue plasminogen activator that is released in a neuronal activity-dependent fashion (Thewke and Seeds, 1999). HGF facilitated LTP in the CA1 region of hippocampal slices taken from 4 to 5 week old rats. This LTP appeared to be NMDA receptor mediated. HGF did not influence LTD. These results agree with the pattern of facilitation seen with Nle^1-AngIV, however, they are not consistent with an NMDA-independent phenomenon as observed in our laboratory.

4.2. Learning, memory and cognition

Memory acquisition can be measured in animals using several protocols including passive and active avoidance conditioning and spatial recognition tasks. Passive and active avoidance conditioning procedures are typically used to assess associative learning, the process of attaching meaning (consequences) to a previously neutral object or event where the consequence is often a foot shock (a punisher). With passive avoidance conditioning (variations are called step-through or step-down tasks) the animal is placed in the lighted side of a two-compartment apparatus and permitted to move to the more preferred dark compartment during several pre-conditioning trials. Once the animal has habituated to the compartment it typically moves to the dark side within 10–20 s. The final "conditioning trial" consists of placing the animal into the illuminated compartment and allowing it to enter the dark compartment. Once in the dark compartment a guillotine door closes off the entrance and a mild foot shock is applied for a short duration, usually 0.5–2 s. Thus, the conditioning paradigm consists of an association among the cues that denote the preferred dark compartment (conditioned stimuli) and the noxious foot shock (unconditioned stimulus). The conditioned response takes the form of an increased latency (reluctance) to move from the lighted compartment to the dark compartment on subsequent retention trials, i.e. passive avoidance conditioning. Retention trials are usually placed at 24-h intervals following conditioning in order to measure the subsequent strength of the conditioned response. Active avoidance protocols usually make use of a two compartment apparatus (shuttlebox) each side equipped with a cue light (or tone). The light comes on in one compartment to signal an impending foot shock at a latency of a few seconds. This permits the animal time to move into the opposite chamber thus avoiding foot shock. Following a brief inter-trial interval the light in the second compartment comes on to cue an impending foot shock in that compartment. Trials proceed until the animal anticipates and thus avoids each foot shock. This anticipatory behavior is considered to be the conditioned response.

Circular water and 8-arm radial mazes are used to measure the acquisition of spatial memory by rodent models. The Morris water maze task (Morris, 1984) requires that the animal be placed into the water at a different location next to the wall of the tank on each training trial. The goal is to locate a submerged platform (2–3 cm below the surface typically fixed in position) using

extra-maze visual cues placed on the walls surrounding the maze. If the animal is unsuccessful at the end of a trial it is placed on the platform for a short rest period permitting an opportunity to orient using these cues. The number of trials per day can vary from one to as many as 20 or 25. The number of days of training may vary from 1 or 2, to a week or longer. The dependent measures may include the latency and distance required to find the platform on each trial, swim speed and efficiency of search patterns. The 8-arm radial maze protocol requires food reward to motivate the animal. Several arms of the maze are baited with food. The animal is placed at the start point in the middle of the maze (origin of all arms) and must run down each arm to determine whether food is present at the end of the arm. The important measures include the latency required to locate the arms that contain food and avoid those arms not baited with food, and the number of errors due to re-entry into a previously visited arm.

4.2.1. Angiotensin converting enzyme (ACE) inhibitors and cognition—

Accompanying the therapeutic benefits of ACE inhibitors (captopril, enalapril, ramipril, ceranapril) in treating hypertension, congestive heart failure, and following mild cardiac infarction, there appears to be facilitated cognitive functioning and feelings of well-being. Croog et al. (1986) employed 626 mild to moderated hypertensive male patients in randomized double-blind trials over a 24-week study. Patient self-reports indicated improved mental acuity at work, less sexual dysfunction, and increased sense of well-being on captopril. There was no change with propranolol treatment, and a decline in those patients placed on methyldopa. Blood pressure was equivalently controlled in all three treatment groups. Deicken (1986) and Zubenko and Nixon (1984) have reported captopril-induced mood elevating effects in depressed patients. Barnes et al. (1992) posited that elevated brain AngII levels may interfere with acetylcholine (Ach) release that in turn interferes with cognitive processing (Bartus et al., 1982). According to this hypothesis ACE inhibitors may facilitate cognitive functioning by reducing the synthesis of AngII, thus removing an inhibitory influence upon Ach release (Barnes et al., 1990). In support of this hypothesis Costall et al. (1989) treated mice with captopril or ceranapril and measured an habituatory response of moving from a brightly lit area to the darker area of a light/dark box. The muscarinic acetylcholine receptor antagonist scopolamine impaired habituation, while captopril and ceranapril were both effective at countering this scopolamine effect (Barnes et al., 1992).

Scopolamine has been shown to delay the time required for rats to locate a submerged platform in the Morris water maze task. Treatment with ceranapril offset this scopolamine-induced impairment such that escape times were equivalent with controls. In further support, Barnes et al. (1991a,b) reported high binding densities for [^{3}H]-ceranapril in rat striatum and hippocampus, and human caudate, attributed to ACE in the mirovasculature and perhaps at extravascular sites. Intravenous pretreatment with captopril reduced subsequent [^{3}H]-ceranapril binding in most areas of the brain, except the striatum and brain stem. Barnes et al. (1989) have also reported AngII-induced interference with potassium-mediated release of [^{3}H]-Ach from rat entorhinal cortex slices. This AngII effect could be blocked by sarthran. Along these lines, Mondadori and Etienne (1990) found that captopril and enalapril reduced electroshock-induced amnesia in mice. These animals were trained to avoid the dark compartment of a two-chamber passive avoidance apparatus by the application of foot shock in the dark side immediately following an electroconvulsive shock. Recall of the conditioned response was facilitated in those mice given ACE inhibitors 1 h prior to the conditioning trial. Flood and Morley (1993) reported similar results using an active avoidance task in mice. Barnes et al. (1990, 1991b) have shown that reasonably low doses of losartan and the AT_2 receptor antagonist P123177, improved scopolamine-impaired performance in the previously described habituation test. Similarly, DeNoble et al. (1991) measured impaired performance on a passive avoidance task in rats icv treated with renin. This impairment could be offset with ACE inhibitor treatment, or by the application of the AT_1 receptor antagonists EXP3312 or EXP3880, but not PD123177. The proposal that ACE inhibitors enhance learning has been

challenged by Chen and Mendelsohn (1992) who found that a high oral dose of ceranapril in rats inhibited ACE at the CVOs, but not within blood–brain barrier protected structures. This suggests that ceranapril does not cross the blood–brain barrier.

At present evidence favoring improved cognitive functioning by ACE inhibitors and AT_1 receptor antagonists is stronger in animal tests of habituation and active or passive avoidance tasks than for animals evaluated using spatial learning paradigms. Our laboratory has measured facilitated Morris water maze performance in scopolamine, or nicotinic acetylcholine receptor antagonist mecamylamine pretreated rats with icv treatment of AngIV analogs (Olson et al., 2004; Pederson et al., 1998; Wright et al., 1999). This suggests a role for AngIV in the facilitation of cognitive processing noted during treatment with ACE inhibitors. It has also been established that Ang(1–7) and AngI(3–10) levels are elevated during treatment with ACE inhibitors (Lawrence et al., 1990). Both AngII(2–7) and AngI(3–10) bind at the AT_4 receptor subtype with affinities generally comparable to that of native AngIV (Harding et al., unpublished observations; Sardinia et al., 1993). Also, conversion of Ang(1–7) to a ligand that acts at the AT_4 receptor is possible.

4.2.2. Angiotensin II—Thirty-five years ago Rolls et al. (1972) placed rats on a progressive ratio schedule-bar press response for food and water, and found that motivational levels were approximately equal following 24 h of water deprivation and when provided water and prepared with an injection of AngII into the preoptic area of the hypothalamus. Graeff et al. (1973) conditioned water-deprived rats to press a bar for water, and then injected AngII into the septal area and measured equivalent bar pressing when rats were satiated. These results suggested that AngII injections may simulate the motivational characteristics present while water-deprived. It was also reported that icv-infused AngII interfered with performance on a variable interval operant task in rabbits (Melo and Graeff, 1975). Similarly, icv renin infused 1 min prior to the initiation of acquisition training on a passive avoidance task in rats interfered with recall of that task 1 and 2 days later (Köller et al., 1979). (Note that renin is responsible for the conversion of angiotensinogen to AngI, thus providing additional substrate for ACE mediated conversion to AngII.) Angiotensin II was assumed to be responsible for disruption of recall given that this performance deficit was attenuated by icv infusion of the ACE inhibitor captopril. It was also reported that AngII injected into the dorsal neostriatum 5 min following passive avoidance conditioning interfered with the recall of the conditioned response 24 h later (Morgan and Routtenberg, 1977). Along these lines, DeNoble et al. (1991) observed that icv infused renin dose-dependently disrupted performance of a passive avoidance task, i.e. as the renin dose was increased the level of retention decreased. The co-application of an AT_1 receptor antagonist (EXP3312 or EXP3880) and the ACE inhibitor captopril, attenuated this renin-induced deficit. Since co-application of an AT_2 receptor antagonist (PD123177) failed to influence the performance deficit produced by renin, it was concluded that the AT_1 receptor subtype mediated this deficit. It follows that compounds that decrease AT_1 receptor activation would be expected to facilitate cognitive processing.

In contrast with the above findings, central injections of AngII have been reported to improve acquisition and recall by some investigators. For example, Baranowska et al. (1983) injected AngII (icv: 1 and 2 μg) 15 min prior to active avoidance conditioning trials in rats. A buzzer served as a conditioned stimulus and foot shock as the unconditioned stimulus. Angiotensin II facilitated acquisition of the response but did not influence extinction. A low icv dose of AngII (0.5 mg) inhibited the acquisition of this conditioned response. Pretreatment with saralasin or sarile (Sar[1], Ile[8]-AngII) failed to block these AngII effects. The authors suggest that AngII exerts a bimodal action upon learning, that is, an inhibitory influence at low doses and a facilitory effect at higher doses. Subsequent reports from this laboratory indicated that icv delivered AngII and AngIV (1 nmol ≈ 1 μg), 15 min prior to testing for retention, facilitated recall of a passive avoidance conditioned response (Braszko et al., 1987; Georgiev et al.,

1988). These treatments also facilitated the acquisition of a shuttlebox active avoidance task (Braszko et al., 1987, 1988; Georgiev et al., 1988). Further, such treatments facilitated T-maze performance when delivered immediately following acquisition training. However, if AngII and AngIV were administered 15 min prior to testing for recall of T-maze performance, no facilitation of performance was noted (Braszko et al., 1987, 1988).

Along these lines, microinjection of AngII into the CA_1 hippocampal field has also been shown to facilitate acquisition of an active avoidance (shuttle box) task in rats (Belcheva et al., 2000). Kulakowska et al. (1996) extended this work to an object recognition task in which AngII facilitation could be blocked by pretreatment with losartan. These results suggest that the AT_1 receptor mediated this AngII-induced improvement in object recognition. However, Braszko (2002) has recently reported that icv AngII-induced facilitation of passive avoidance conditioning, conditioned avoidance responding, and open field locomotor behavior. This improvement in behavior could be blocked by combined pretreatment with losartan plus an AT_2 receptor antagonist (PD123319), but not by each alone. Further, Braszko et al. (2003) have attempted to explain these variable AngII effects upon acquisition by measuring changes in motor and anxiety responses to icv infusion of AngII. They found significant increases in anxiety as measured using an elevated "plus" maze, and impaired motor coordination as measured with the "chimney" test. Pretreatment with either losartan or PD123319 counteracted the AngII-induced heightened anxiety effects, but only losartan offset the impaired motor coordination effects.

The vast majority of the above studies utilized native angiotensins rather than analogs that resist conversion to shorter chain peptides. Thus, it is likely that these results are due to a combination of effects resulting from the conversion of AngII to AngIII and perhaps to Ang (1–7), Ang(2–7), Ang(3–7), and AngIV.

4.2.3. Angiotensin IV—The often noted failure of AT_1 and AT_2 receptor antagonists to influence performance on cognitive tasks, or block subsequent AngII facilitation of a conditioned response, may indicate that AngII is converted to AngIII, and then to AngIV (or an AngIV-like compound), and it is this ligand that acts at the AT_4 receptor subtype to improve performance. Our laboratory has discovered that the icv infusion of AngIV leads to c-Fos expression in the hippocampal and piriform cortices; while similar injection of AngII failed to induce c-Fos-like immunoreactivity in these structures, but did activate c-Fos expression in circumventricular organs (Roberts et al., 1995) and the hypothalamus (Zhu and Herbert, 1996). Pretreatment with losartan prevented this AngII-induced c-Fos immunoreactivity, while pretreatment with the AT_4 receptor antagonist, divalinal-AngIV [Val^1(CH$_2$-NH$_2$)$^{1-2}$,Tyr^2(CH$_2$-NH$_2$)$^{2-3}$,Val^3-AngIV], blocked AngIV-induced c-Fos expression. There were no crossover effects exhibited by these antagonists. Along these lines, Braszko et al. (1988, 1991) were the first to report that icv injected AngII and AngIV were equivalent at facilitating exploratory behavior in rats tested in an open field, improved recall of passive avoidance conditioning, and the acquisition of active avoidance conditioning. Our laboratory confirmed and extended the above findings in that icv infused AngIV improved the recall of a passive avoidance response in a dose-dependent fashion, with the most prominent facilitation at the highest dose (1 nmol, Wright et al., 1993, 1995). We also found that icv treatment with divalinal, disrupted recall of this response (Wright et al., 1995). Along these lines osmotic pump icv delivery of divalinal during 6 days of training significantly impaired acquisition of the Morris water maze task (Wright et al., 1999). We further determined that icv injected metabolically resistant analogs of AngIV could be utilized to facilitate acquisition of successful search patterns in spatial memory tasks as compared with control animals treated with artificial cerebrospinal fluid, or a pentapeptide that did not bind at the AT_4 receptor subtype (Stubley-Weatherly et al., 1996; Wright et al., 1999). A similar facilitation of acquisition by AngIV

analogs (eg. Nle[1]-AngIV) has been observed in scopolamine pretreated rats (Pederson et al., 1998, 2001), and perforant path knife-cut damaged rats (Wright et al., 1999).

Recently Olson et al. (2004) reported that icv treatment with the nicotinic receptor antagonist, mecamylamine, disrupted acquisition of the Morris water maze task (Olson et al., 2004). Once again the icv application of Nle[1]-AngIV overcame this deficit in spatial learning. However, Nle[1]-AngIV could not compensate for impaired acquisition resulting from the combined application of scopolamine plus mecamylamine. These results suggest that Nle[1]-AngIV-induced compensation via the AT_4 receptor subtype may be dependent upon the brain cholinergic system. This notion is supported by the observation that AngIV and leucine-valine-valine-hemorphin-7 (LVV-H7) induced the release of Ach from rat hippocampal slices in a dose-dependent fashion (Lee et al., 2001). This release of Ach could be blocked by divalinal. These investigators have also reported AngIV- and LVV-H7-induced facilitation of spatial learning using the Barnes circular maze in which the animal must locate one escape tunnel among eight possible locations (Lee et al., 2004). The rats were tested three trials per day for 10 training days, but received only one icv bolus injection of AngIV or LVV-H7 on day 1, 5 min prior to testing.

Braszko et al. (2006) have recently demonstrated that icv infused AngII must be converted to AngIV in order to facilitate performance on passive avoidance conditioning and object recognition tasks in rats. AngII injected at 5 or 10 min prior to testing was ineffective; while at 15 min prior to testing it was effective at improving performance. AngIV facilitated performance at 5, 10 and 15 min prior to testing. The authors concluded that degradation of AngII to AngIV is necessary for cognitive facilitation. This laboratory has argued that D_2 dopamine (DA) receptors at least partially mediate this AngIV-induced cognitive effect (Braszko, 2006).

Taken together, these results suggest an important role for the AngIV/AT_4 receptor system in learning and memory processes.

4.3. Cerebroprotection

4.3.1. Ischemia-induced damage—A number of studies have investigated the potential positive effects of angiotensins as cerebroprotective agents against ischemia-induced damage. It has been known for some time that systemically infused AngII influences regional cerebral blood flow (Reynier-Rebuffel et al., 1987) especially as related to CVO versus non-CVO structures (Tuor et al., 1988). Tamake et al. (1992) reported that AngII increased cerebral blood flow in the rabbit. Haberl et al. (1990) evaluated cerebral arteriole responses to AngII in anesthetized rats prepared with a closed cranial window and found Ang II to dilate cerebral arteries. These investigators also used this closed cranial window technique in rabbits and noted that topical application of renin to the surface of the brain induced dilation of pial arterioles within a few minutes, with blood flow increasing and peaking at 50 min following application (Haberl et al., 1996). These changes were inhibited by intravenous or topical captopril.

The gerbil has an incomplete anastomotic Circle of Willis that permits ipsilateral focal brain ischemia with unilateral carotid artery ligation. Mortality rate is about 50% at 48 h post-surgery. The infusion of AngII has been shown to reduce this rate to approximately 15% (Fernandez et al., 1986). In contrast, treatment with losartan or candesartan failed to change the survival rate; while enalapril or lisinopril reduced the survival rate to approximately 18–25% (Dalmay et al., 2001a). These AngII protective effects appear to be mediated by the AT_2 receptor subtype (Brix and Haberl, 1992; Kagiyama et al., 2003; Li et al., 2005; Stromberg et al., 1992). Along these lines, Iwai et al. (2004) have tested AT_2-null transgenic mice with permanent middle cerebral artery occlusion and found more severe cerebral damage than in wild-type controls.

Pretreatment with an AT_1 receptor blocker (valsartan) for 10 days reduced the area of ischemic-induced damage and this protective effect was weaker in the AT_2-null than in wild-type mice.

The observation that the protective effect of valsartan only diminished cerebral damage in the AT_2-null mice suggests that an additional receptor subtype could be involved in mediating the neuroprotective effect. Our laboratory has shown that AngIV infusion yields a dose-dependent increase in cerebral blood flow without significantly influencing systemic blood pressure (Kramár et al., 1997). This effect was not changed by pretreatment with AT_1 or AT_2 receptor antagonists, but was abolished by divalinal. In addition, AngIV infusion was shown to restore cerebral blood flow following subarachnoidal hemorrhage (Naveri et al., 1994). Dalmay et al. (2001b) reported that AngIV infusion in the candesartan pretreated gerbil model of unilateral carotid artery ligation, only slightly decreased mortality at post-surgery day 3, but significantly decreased the lisinopril-induced increase in mortality. These results support the notion that AT_4 receptor activation contributes to cerebroprotection.

HGF has been shown to positively impact ischemic-induced injuries such as cardiac ischemia (Nakamura et al., 2000) and hind limb ischemia (Morishita et al., 1999; Van Belle et al., 1998). HGF has also been shown to eliminate hippocampal neuronal cell loss in transient global cerebral ischemic gerbils (Miyazawa et al., 1998) and transient focal ischemic rats (Tsuzuki et al., 2001). Date et al. (2004) have reported HGF-induced improvements in escape latencies by microsphere embolism-induced cerebral ischemic rats using a circular water maze task. The authors measured reduced damage to cerebral endothelial cells in ischemic animals treated with HGF. Nagayama et al. (2004) have observed up-regulation of HGF and c-Met mRNAs in the peri-infarct region at 14 and 28 days, respectively, following permanent middle cerebral artery occlusion in mice. Along these lines, Shimamura et al. (2006) have recently shown that over-expression of HGF following permanent middle cerebral artery occlusion resulted in significant recovery of performance using the circular water maze and passive avoidance conditioning tasks. Treatment with HGF was also found to increase the number of arteries in the neocortex some 50+ days following the onset of ischemia.

Taken together these findings suggest a role for the AT_4–c-Met receptor in cerebroprotection and are consistent with the notion that AngIV increases blood flow by a NO-dependent mechanism (Kramár et al., 1997). In agreement with this hypothesis is recent work by Faure et al. (2006) indicating that increasing internal carotid artery doses of AngIV significantly decreased mortality and cerebral infarct size in rats 24 h following embolic stroke due to the intracarotid injection of calibrated microspheres. Pretreatment with either divalinal or nomega-nitro-1-arginine methylester (L-NAME) abolished this protective effect. Sequential cerebral arteriography indicated that AngIV caused the redistribution of blood flow to the ischemic areas within a few minutes. Thus, AngIV may yield its cerebroprotective effect against acute cerebral ischemia via an intracerebro-hemodynamic AT_4–c-Met receptor-mediated NO-dependent mechanism. These HGF results offer exciting possibilities concerning the treatment of ischemia-induced damage.

4.3.2. Seizure—There is a growing literature suggesting that angiotensins mediate seizure susceptibility. Georgiev and Kambourova (1983; Georgiev et al., 1986) were the first to show that AngII elevated the threshold of pentylenetetrazol, bicuculline, or picrotoxin-induced seizures in mice. They further reported that the AngII analog, sarmesin (Sar[1],methyl Tyr[4]-AngII; Matsoukas et al., 1985) also provided some protection against seizuring in these models (Tchekalarova et al., 2003). Such AngII and sarmesin effects appear to be via the AT_1 receptor subtype given that pretreatment with losartan blocked their protective ability (Tchekalarova and Georgiev, 1999). Angiotensin III and AngIV were also shown to dose-dependentally increase the threshold to pentylenetetrazol-induced brain excitability in mice (Tchekalarova et al., 2001a). Nearly equivalent increases in seizure threshold in these seizure models has been

observed with the tetrapeptide AngII (3–6) and the tripeptide AngII (1–3) (Klusha et al., 1986; Svirskis et al., 1991).

A functional relationship between angiotensins and dopamine neurotransmission has been proposed by Tchekalarova and Georgiev (2005). In support of this notion activation of AT_1 receptors potentiated depolarization-dependent DA release in rat brain (Simonnet and Giorguieff-Chesselet, 1979; Georgiev et al., 1990; Brown et al., 1996). It is also clear that vasopressinergic neurons may be activated by AngII to synthesize DA (Rossi, 1998). Most recently Tchekalarova and Georgiev (2006) have suggested an important role for norepinephrine in the neural protection offered by AngII and AngIII. Along these lines, Tchekalarova and Georgiev (2005) have recently noted anticonvulsive effects accompanying pretreatment with AngIV in the pentylenetetrazol kindling model that revealed increased dopamine D_1 and D_2 receptor subtype binding. These authors concluded that the cerebroprotective ability of AngIV could be via a modulatory effect on DA receptors in the basal ganglia given the high densities of the AT_4 receptor subtype in the caudate putamen and nucleus accumbens (Wright and Harding, 2004). Further, Stragier et al. (2006) have reported that icv infusion of either AngIV or somatostatin-14 in rats produced an elevation in hippocampal DA and serotonin levels, as measured by microdialysis, and protected against pilocarpine-induced seizures. Such neural protective effects could be blocked by simultaneous treatment with the somatostatin receptor antagonist, Cyanamid 154806. These results were interpreted to indicate an AngIV-induced anti-convulsive effect mediated via somatostatin receptor-2 activation.

4.4. Renal blood flow and natriuresis

In mammalian species there is generally a high level of circulating angiotensinogen such that the limiting factor concerning AngI production is the availability of plasma renin (Campbell et al., 1991). The level of renin release is governed by the kidney juxtaglomerular cells, and the formation of AngII is dependent upon the availability of ACE on endothelial cells of vascular beds (Erdos, 1990). AngII acts to constrict vascular smooth muscle cells, facilitate myocardial contractility, promote the release of catecholamines from the adrenal medulla and sympathetic nerve endings, stimulate aldosterone release as well as thirst and sodium appetite. AngII also regulates sodium transport in epithelial cells in the kidney and intestine (Navar et al., 2000).

The AT_1 receptor subtype is distributed throughout the renal microvasculature, the proximal tubule brush border, the basolateral membranes and the cortical collecting duct (Burns et al., 1993; Harrison-Bernard et al., 1997). In rats and rabbits intravenous infusion of AngII reduces renal blood flow and cortex blood flow at doses that do not effect medullary blood flow (Evans et al., 2000a, b; Walker et al., 1999). In dogs intravenous AngII somewhat reduces medullar blood flow (Chou et al., 1990). It has been suggested that AngII binds at AT_1 receptors to constrict the vasculature of the renal cortex; however such constriction in the medulla is countered by prostaglandin E2 (Sadowski and Badzynska, 2006), and perhaps by NO (Patzak and Persson, 2007). The AT_2 receptor subtype has also been implicated in this blunting of AT_1 mediated vasoconstriction (Arima, 2003; Rajapakse et al., 2006). Thus, medullary blood flow is key to tubular salt and water reabsorption, and in turn, the regulation of systemic blood pressure. In this regard medullary ischemia may produce salt and water retention and result in elevated blood pressure (Evans et al., 2004).

Autoradiographic and radioligand binding experiments have localized the AT_4 receptor subtype on microvilli and cell bodies of rat proximal convoluted and straight tubules (Handa et al., 1998), cultured rat mesangial cells (Chansel et al., 1998), cultured opossum proximal tubule cells (Dulin et al., 1995), apical and basolateral membranes of rabbit cortical tubules

(Dulin et al., 1994), cultured rabbit (Garreau et al., 1998) and human (Czekalski et al., 1996) collecting duct cells, and cultured human proximal tubule epithelial cells (Handa, 2001).

Several studies have compared the influences of AngII and AngIV on renal blood flow. Our laboratory reported that renal artery infusion of AngII in the anesthetized rat produced significant elevations in systemic blood pressure, decreases in cortical blood flow, glomerular filtration rate, urine volume and urine sodium excretion (Hamilton et al., 2001). Similar infusion of AngIV produced increases in renal cortical blood flow, and urine sodium excretion, with minimal influence on glomerular filtration rate, urine volume and systemic blood pressure. Thus, in our hands AngIV acted as a natriuretic agent. Li et al. (2006) noted AngII and AngIV to cause dose-dependent elevations in systemic blood pressure in the rat, accompanied by a decrease in renal cortical blood flow. In addition, AngII produced a reduction in renal medullary blood flow; while AngIV did not. These AngIV effects could be blocked by the AT_1 receptor antagonist losartan. The authors concluded that at the doses used (nM concentrations) AngIV influenced renal cortical blood flow by interacting with the AT_1 receptor subtype. Other laboratories have confirmed that renal artery infusion of AngIV in anesthetize rats produces a decrease in regional renal blood flow that is mediated by the AT_1 receptor subtype (Fitzgerald. et al., 1999; Li et al., 2006). Similar results have been obtained via direct measurement of renal microvasculature in the isolated rat kidney (Van Rodijnen et al., 2002). However, Handa (2006) has recently measured total renal blood flow in anesthetized rats using transient doses of AngII, AngIII, and AngIV infused into the renal artery of anesthetized rats. Both AngII and AngIII induced a dose-dependent vasoconstriction; while AngIV produced an immediate dose-dependent vasoconstriction followed by a prolonged vasodilation. This biphasic response to AngIV could be attenuated by losartan but not by divalinal, suggesting that it was AT_1 receptor dependent. The vasodilation phase of this AngIV response was not influenced by indomethacin. Thus, it was concluded that this AngIV induced renal vasodilatory effect was not prostaglandin mediated.

Despite its name, HGF is found at higher levels in the adult kidney and lungs with about equivalent levels in the liver and spleen (Liu, 2002). The level of HGF protein measured in the kidney is approximately four times that in the liver. This organ distribution is also true of the c-Met receptor. While HGF is found in glomerular mesangial cells, endothelial cells, interstitial fibroblasts and macrophages, the c-Met receptor is more widespread in the kidney, particularly in tubular epithelial cells and collecting duct (Liu et al., 1996). The expression of HGF is triggered by acute renal failure induced by ischemia or nephrotoxic agents (Liu et al., 1999; Matsumoto and Nakamura, 2001). It has been hypothesized that this upregulation of HGF is designed to encourage recovery from the damage caused by acute renal failure given its known ability to stimulate cell proliferation, migration and differentiation (Liu, 2002; Matsumoto and Nakamura, 2001). Nakatani et al. (2002) have shown that the addition of HGF to the preservation medium of an excised dog kidney improved recovery of renal blood flow and glomerular filtration rate following 3 h of cold ischemia. The authors concluded that such an approach may counter the ischemic injury that occurs with transplanted human kidneys and thus improve graft survival.

The importance of AngIV and HGF in the kidney remains an open question. The resolution of this issue is particularly important given that both are locally synthesized in the kidney (Handa, 2000; Liu, 2002) and the AT_4–c-Met receptor is prominently represented in the kidney (Coleman et al., 1998) and renal artery (Handa, 2001).

4.5. Stress

Considerable evidence supports an important role for the brain RAS in the control of stress-induced physiologies. AT_1 receptors are prominent in structures that control stress responses including median eminence, PVN, anterior pituitary gland, adrenal medulla and zona

glomerulosa (reviewed in Armando et al., 2003; Wright and Harding, 1992). Elevations in brain AngII have been shown to facilitate the release of norepinephrine *in vivo* and in cell culture (reviewed in Gard, 2002; Phillips, 1987). In turn, elevations in norepineprine were shown to block AngII release and down-regulation of angiotensin receptors. The application of stressors elevated circulating and brain levels of renin and AngII (Peng and Phillips, 2001; Yang et al., 1996). Stress also up-regulates the expression of AT_1 receptors within the PVN where corticotrophin-releasing hormone (CRH) cell bodies are located (Castren and Saavedra, 1988; Jezova et al., 1998), and in the anterior pituitary (Leong et al., 2002). During stress synthesized AngII within the anterior pituitary facilitates release of adrenocorticotrophin hormone (ACTH; Ganong and Murakami, 1987). Thus, stress-induced upregulation of PVN AT_1 receptors appears to provoke CRH synthesis that precludes the facilitation of ACTH release and elevated adrenal corticoid secretion. Short periods of isolation stress have been shown to elevate AT_1 receptor expression in the PVN, along with correlated elevations in pituitary ACTH, adrenal corticosterone, catecholamines, and aldosterone. Nishimura et al. (2000) have shown that peripheral treatment with the AT_1 receptor antagonist, candesartan, prevented AT_1 receptor binding following isolation both in the anterior pituitary and adrenal glands, and in the PVN. This treatment also interfered with expected elevations of pituitary ACTH and adrenal corticosterone.

A second model that has been examined is gastric ulceration induced by cold restraint. This procedure induces gastric mucosa damage (Overmier and Murison, 2000) due to reduced blood flow and elevated free radical formation (Tuncel et al., 1998). Of particular interest, AngII mediated constriction of the stomach vasculature via AT_1 receptor stimulation appears to be an important mediator of this reduction in blood flow (Heinemann et al., 1999). Bregonzio et al. (2003) reported that administration of candesartan significantly decreased the occurrence of gastric ulcerations induced by cold restraint stress.

Taken together these results point to an important role for the AngII/AT_1 receptor system in the etiology of stress response. Saavedra and colleagues (Armando et al., 2003) have recently recommended that AT_1 receptor antagonists be evaluated for clinical efficacy in the treatment of stress-related disease states.

4.6. Depression

The first suggestion that the brain RAS may be important in depression came with the observation that captopril induced an anti-depressant effect in hypertensive patients that also suffered from depression (Deicken, 1986; Germain and Chouinard, 1988, 1989; Zubenko and Nixon, 1984). There had been previous hints concerning this relationship from animal studies. Specifically, rats treated with antidepressants revealed decreased water intake induced by peripherally or centrally injected isoprenaline, either in the presence or absence of an α_2-adrenoceptor antagonist (Goldstein et al., 1985; Przegalinski et al., 1988). Further testing indicated that each of the antidepressant drugs fluoxetine, desipramine, and tranylcypromine, reduced AngII-induced dipsogenicity in rats (Gard and Mycroft, 1991; Gard et al., 1994).

Captopril treatment has also been shown to protect animals against the forced swim induction method of learned helplessness/depression. This protocol requires the animal to swim within a small pool of water that has no escape. Eventually the animal stops swimming and becomes immobile. When placed in the pool the next day it assumes immobility significantly sooner than during the initial trial. On each subsequent test day the latency to evidence immobility decreases, i.e. learned helplessness. Pretreatment with captopril reduced immobility by mice equivalent to treatment with the antidepressants imipramine or mianserine (Giardina and Ebert, 1989). Learned helplessness induced by foot shock in rats could be prevented by pretreatment with captopril to the same degree as imipramine (Martin et al., 1990). Under both protocols the protective effects of captopril were reversed by naloxone, suggesting that the ACE inhibitor

was exerting its antidepressant effects, at least in part, via opioid receptors. In addition, this effect is also dependent upon the brain RAS since pretreatment with losartan provided protection from immobility in the forced swim test (Gard, 2002; Gard et al., 1999). These results suggest that antidepressants exert their positive effects to some degree by inhibiting the brain RAS. The precise mechanism(s) of this inhibition remains to be determined.

5. Potential therapeutic applications

5.1. The angiotensin II/AT$_1$ receptor subtype system

Treatment strategies for controlling hypertension include diuretics, central and peripheral sympathicolytics, calcium channel blockers, vasodilators, RAS inhibitors and receptor antagonists. As previously discussed it has been assumed that the AngII/AT$_1$ receptor system is the primary regulator of blood pressure and body water balance. However, several years ago our laboratory reported that spontaneously hypertensive rats (SHRs) revealed increased pressor sensitivity to the icv infusion of AngII and AngIII as compared with normotensive Wistar–Kyoto and Sprague–Dawly rats (reviewed in Wright and Harding, 1992). These angiotensin-induced elevations in blood pressure persisted for a prolonged period of time in the SHR as compared with the normotensive strains. Subsequently we utilized icv delivery of the AP-N inhibitor, bestatin, to slow conversion of AngIII to AngIV resulting in a prolonged and heightened pressor response (Jensen et al., 1989); while the infusion of leucine aminopeptidase M that facilitated conversion of AngIII to AngIV significantly reduced blood pressure in SHRs (Wright et al., 1989). The more recent finding that inhibition of brain AP-A by the icv infusion of EC33 blocked blood pressure elevation due to the injection of AngII, further supports the notion that conversion of brain AngII to AngIII is necessary to the angiotensin-induced pressor response (Llorens-Cortes and Mendelsohn, 2002; Reaux et al., 1999; Zini et al., 1996). The selective AP-N inhibitor, PC18, administered icv prevented conversion of AngIII to AngIV and resulted in significant elevations in blood pressure. This response could be blocked by pretreatment with the AT$_1$ receptor antagonist losartan. These findings offer a new level of insight into our understanding concerning the importance of AP-A mediated conversion of AngII to AngIII in the control of blood pressure, and represent an important therapeutic target for antihypertensive drug development.

5.2. The angiotensin IV/AT$_4$ receptor subtype system

When our laboratory discovered the AT$_4$ receptor in 1991 (Harding et al., 1992) we were attempting to purify the AT$_1$ receptor subtype, and identify the binding site responsible for improvements in memory associated with icv infusion of AngIV (Braszko et al., 1988, 1991; Wright et al., 1993, 1995). Subsequent work by members of our laboratory indicated that spatial memory impairments induced by chemical disruption of the muscarinic cholinergic receptor system by scopolamine hydrobromide (Pederson et al., 1998, 2001), or perforant path knife cuts (Wright et al., 1999), could be over come with icv infusion of AngIV or AngIV analogs. These results were confirmed and extended by other laboratories (Holownia and Braszko, 2003; Lee et al., 2004; Tchekalarova et al., 2001b). We further showed that AngIV and its analogs enhanced long-term potentiation (LTP) in the CA1 region of rat hippocampal slices (Kramár et al., 2001) and in the dentate gyrus *in vivo* (Wayner et al., 2001). AngIV was shown to facilitate potassium-evoked acetylcholine release from rat hippocampal slices (Lee et al., 2001) suggesting that the brain cholinergic system may underlie, at least in part, the mechanism of AT$_4$ receptor ligand memory enhancement. The potential use of angiotensin receptor agonists to treat dementias, including Alzheimer's disease, has been suggested (Albiston et al., 2004; Gard and Rusted, 2004; Poljak et al., 2004; Savaskan, 2005), and represents a new therapeutic target.

Given the previous descriptions concerning the ability of AngIV and HGF to impact ischemia-induced injuries (Faure et al., 2006), seizures (Stragier et al., 2006), and renal blood flow (Handa, 2006), the AT_4–c-Met receptor is also an exciting therapeutic target for the possible treatment of these disorders. Finally, emerging evidence suggests that the brain RAS is involved in the mediation of stress responses (Ruiz-Ortega et al., 2001) and depression (Gard, 2004). The intimate role played by angiotensin receptor subtypes in these disorders encourages the development of new treatment strategies.

6. Conclusion

This review considers available information regarding the synthesis and degradation of active angiotensins and the brain distributions of the three angiotensin receptor subtypes thus far characterized. The AT_1 and AT_2 receptor subtypes have been cloned and sequenced and are G-protein linked. There is debate concerning the AT_4 subtype. Specifically, this subtype has been identified as insulin regulated aminopeptidase (IRAP); however recent findings challenge this assumption and indicate that the AT_4 subtype is the c-Met receptor. This review provides relevant findings concerning the c-Met receptor where appropriate. Each of these subtypes is discussed and emphasis is placed on newly discovered functions and clinical applicability. The most promising targets include the development of an AP-A inhibitor to prevent conversion of AngII to AngIII to control hypertension, and the use of AngIV analogues to treat dementia, seizure and ischemia. The RAS continues to offer research challenges and the promise of an ever increasing constellation of important physiologies and behaviors. It is clear that the clinical importance of this system goes far beyond the treatment of dysfunctional blood pressure and body water balance.

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Abbreviations

ACD

acyl-coenzyme A dehydrogenase

ACE

angiotensin converting enzyme

ACE$_2$

human angiotensin converting enzyme homologue

Ach

acetylcholine

ACTH

adrenocorticotrophin releasing hormone

Ang

angiotensin

Ang(1-9)

angiotensin I(1-9)

Ang(1–7)

angiotensin II(1–7)

Ang(2–7)

angiotensin II(2–7)

Ang(3–7)

angiotensin II(3–7)

AngI
> angiotensin I

AngII
> angiotensin II

AngIII
> angiotensin III

AngIV
> angiotensin IV

AP
> area postrema

AP-A
> aminopeptidase A

AP-N
> aminopeptidase N

Arg
> arginine

Asp
> aspartate

AT
> angiotensin receptor subtype

CA
> Ammon's horn

Carb-P
> carboxypeptidase P

CRH
> cortiocotrophin-releasing hormone

CVOs
> circumventricular organs

DA
> dopamine

EC27
> 2-amino-pentane-1,5-dithiol

EC33
> 3-amino-4-mercaptobutyl-sultonic acid

ERK
> extracellular signal-regulated kinase

GLUT
> glucose transporter molecules

GST
> glutathione-S-transferase

GTPγS

guanosine triphosphate γ sulfate

HEK

human embryonic kidney

HGF

hepatocyte growth factor

His

histidine

icv

intracerebroventricular

Ile

isoleucine

IRAP

insulin-regulated aminopeptidase

Leu

leucine

L-NAME

nomega-nitro-1-arginine methylester

LTD

long-term depression

LTP

long-term potentiation

LVV-H7

leucine-valine-valine-hemorphin-7

Nle

norleucine

NMDA

N-methyl-$_D$-aspartate

NO

nitric oxide

NTS

nucleus of the solitary tract

OVLT

organum vasculosum of the lamina terminalis

PAI-1

plasminogen activator inhibitor-1

PC18

2-amino-4-methylsulfonyl butane thiol

Phe

phenylalanine

PL
> phospholipase

PO
> propyl oligopeptidase

Pro
> proline

PVN
> paraventricular nucleus

RAS
> renin–angiotensin system

Sar
> sarcosine

Sar^1,Ala^8-AngII
> saralasin

Sar^1,Ile^8-AngII
> sarile

SFO
> subfornical organ

SH
> sulfhyrdryl

SHRs
> spontaneously hypertensive rats

SON
> supraoptic nucleus

Tyr
> tyrosine

Val
> valine

VDCCs
> voltage dependent calcium channels

VMN
> ventral medial nucleus
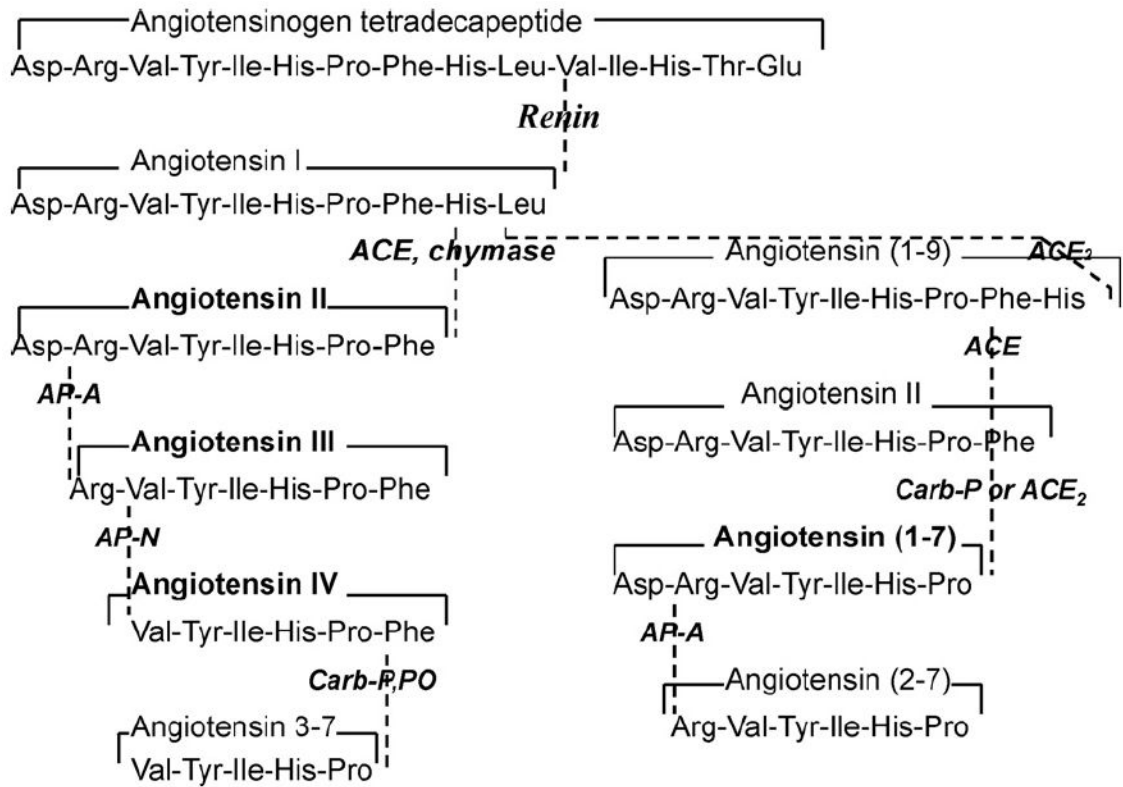
VTA
> ventral tegmental area

Fig. 1.
Description of the peptide structures and enzymes involved in the conversion of angiotensinogen to angiotensin I through shorter fragments. The biologically active forms include angiotensin II, III, IV and (1–7). Adapted from Wright and Harding (2004).
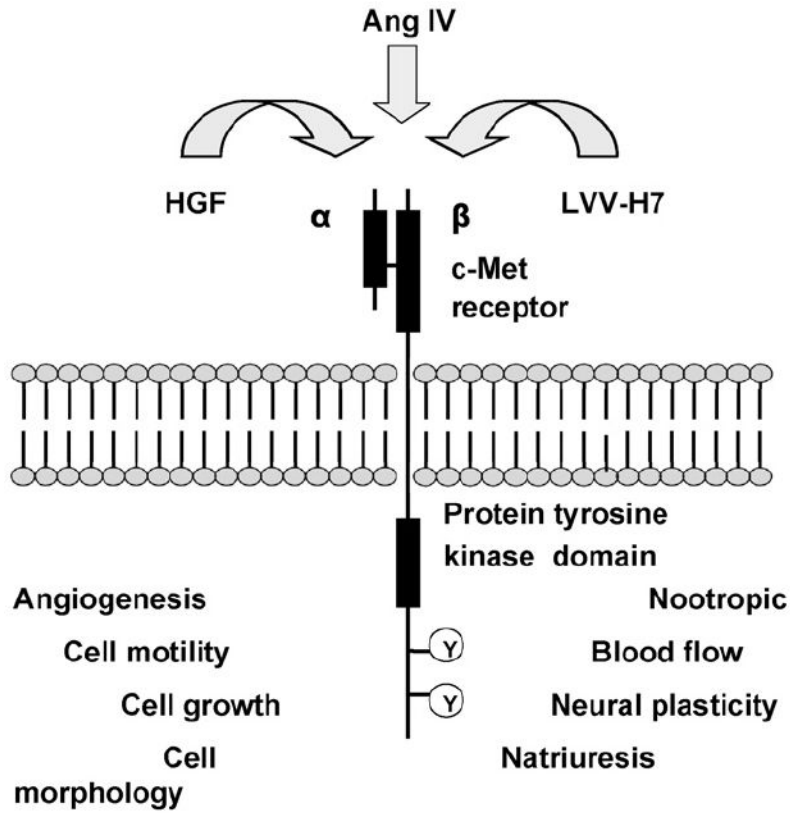
Fig. 2.
Hepatocyte growth factor (HGF), angiotensin IV (AngIV) and leucine–valine–valine–hemorphin-7 (LVV–H7) appear to each be capable of activating the c-Met receptor. The functions to the bottom left are known to be mediated by the c-Met receptor. Those functions listed to the right are tentative. Adapted from Birchmeier et al. (2003) and Jiang et al. (2005).
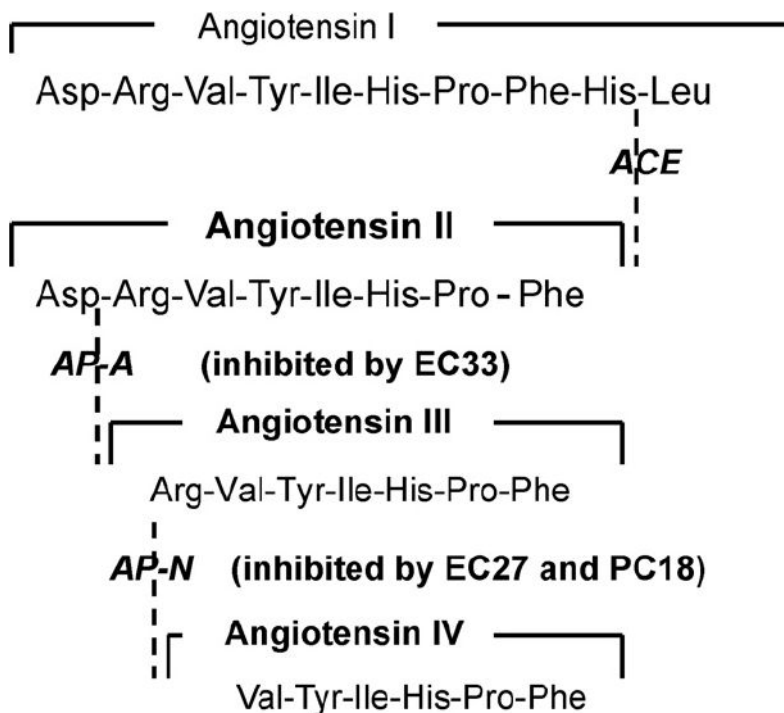
Fig. 3.
The metabolic conversion pathway of angiotensin II to angiotensin III can be blocked by the specific AP-A inhibitor, [S]-3-amino-4-mercaptobutyl sulfonic acid (EC33). The conversion of angiotensin III to angiotensin IV can be blocked by the specific AP-N inhibitors, [S]-2-amino-pentan-1,5-dithiol (EC27) and 2-amino-4-methylsulfonyl butane thiol (PC18). EC33 is 100-fold better at inhibiting AP-A (K_i = 0.29 μM) than AP-N (K_i = 25 μM). EC27 is approximately 100-fold better at inhibiting AP-N (K_i = 0.03 μM) than AP-A (K_i = 2.4 μM). Adapted from Llorens-Cortes and Mendelsohn (2002).

Table 1

Characteristics of the angiotensin receptor subtypes

Characteristics	AT$_1$	AT$_2$	AT$_4$–c-Met
Affinity	AngII > AngIII > AngI	AngIII > AngII > AngI	Nle^1, Leual^3-AngIV > HGF = AngIV > LVV-H7^a
Selective antagonists	CGP46027, DuP753, DuP 532, EXP3174, L158809, GR117289, SK/F108566, SC51316, UP269-6, LR-B/081	CGP42112A, PD123177, PD121981, PD123319, PD124125	Nle^1, Leual^3-AngIV, Divalinal-AngIV
Coupling to	G-protein	G-protein	Tyrosine kinase
Signal transduction	↑Ca^{2+}, ↑IP3, DAG, ↓Adenylyl cyclase, Src, JAK/STAT, ↑Prostaglandins, PL-A, -C, and -D	↓cGMP/↑cGMP, ↑Prostaglandins PL-A$_2$, NO	Gab1, Grb2, Grb10, PI3K, PLC-8, SHP2, Shc
Structure	359 amino acids; 7 transmembrane domains	363 amino acids; 7 transmembrane domains	dimer linked by disulfide bonds
Molecular size	41–42 kDa	40–41 kDa	α 50 kDa; β 140 kDa

Adapted from Birchmeier et al. (2003), de Gasparo et al. (2000), Ma et al. (2003), Mehta and Griendling (2007), Speth et al. (2003) and Wright and Harding (1997, 2004).

^{a}Tentative order regarding relative affinities.

Table 2

Predominant mammalian brain distributions of the three angiotensin receptor subtypes identified to date

Subtype	AT_1	AT_2	AT_4
Structures			
Amygdala	M	H	M
Anterior pituitary	H	H	
Area postrema (AP)	H		
Caudate putamen	H	H	H
Cerebellum	M	M	H
Cerebral cortex			H
Claustrum			H
Dentate gyrus			M
Geniculate, lateral	H		H
Geniculate, medial		H	M
Globus pallidus		H	H
Habenula	M	H	H
Hippocampus			H
Hypoglossal nucleus		H	
Inferior colliculus		H	M
Inferior olivary nucleus	H	H	H
Lateral olfactory tract	M		M
Locus coeruleus	M	H	M
Mammillary body			M
Medial preoptic nucleus	M		
Median eminence	H		
Nucleus accumbens			M
Nucleus basalis of Meynert			H
Nucleus of lateral olfactory tract	M		
Nucleus of solitary tract (NTS)	H		
Organum vasculosum of the lateral terminalis (OVLT)	H		
Paraventricular nucleus (PVN)	H		
Periaqueductal gray			H
Piriform cortex	L		H
Preoptic nucleus	H		L
Red nucleus			L
Septum	M	M	M
Subfornical organ (SFO)	H		
Substantia nigra			M
Superior colliculus	M		H
Suprachiasmatic nucleus			M
Supraoptic nucleus (SON)	H		
Thalamus		H	H
Ventromedial nucleus (VMN)	M		
Ventral tegmental area (VTA)		H	H
Zona incerta			M

L: low density; M: moderate; H: heavy. Adapted from Chai et al. (2000), Gard (2002), Wright and Harding (1997, 2004) and Wright et al. (1995).

Table 3

Summary of angiotensin mediated physiologies and behaviors

AT$_1$	AT$_2$	AT$_4$–c-Met	Ang(1–7)/Mas?
Receptor subtype			
Blood pressure	Blood pressure	Blood flow	Blood pressure
Thirst	Thirst	Kidney natriuresis	Vasopressin release
Sodium appetite	PAI-expression	NO release	Prostaglandin release
Renal function	Vascular growth	Enhance LTP	NO release
Cyclicity of reproductive		Memory consolidation	Baroreceptor reflex
Hormones and behaviors		Cognitive affect	Modulation
Sympathetic activation		Cerebroprotection	Antithrombosis
ACTH release			Anti-preeclampsia
Vasopressin release			
Baroreceptor reflex			
Memory inhibition			