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Review

The brain renin–angiotensin system: location and physiological roles

M.J. McKinley*, A.L. Albiston, A.M. Allen, M.L. Mathai, C.N. May, R.M. McAllen, B.J. Oldfield, F.A.O. Mendelsohn, S.Y. Chai

Howard Florey Institute of Experimental Physiology and Medicine, University of Melbourne, Melbourne 3010, Vic., Australia

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Abstract

Angiotensinogen, the precursor molecule for angiotensins I, II and III, and the enzymes renin, angiotensin-converting enzyme (ACE), and aminopeptidases A and N may all be synthesised within the brain. Angiotensin (Ang) AT_1, AT_2 and AT_4 receptors are also plentiful in the brain. AT_1 receptors are found in several brain regions, such as the hypothalamic paraventricular and supraoptic nuclei, the lamina terminalis, lateral parabrachial nucleus, ventrolateral medulla and nucleus of the solitary tract (NTS), which are known to have roles in the regulation of the cardiovascular system and/or body fluid and electrolyte balance. Immunohistochemical and neuropharmacological studies suggest that angiotensinergic neural pathways utilise Ang II and/or Ang III as a neurotransmitter or neuromodulator in the aforementioned brain regions. Angiotensinogen is synthesised predominantly in astrocytes, but the processes by which Ang II is generated or incorporated in neurons for utilisation as a neurotransmitter is unknown. Centrally administered AT_1 receptor antagonists or angiotensinogen antisense oligonucleotides inhibit sympathetic activity and reduce arterial blood pressure in certain physiological or pathophysiological conditions, as well as disrupting water drinking and sodium appetite, vasopressin secretion, sodium excretion, renin release and thermoregulation. The AT_4 receptor is identical to insulin-regulated aminopeptidase (IRAP) and plays a role in memory mechanisms. In conclusion, angiotensinergic neural pathways and angiotensin peptides are important in neural function and may have important homeostatic roles, particularly related to cardiovascular function, osmoregulation and thermoregulation.
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Keywords: Cardiovascular regulation; Fluid and electrolyte balance; AT_1 receptors; Ventrolateral medulla; Hypothalamus

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* Corresponding author. Fax: +61-3-93481707.
E-mail address: mmck@hfi.unimelb.edu.au (M.J. McKinley).

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1. Introduction

Angiotensin (Ang) II is a neuropeptide with multiple actions on the brain. The distribution of its AT_1 receptor in the CNS (Fig. 1) coincides with several cerebral regions known to regulate cardiovascular and body fluid homeostasis (Allen et al., 2000; Lenkei, Palkovits, Corvol, & Llorens-Cortes, 1997). It is likely that an intrinsic brain renin–angiotensin system (RAS) exists (Bader & Ganten, 2002). However, the exact modus operandi of such a system, and whether it is a network of angiotensinergic neural pathways rather than a brain RAS is still to be clarified.

Neither renin nor Ang peptides pass readily from the blood into the brain interstitium (Fei et al., 1982; Ganten, Hutchinson, Schelling, Ganten, & Fischer, 1976). Therefore, it is necessary to distinguish those cerebral regions that are separated by the blood–brain barrier from the environment of the systemic circulation, from those few regions—the circumventricular organs (CVOs), that lack the blood–brain barrier (McKinley et al., 1990) and are influenced directly by the peripheral RAS. This review focuses on angiotensin's influence in brain regions with a blood–brain barrier, but its actions on the subfornical organ, OVLT and area postrema (the sensory CVOs) will be briefly considered. Blood-borne Ang II interacts with the brain through AT_1 receptors located on neurons in these CVOs and these neurons may project to many other brain regions behind the blood–brain barrier (Giles et al., 1999; McKinley et al., 1990).

Activation of these neural circuits by circulating Ang II acting on the subfornical organ or organum vasculosum laminae terminalis (OVLT) may cause thirst, vasopressin secretion and an appetite for salt (Fitts, Starbuck, & Ruhf, 2000a; Mangiapane, Thrasher, Keil, Simpson, & Ganong, 1984; Menani, Colombari, Beltz, Thunhorst, & Johnson, 1998; Simpson, Epstein, & Camardo, 1978). The main action of circulating Ang II on the area postrema is to increase arterial pressure (Otsuka, Barnes, & Ferrario, 1986). It is possible that some neural pathways activated by Ang action on the CVOs may utilise Ang II or Ang III generated in the brain as transmitter molecules (Lind & Johnson, 1982). It is also probable that high concentrations of angiotensin-converting enzyme (ACE) in the CVOs results in local generation of Ang II within the CVOs (Brownfield, Reid, Ganten, & Ganong, 1982).

2. Angiotensinogen in the brain

Angiotensinogen is synthesised in most regions of the brain, although some regions e.g. medulla,

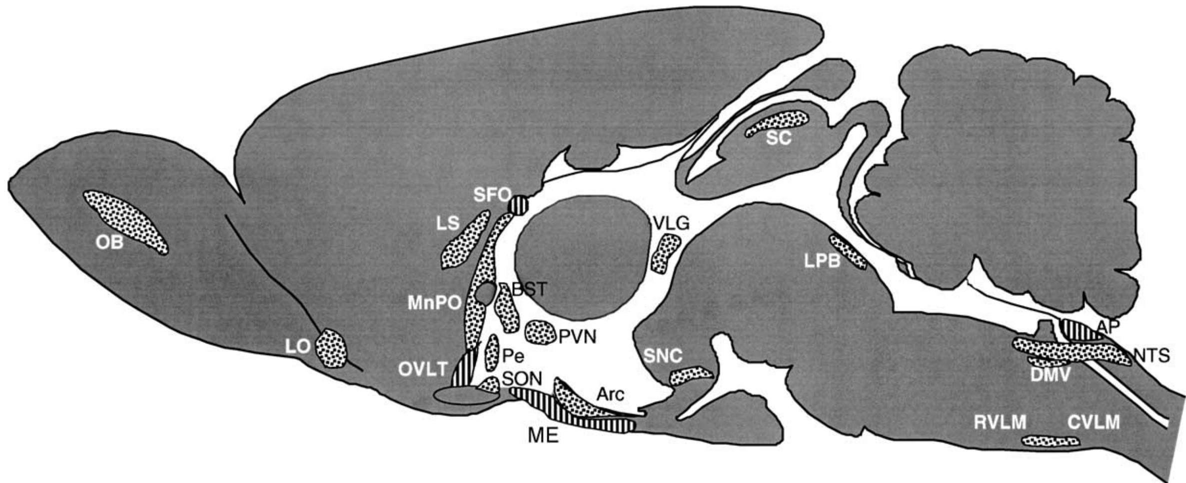

Fig. 1. Diagram of the major locations of AT_1 receptors in the mammalian brain. Regions with high densities of AT1 receptors are shown by the stippling projected onto a mid-sagittal diagram of the rat brain. Vertical stippling indicates the circumventricular organs that lack a blood–brain barrier and are exposed to influences of the peripheral renin–angiotensin system. Abbreviations: Arc, arcuate nucleus; AP, area postrema; BST, bed nucleus of the stria terminalis; CVLM, caudal ventrolateral medulla; DMV, dorsal motor nucleus of the vagus; LPB, lateral parabrachial nucleus; LO, nucleus of the lateral olfactory tract; LS, lateral septum; ME, median eminence; MnPO, median preoptic nucleus; NTS, nucleus of the solitary tract; OB, olfactory bulb; OVLT, organum vasculosum of the lamina terminalis; Pe, periventricular nucleus; RVLM, rostral ventrolateral medulla; SC, superior colliculus; SFO, subfornical organ; SNC, substantia nigra pars compacta; SON, supraoptic nucleus; VLG, ventrolateral geniculate nucleus.

hypothalamus, predominate over others in this regard (Lynch, Hawelu-Johnson, & Guyenet, 1987; Stornetta, Hawelu-Johnson, Guyenet, & Lynch, 1988). It is a constituent of brain extracellular fluid and one of the more abundant proteins found in cerebrospinal fluid (Hilgenfeld, 1984). By far the greatest proportion of angiotensinogen synthesis within the CNS occurs in glial cells (Stornetta et al., 1988; Intebi, Flaxman, Ganong, & Deschepper, 1990). Immunohistochemical and in situ hybridisation studies located angiotensinogen and its mRNA in astrocytes (Intebi et al., 1990; Stornetta et al., 1988). These astrocytes constitutively secrete angiotensinogen into brain extracellular fluid (Hilgenfeld, 1984; Intebi et al., 1990). The rate of angiotensinogen production may be increased by factors such as glucocorticoid levels (Deschepper & Flaxman, 1990). Although there is also evidence from immunohistochemical studies in rats (Thomas & Sernia, 1988), and from transgenic mice showing expression of angiotensinogen in neurons (Yang, Gray, Sigmund, & Cassell, 1999), it is probably of much less magnitude than that expressed by astrocytes.

Recent studies have been made on transgenic rats in which the glial fibrillary acidic protein (GFAP) promoter was coupled to the expression of an antisense construct targeted to angiotensinogen mRNA, so that glial angiotensinogen production was disrupted. In these rats, the levels of angiotensinogen and angiotensin in the brain fell by more than 90%, indicating that astrocytes are the major source of angiotensinogen (Schinke et al., 1999).

3. Processing enzymes

3.1. Renin

Evidence for angiotensin production within the CNS is over 30 years old, although the enzyme responsible was probably cathepsin D (Fischer-Ferraro, Nahmod, Goldstein, & Finkielman, 1971; Ganten, Boucher, & Genest, 1971; Reid, 1979). More recent studies show that while mRNA encoding renin is present in the CNS, its concentration is low (Dzau, Ingelfinger, Pratt, & Ellison, 1986), and its spatial relationship to centrally synthesised angiotensinogen is unclear. Recently, transgenic strains of mice in which a large part of the gene encoding the human renin gene

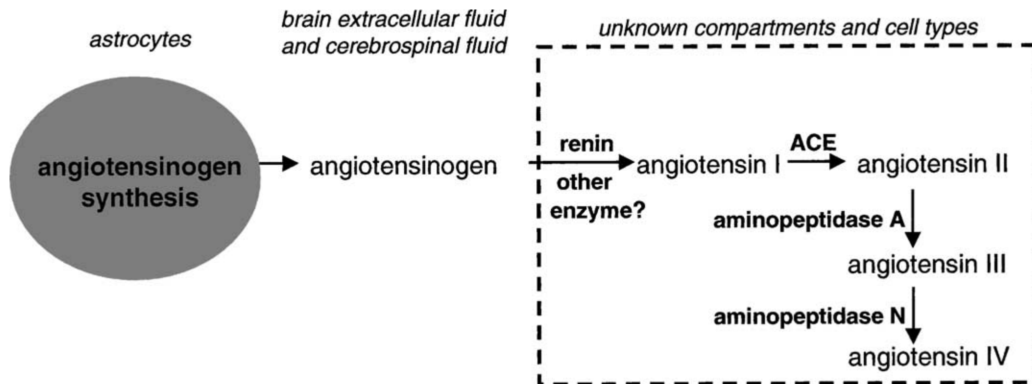

Fig. 2. Diagram of enzymatic pathways that have been proposed for the production of angiotensin peptides from angiotensinogen within the brain.

was incorporated into an artificial chromosome were generated. Various strains had up to seven copies of the human renin gene comprising 140–160 kb. These investigators reasoned that such a large segment of the renin gene would contain most of its regulatory regions and found expression of this transgene in both brain and kidney. However, the main isoform expressed in the brain was a shorter form of renin lacking some of the preprorenin sequence. They proposed that it may be acting as an intracellular enzyme in the brain (Morimoto, Cassell, & Sigmund, 2002a). Proposed enzymatic processing of angiotensinogen in the brain is shown diagrammatically in Fig. 2.

3.2. Angiotensin-converting enzyme

ACE is located extensively within the CNS. In the brain, very high concentrations of ACE are found in the circumventricular organs such as the subfornical organ, OVLT, area postrema and median eminence (Saavedra & Chevillard, 1982). In these CVOs, Ang I reaching them from the peripheral circulation may be locally converted to Ang II and have actions on Ang receptors within these regions. This is exemplified by studies in rats showing that angiotensin-dependent water intake can be inhibited by local injection of an ACE inhibitor directly into the subfornical organ (Thunhorst, Fitts, & Simpson, 1989), and that locally generated Ang II stimulates neurons within these sensory CVOs (McKinley, Colvill, Giles, & Oldfield, 1997).

In other brain regions e.g. caudate nucleus, putamen, substantia nigra pars reticularis, nucleus of the solitary tract (NTS), dorsal motor nucleus, median preoptic nucleus, ACE has been identified by binding studies or immunohistochemistry in rat, human, rabbit, sheep, monkey (Chai, McKenzie, McKinley, & Mendelsohn, 1990; Chai, McKinley, & Mendelsohn, 1987; Chai, McKinley, Paxinos, & Mendelsohn, 1991; Chai, Mendelsohn, & Paxinos, 1987; Rogerson et al., 1995; Saavedra & Chevillard, 1982). In the choroid plexus, ACE is found at high concentration on the microvilli of its epithelial cells, where it is in contact with the CSF (McKinley et al., 1990). While this ACE may generate Ang II locally in the brain, it may also catalyse the breakdown of several other peptides (Rogerson et al., 1995).

3.3. Aminopeptidases A and N

Aminopeptidase A is a zinc metallopeptidase that cleaves the N-terminal aspartyl residue of Ang II resulting in the formation of the heptapeptide Ang III, that can be further degraded to hexapeptide Ang IV by the enzyme aminopeptidase N. Both of these enzymes are present in the rodent brain (Reaux et al., 1999a, 1999b; Zini et al., 1996). Administration of a selective inhibitor of aminopeptidase A (EC33) blocks the pressor response to centrally administered Ang II, indicating that it may be necessary for Ang II to be converted to Ang III for angiotensin to exert its central pressor response (Reaux et al., 1999b). As well, central

administration of an inhibitor of aminopeptidase N (PC18), had a pressor action that was blocked by ICV injection of the AT_1 antagonist losartan in WKY rats, suggesting that Ang III binds to AT_1 receptors (Reaux et al., 1999a). In spontaneously hypertensive rats (SHR), centrally administered PC18 caused a greater pressor response, suggesting that endogenous Ang III was influencing arterial pressure in both strains, but that greater levels of brain Ang III were responsible for the larger response in the SHR (Reaux et al., 1999a).

4. Angiotensin peptides

Ang I, Ang II, Ang III and Ang 1–7 have all been identified in brain tissue, although the latter two are found in very low concentrations (Chappell, Brosnihan, Diz, & Ferrario, 1989; Chappell, Brosnihan, Welches, & Ferrario, 1987; Lawrence, Clarke, & Campbell, 1992). Immunohistochemical identification of Ang II or Ang III in rat brain reveals that an extensive system of Ang-containing fibres and nerve terminals occur in specific brain regions (Lind, Swanson, Bruhn, & Ganten, 1985; Oldfield, Ganten, & McKinley, 1989). However, neuronal cell bodies exhibiting Ang-like immunoreactivity have been observed in only a few brain regions such as the nucleus of the solitary tract, hypothalamic PVN, and the subfornical organ. Major terminal fields containing Ang II-like immunoreactivity include the central nucleus of the amygdala, bed nucleus of the stria terminalis, core of the subfornical organ, amygdalo-hippocampal zone, lateral parabrachial nucleus, NTS and median eminence (Chappell et al., 1987, 1989). Ang 1–7 may also have central actions (Chappell et al., 1989).

5. Angiotensin receptors

Angiotensin receptors are located in many specific regions of the brain (Fig. 1) and spinal cord (Allen et al., 2000; Lenkei et al., 1997; Allen et al., 1988a; Gehlert, Speth, & Wamsley, 1986; McKinley, Allen, Clevers, Paxinos, & Mendelsohn, 1987; Mendelsohn, Quirion, Saavedra, Aguilera, & Catt, 1984). These receptors are of the AT_1, AT2 and AT4 subtypes. AT_1 receptors are further subgrouped in the rodent brain into AT_{1A} and AT_{1B} receptors. In regard to AT_1 receptors, in vitro autoradiographic binding studies, in situ hybridisation histochemistry, and immunohistochemical results have shown great consistency in localising these receptors to several key areas of relevance to cardiovascular and body fluid homeostasis. Although there are a few exceptions, there is considerable consistency across mammals in the regions of the CNS that exhibit AT_1 receptors (Allen et al., 2000; Lenkei et al., 1997).

6. AT_1 receptors

The highest densities of AT_1 receptor binding are usually found on neurons in the lamina terminalis, hypothalamic paraventricular nucleus and the NTS (Allen et al., 2000). Within the lamina terminalis, the subfornical organ and OVLT that are exposed to circulating angiotensins contain AT_1 receptors. The other sensory CVO, the area postrema contains a lower density of AT_1 receptors, although in humans it appears to lack such receptors (Allen et al., 1988a). The other component of the lamina terminalis, the median preoptic nucleus, is also rich in AT_1 receptors. Some neurons in the subfornical organ, OVLT and median preoptic nucleus that express AT_1 receptor mRNA, have polysynaptic connections to peripheral organs such as the kidney via renal sympathetic nerves (Giles, Sly, McKinley, & Oldfield, 2001).

Regions of the hindbrain that have crucial roles in cardiovascular regulation, the NTS, the rostral and caudal ventrolateral medulla, and the midline raphe, also exhibit AT_1 receptors (Allen et al., 2000; Lenkei et al., 1997). In the NTS, a considerable proportion of these receptors may exist presynaptically on vagal afferent terminals (Diz, Barnes, & Ferrario, 1986; Lewis et al., 1986). In the spinal cord, AT_1 receptors are observed in the intermedio-lateral cell column and in the dorsal horn (Oldfield et al., 1994). These latter receptors may be presynaptic receptors on sensory afferent fibres, because AT_1 receptors are expressed in neurons within dorsal root ganglia (Oldfield et al., 1994). In the midbrain, moderate to high densities of AT_1 receptors are observed in the lateral parabrachial nucleus, substantia nigra and periaqueductal gray (Lenkei et al., 1997).

In the hypothalamus, most species exhibit high concentrations of AT_1 receptors in the supraoptic and

paraventricular nuclei, although in the rat these receptors are only seen in the parvocellular division of the PVN, with little or no binding in its magnocellular division or in the supraoptic nucleus (Lenkei et al., 1997). The majority of the AT_1 receptors in the PVN are associated with corticotrophin-releasing hormone (CRH)-containing neurons that have projections to the median eminence (Aguilera, Kiss, & Luo, 1995a; Oldfield et al., 2001). The high concentrations of AT_1 receptors that occur in the median eminence are not associated with expression of AT_1 mRNA there (Allen et al., 2000). It is likely that the AT_1 receptors in the median eminence are located on neurosecretory terminals of nerve fibres that originate in the PVN.

AT_1 receptors are located in parts of the limbic system e.g. amygdala, bed nucleus of the stria terminalis and cingulate cortex. Other notable central regions that express the AT_1 receptor are the hippocampus, the olfactory bulb, the piriform cortex (Allen et al., 2000; Lenkei et al., 1997). Some regions that exhibit significant Ang II receptor binding that is displaced by AT_1 antagonists do not express AT_1 receptor mRNA as detected by in situ hybridisation (e.g. bed nucleus of the stria terminalis, median eminence (Lenkei et al., 1997)). This result indicates that the AT_1 receptors in these sites are located on presynaptic nerve terminalis. AT_1 receptors are also reported to exist on glial cells in the brain (Bottari, Obermuller, Bogdal, Zahs, & Deschepper, 1992).

AT_1 receptors may be up- or down-regulated in specific regions of the brain depending on the physiological state of the animal. Dehydration, sodium or chloride depletion, hypertension and stress may all influence the number of AT_1 receptors expressed in particular brain regions (Barth & Gerstberger, 1999; Charron, Laforest, Gagnon, Drolet, & Mouginot, 2002; Saavedra, Correa, Kurihara, & Shigematsu, 1986; Sandberg, Ji, & Catt, 1994; Ray, Castren, Ruley, & Saavedra, 1990). This may then influence the resulting physiological responses of animals to activation of angiotensinergic circuits.

7. AT_2 receptors

AT_2 receptors have been detected by in vitro autoradiographic techniques using selective AT_2 antagonists to displace binding of radiolabelled Ang II peptide analogues such as sarile (Rowe, Grove, Saylor, & Speth, 1990). In the rat, several brain regions exhibit AT_2 receptor binding, especially in the molecular layer of the cerebellum and in the thalamus. In situ hybridisation studies show that AT_2 receptor mRNA is also expressed in these regions (Lenkei et al., 1997; Millan, Jacobowitz, Aguilera, & Catt, 1991). The cerebellum has also been shown to exhibit AT_2 receptor binding in human, rabbit and sheep brain (Allen et al., 2000). The functions of the AT_2 receptor in the brain remain unclear, although the receptors are numerous in rat brain during development (Millan et al., 1991), and may oppose some actions of the AT_1 receptor in the adult rat brain (Hohle, Spitznagel, Rascher, Culman, & Unger, 1995). A recent report indicates that mutations in the AT_2 receptor may lead to intellectual retardation (Vervoort et al., 2002).

8. AT_4 receptors

The AT_4 receptor is defined as the high affinity binding site that selectively binds Ang IV with affinity ranging from 1 to 10 nM (Swanson et al., 1992). Ang IV, VYIHPF is produced by the consecutive actions of aminopeptidases A and N on angiotensin II. This hexapeptide was initially thought to be inactive because of its inability to activate the classical angiotensin AT_1 and AT_2 receptors except at high micromolar concentrations. This peptide has subsequently been shown to elicit dramatic actions on memory and acts via its own specific binding site-named the AT_4 receptor (Braszko, Kupryszewski, Witczuk, & Wisniewski, 1988). In addition to Ang IV, we isolated a decapeptide LVVYPWTQRF (LVV-H7) (Moeller, Chai, Smith, Lew, & Mendelsohn, 1998) from sheep brain that binds with high affinity to the AT_4 receptor and can mimic the actions of Ang IV. AT_4 receptors are widely distributed in the guinea-pig, rat, sheep, monkey and human brain, and the distributions are highly conserved throughout these species (Chai et al., 2000; Miller-Wing et al., 1993; Moeller et al., 1995, 1996; Roberts et al., 1995). The receptor sites occur in high abundance in the basal nucleus of Meynert, in the CA1 to CA3 regions of the hippocampus, and throughout the neocortex, a distribution that closely resembles cholinergic neurones and their projections and is consistent with the memory enhancing properties of

the AT_4 ligands. High levels of the receptors are also found in most brain regions involved in motor control.

We have recently isolated the AT_4 receptor and shown it to be insulin-regulated aminopeptidase (IRAP) (Albiston et al., 2001). IRAP was initially cloned from rat adipocytes and is an abundant protein found in specific vesicles that also contain the glucose transporter, GLUT4 (Keller, Scott, Mastick, Aebersold,& Lienhard, 1995). In response to insulin, these GLUT4 vesicles translocate to the cell surface to enable increased glucose uptake into the cell. Although IRAP, like GLUT4, translocates rapidly and markedly to the cell surface after insulin stimulation, the physiological role of the enzyme is unknown. IRAP was also independently isolated from human placenta as the enzyme that hydrolyses oxytocin (Rogi, Tsujimoto, Nakazato, Mizutani, & Tomoda, 1996), hence its other name, oxytocinase. IRAP is a type II integral membrane protein belonging to the M1 family of zinc-dependent metallopeptidase and has been shown to cleave a number of peptides including vasopressin, lys-bradykinin (Herbst et al., 1997), met-enkephalin, dynorphin A (1–8), somatostatin and cholecystokinin (CCK8) in vitro (Matsumoto et al., 2001). We have also shown that both Ang IV and LVV-H7 dose-dependently inhibited the catalytic activity of IRAP in vitro (Albiston et al., 2001). We therefore propose that the AT_4 ligands, Ang IV and LVV-H7, bind to IRAP and inhibit its enzymatic activity.

9. Arterial pressure

Ang II may influence arterial pressure at any one of a number of brain sites. Micro-injection of Ang II into the lateral or third ventricle, hypothalamic PVN, several forebrain regions, rostral ventrolateral medulla, NTS, the area postrema and subfornical organ increases arterial pressure (Allen, Dampney, & Mendelsohn, 1988b; Andreatta, Averill, Santos, & Ferrario, 1988; Averill, Diz, Barnes, & Ferrario, 1987; Jensen, Harding, & Wright, 1992; Severs & Daniels-Severs, 1973; Simpson, 1981; Thornton & Nicolaidis, 1993). The many observations that ICV administration of drugs that block brain Ang production or action reduce arterial blood pressure in several physiological or pathophysiological conditions is compelling evidence that Ang that is endogenous to the brain may influence arterial pressure (Gyurko, Wielbo, & Phillips, 1993; Kubo, Ikezawa, Kambe, Hagiwara, & Fukumori, 2001; Phillips, 1978; Sun, Cade, & Morales, 2002).

Attention has been focussed recently on the ventrolateral medulla as a site of action at which centrally generated angiotensin II may influence arterial pressure. Ang II binding sites (AT_1 receptors) are present in the rostral and caudal parts of the ventrolateral medulla in several species (Allen et al., 2000; Lenkei et al., 1997; Mendelsohn et al., 1988). The sympathetic pre-motor neurons in the RVLM play a crucial role in maintaining sympathetic vasomotor tone (Dampney, 1994; Guyenet, 1990). The caudal ventrolateral medulla relays signals from the baroreceptors to sympathetic pre-motor neurons in the RVLM (Badoer, McKinley, Oldfield, & McAllen, 1994).

Initially, it was shown that as well as the pressor response to injection of Ang II into the RVLM, micro-injection of non-subgroup-specific peptide antagonists of Ang II, sarthran or sarile, caused a pronounced reduction of blood pressure (40 mmHg) when administered into the RVLM of anaesthetised rats or rabbits and an inhibitor of sympathetic nerve activity, indicating a likely role of brain Ang in the generation of basal sympathetic tone (Ito & Sved, 1996; Tagawa, Horiuchi, Potts, & Dampney, 1999). Such injections of peptidic Ang antagonists into the RVLM also reduced the increase in arterial pressure caused by muscimol-induced inhibition of the CVLM, but did not inhibit the pressor response elicited by injection of glutamate into the RVLM (Ito & Sved, 1996). However, injections of either AT_1 antagonists or an antagonist of Ang 1–7 into the RVLM did not reduce arterial pressure or sympathetic activity in anaesthetised rats, nor was there any effect of these treatments on the depressor response to injection of sarile or sarthran into the RVLM (Potts, Allen, Horiuchi, & Dampney, 2000). Analogously, injection of sarthran or sarile into the CVLM caused increases in arterial pressure and renal sympathetic nerve activity in anaesthetised rats, but injections of AT_1 antagonists were ineffective (Potts et al., 2000). Thus, the type of receptors mediating the depressor effects of peptidic Ang antagonists in the RVLM and their pressor effects in the CVLM in anaesthetised rats remain to be determined.

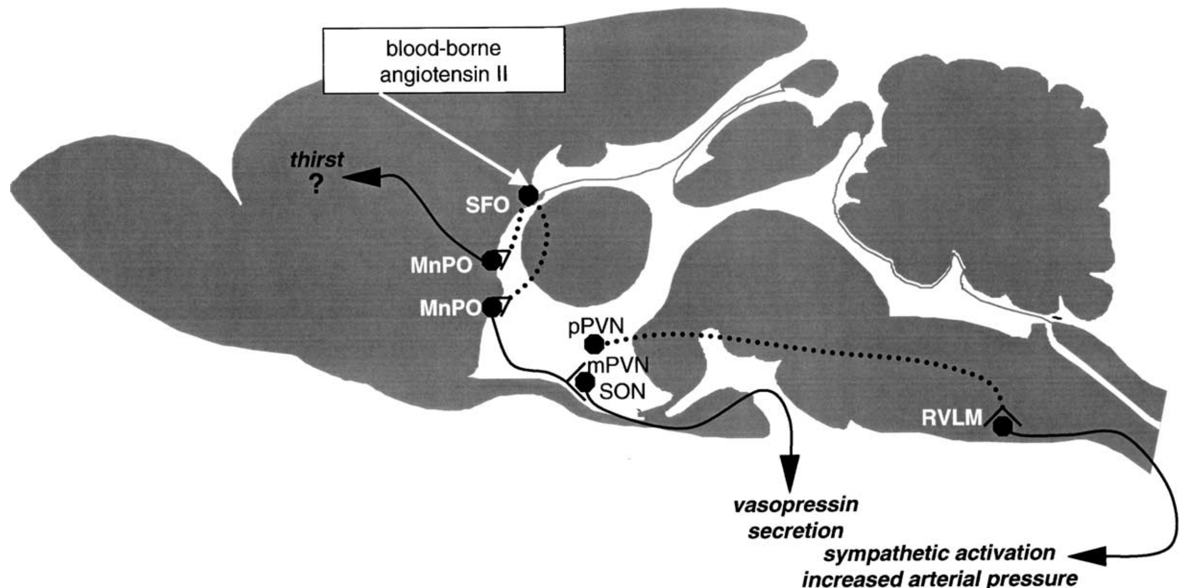

Fig. 3. Diagram of the rat brain indicating some neural pathways that may influence cardiovascular control, vasopressin release and thirst. Angiotensinergic pathways that may utilise Ang II or Ang III as a neurotransmitter are indicated by the dotted lines. Circulating angiotensin II may stimulate neurons in the subfornical organ (SFO) which have efferent connections to the median preoptic nucleus (MnPO) and utilise angiotensin II as a neurotransmitter. These angiotensinergic inputs to the MnPO drive neural pathways that connect to vasopressin-containing neurons in the supraoptic nucleus (SON) and magnocellular parts of the paraventricular nucleus (mPVN) to release vasopressin. Angiotensinergic inputs to the MnPO may also drive neural pathways that subserve thirst. The question mark indicates that the remainder of this pathway is unknown. An angiotensinergic neural pathway from parvocellular neurons (pPVN) of the hypothalamic paraventricular nucleus may drive pre-motor neurons in the rostral ventrolateral medulla (RVLM) to increase sympathetic activity and arterial blood pressure.

By contrast, injection of AT_1 antagonists into the RVLM of anaesthetised sodium depleted or spontaneously hypertensive rats inhibits renal sympathetic activity and reduces arterial pressure, indicating that brain Ang acting via AT_1 receptors mediates increases in sympathetic tone under certain conditions (Allen, 2001; DiBona & Jones, 2001). AT_1 receptors may also mediate a pressor pathway from the hypothalamic PVN to the RVLM (Tagawa & Dampney, 1999) (see Fig. 3). In contrast to these results in anaesthetised rats, micro-injection of the AT_1 antagonist losartan or the AT_2 antagonist CGP42112A into the RVLM of conscious freely moving Wistar rats increased arterial pressure, while injection of sarthran or an Ang 1–7 antagonist caused a small decrease of blood pressure, but surprisingly, micro-injections of either AT_1 or AT_2 antagonists into the RVLM of conscious rats caused small increases of blood pressure (Fontes et al., 1997) which seems paradoxical when it was observed that micro-injections of both Ang II and Ang 1–7 into the RVLM of these conscious rats also caused moderate increases in arterial pressure. These results suggest the possibility that brain Ang acting within the RVLM may influence both pressor and depressor pathways, and that there may be considerable differences between conscious and anaesthetised rats in the tonic activity of angiotensinergic input in the RVLM.

10. Thirst

ICV administration of Ang II or Ang III causes many species to drink relatively large volumes of water within a few minutes (Abraham, Baker, Blaine, Denton, & McKinley, 1975; Epstein, Fitzsimons, & Rolls, 1970; Fitzsimons & Kucharczyk, 1978; Sharpe & Swanson, 1974). This effect of centrally administered Ang II is abolished by ablation of the AV3V region, but not by ablation of the subfornical organ (Buggy & Johnson, 1978; Lind, Thunhorst, &

Johnson, 1984). Therefore, Ang II infused by the ICV route is unlikely to be acting on the Ang II receptors in the subfornical organ that mediate the dipsogenic response to systemic Ang II. Rather, the median preoptic nucleus, which is mostly contained within the AV3V region is the central site at which ICV Ang II most likely acts to induce drinking. This site is strongly activated by intracerebroventricularly injected Ang II as shown by the expression of c-*fos* (Herbert, Forsling, Howes, Stacey, & Shiers, 1992; McKinley, Badoer, Vivas, & Oldfield, 1995), and direct micro-injection of Ang II into the MnPO stimulates water drinking in rats (O'Neill & Brody, 1987). However, is Ang II that is intrinsic to the brain involved in the generation of thirst? Evidence that centrally administered AT_1 antagonists inhibit dipsogenic responses to several physiological or pharmacological stimuli suggest that this is the case, particularly if circulating levels of Ang II were not elevated by the stimuli. Thus, the inhibition by centrally administered AT_1 antagonist of the water drinking in response to ICV injection of hypertonic saline (Blair-West et al., 1993; Weisinger et al., 1996; Mathai, Evered, & McKinley, 1997), or the hormone relaxin (Sinnayah, Burns, Wade, Weisinger, & McKinley, 1998; Summerlee & Robertson, 1995; Thornton & Fitzsimons, 1995) suggests that central Ang is mediating these dipsogenic responses, possibly as a neurotransmitter in neural pathways subserving thirst. The physiological significance of this proposal is borne out by observations that centrally administered losartan also blocks prandial drinking in sheep (Mathai et al., 1997).

In studies that utilised the central administration of an antisense oligonucleotide directed against angiotensinogen synthesis, drinking in response to ICV injection of renin was strongly inhibited, suggesting that there was depressed synthesis of angiotensinogen in the brain. Drinking in response to subcutaneously injected isoproterenol, but not that to several other dipsogenic stimuli, was also inhibited by this antisense treatment (Sinnayah, Kachab, Haralambidis, Coghlan, & McKinley, 1997). Because isoproterenol-induced thirst is dependent on circulating Ang II acting on the subfornical organ (Fitts, 1994), these data suggest that a central angiotensinergic pathway distal to the subfornical organ mediates drinking stimulated by circulating Ang II. The median preoptic nucleus has been proposed as the site of an angiotensinergic synapse that mediates thirst caused by circulating angiotensin II (Johnson, Cunningham, & Thunhorst, 1996) (see Fig. 3).

11. Vasopressin secretion

ICV infusion of Ang II is a potent stimulus to the release of vasopressin (Andersson, Eriksson, Fernandez, Kolmodin, & Oltner, 1972; Fyhrquist, Eriksson, & Wallenius, 1979; Mouw, Bonjour, Malvin, & Vander, 1971). This effect is abolished by ablation of the AV3V region (Bealer, Phillips, Johnson, & Schmid, 1979) or prior ICV administration of an AT_1 antagonist (Mathai, Evered, & McKinley, 1998). There are efferent neural pathways from the AV3V region to the magnocellular neurons of the supraoptic and paraventricular nuclei (Wilkin, Mitchell, Ganten, & Johnson, 1989)—sites of vasopressin-synthesising and secreting neurons. Signals from the subfornical organ may be relayed to the magnocellular neurons of the PVN via an angiotensinergic synapse within the median preoptic nucleus (Tanaka, Saito, & Kaba, 1987) (Fig. 3).

In addition to an action on the AV3V region, micro-injection of Ang II into the caudal ventrolateral medulla a site of AT_1 receptor expression, stimulates vasopressin release (Allen, Mendelsohn, Gieroba, & Blessing, 1990). A direct efferent neural pathway from the CVLM to the supraoptic and paraventricular nuclei exists (Wilkin et al., 1989), which may mediate this response.

Results of experiments manipulating endogenous Ang support a role for brain-derived Ang in the physiological regulation of vasopressin secretion. Central administration of the AT_1 antagonist losartan reduces AVP secretion in response to intravenous or ICV infusion of hypertonic saline in the rat or sheep (Hogarty, Tran, & Phillips, 1994; Mathai et al., 1998; Rohmeiss et al., 1995). Preventing Ang III production in the rat brain also reduces AVP secretion in response to ICV Ang II (Zini et al., 1996).

Transgenic rats expressing an antisense oligonucleotide sequence against the synthesis of angiotensinogen in astrocytes, have a reduced blood level of vasopressin. The amount of angiotensinogen in the brains, but not plasma, of these rats was greatly reduced and they exhibit moderate diabetes insipidus, with a doubling of daily urine output (Schinke et al.,

1999). These data show that angiotensinogen synthesised in astrocytes within the brain, and presumably brain Ang, is necessary for the neural control of the basal secretion of vasopressin by the posterior pituitary gland.

12. Effects on kidney function

12.1. Renal nerves

In the anaesthetised rat, ICV infusion of Ang II increases RSNA (Huang & Leenen, 1996). By contrast, ICV infusion of Ang II in the conscious rat, rabbit or sheep causes a very large and long-lasting depression of RSNA (Dorward & Rudd, 1991; Kannan, Nakamura, Jin, Hayashida, & Yamashita, 1991; May & McAllen, 1997a). This effect was partially independent of the baroreceptor activation, which results from the increase in arterial pressure caused by centrally injected Ang II (Dorward & Rudd, 1991; May & McAllen, 1997a). AT_1 receptors in the lamina terminalis probably mediate this inhibition of RSNA because ablation of the lamina terminalis abolishes the depression of RSNA caused by ICV infusion of Ang II in conscious animals (May, McAllen, & McKinley, 2000). ICV infusion of hypertonic NaCl also inhibited RSNA in conscious sheep, but increased RSNA in anaesthetised rats. Both these effects were blocked by centrally administered losartan (Chen & Toney, 2001; May & McAllen, 1997b), suggesting that Ang II endogenous to the brain may influence RSNA.

Polysynaptic neural pathways have been shown by viral tracing techniques to proceed from the lamina terminalis to the kidney in the rat (Sly, Colvill, McKinley, & Oldfield, 1999). A proportion of neurons within the lamina terminalis that are polysynaptically connected to the kidneys are activated by ICV infusion of Ang II (Sly, McKinley, & Oldfield, 2001). AT_1 receptors are located on neurons in the lamina terminalis that have polysynaptic connections to the renal nerves (Giles et al., 2001). This pathway may mediate the influences of central Ang II on RSNA.

12.2. Renin secretion

Notwithstanding that circulating Ang II exerts a direct feed-back inhibition on renin secretion by the kidney, brain Ang II may also have an inhibitory influence on renal renin secretion. ICV infusion of Ang II or renin reduces plasma renin activity in several species (Eriksson & Fyhrquist, 1976; Malayan, Keil, Ramsay, & Reid, 1979; McKinley, McBurnie, & Mathai, 2001) This effect is due to reduced renin secretion by the kidney (Weekley, 1992), and is probably mediated by a reduction in RSNA as described in the preceding paragraph. ICV infusion of Ang II reduces plasma renin concentration in sodium depleted animals without a change in arterial pressure, showing that this effect is not secondary to increased arterial pressure, while ICV infusion of losartan increased plasma renin, suggesting that a tonic central angiotensinergic influence inhibits renin secretion in sodium depleted animals (McKinley et al., 2001).

12.3. Sodium excretion

Injection of hypertonic saline or angiotensin II into the lateral or third cerebral ventricle results in a large increase in renal sodium excretion (Andersson, Jobin, & Olsson, 1966; McKinley, Evered, Mathai, & Coghlan, 1994). Reduced RSNA, increased arterial pressure and vasopressin secretion, or the secretion of an unidentified hormone could all have contributory roles in the natriuresis induced by centrally administered Ang II. Centrally injected losartan blocks the natriuretic response to ICV infusion of hypertonic saline (McKinley et al., 1994), suggesting a role for an angiotensinergic neural pathway within the CNS in the central regulation of renal sodium excretion.

13. Regulation of body temperature

Brain Ang is implicated in the regulation of body temperature. Ang II administered centrally reduces core temperature. Both decrease in metabolic heat production (thermogenesis) and an increase in radiated heat contributed to the hypothermic effect of centrally administered Ang II (Lin, 1980; Shido & Nagasaka, 1985). ICV administration of the AT_1 antagonist losartan to rats exposed to a hot environment for 1 h appeared to inhibit thermoregulatory cooling mechanisms because there was a much larger increase in body temperature in losartan treated rats than the controls administered artificial cerebrospinal fluid.

The losartan treated rats lost the same amount of saliva as the controls, so this aspect of thermoregulation was not disrupted. Nor is tail skin vasodilatation inhibited by central AT_1 receptor blockade (Mathai, Hubschle, & McKinley, 2000). It has been shown that central AT_1 receptor blockade with losartan prevented the increase in splanchnic nerve activity that occurs with heat exposure (Kregel, Stauss, & Unger, 1994). This may reduce the redistribution of blood to the skin, thereby reducing the efficiency of cutaneous cooling mechanisms, eventually leading to excessive hyperthermia.

The central site at which brain Ang II may exert an action on thermoregulation is unknown. However, there is evidence from in vitro studies of slices of PVN that the actions of Ang II on bursting neurons in the PVN was potentiated by increased ambient temperature (Dewald et al., 2002). Another potential site for brain Ang II is the median preoptic nucleus, where many heat sensitive thermoregulatory neurons are located as well as AT_1 receptors. Whether, they are co-localised remains to be determined.

14. Adrenocorticotropin secretion

Centrally administered Ang II has been shown to cause stimulation of the hypothalamo-pituitary–adrenal axis, resulting in increased blood levels of adrenocorticotropic hormone (ACTH), and consequently cortisol or corticosterone (Ganong & Murakami, 1987; Scholkens, Jung, Rascher, Dietz, & Ganten, 1982; Sumitomo et al., 1991). This effect is not inhibited by the Ang II antagonist saralasin administered peripherally, indicating that the action of Ang II injected intracerebroventricularly is occurring behind the blood–brain barrier, and it is additional to an action of circulating Ang II on CVOs to stimulate ACTH release (Ganong & Murakami, 1987; Murakami & Ganong, 1987). ICV administration of Ang II also results in a reduction of the corticotrophin-releasing hormone in the median eminence (Sumitomo et al., 1991), and an increase in mRNA that encodes CRH in the hypothalamus (Aguilera, Young, Kiss, & Bathia, 1995b; Sumitomo et al., 1991). Neurons that synthesise CRH in parvocellular regions of the PVN express AT_1 receptor mRNA (Aguilera et al., 1995b) and immunohistochemical studies show that CRF-containing neurons of the PVN that have efferent connections to the median eminence are rich in AT_1 receptors (Oldfield et al., 2001). These data suggest that the CRF-containing neurons of the PVN are likely sites where brain Ang may influence the HPA axis. While stressors and glucocorticoid treatment increase the expression of AT_1 receptor mRNA in the PVN (Jezova, Ochedalski, Kiss, & Aguilera, 1998), it is still not clear how particular stressors may utilise angiotensinergic pathways to influence CRF release and therefore ACTH secretion.

15. Sodium appetite

Centrally injected Ang II or renin are potent stimuli for the ingestion of NaCl in several species (Avrith & Fitzsimons, 1980; Bryant, Epstein, Fitzsimons, & Fluharty, 1980; Coghlan et al., 1981; Fitzsimons, 1998), although the onset is slower than that of Ang-induced water drinking. This action is blocked by centrally administered AT_1 or AT2 receptor antagonists (Fitzsimons, 1998; Rowland, Rozelle, Riley, & Fregly, 1992). Further evidence that brain Ang regulates the intake of NaCl comes from experiments showing that centrally administered AT_1 antagonists inhibit sodium appetite in rats and baboons (Blair-West, Carey, Denton, Weisinger, & Shade, 1998; Sakai, Chow, & Epstein, 1990; Sakai & Epstein, 1990). It has been proposed that central Ang and mineralocorticoids have a synergistic action within the brain to initiate salt appetite (Sakai, Nicolaidis, & Epstein, 1986), but the central sites mediating Ang-induced Na appetite remain to be determined. Brain Ang may be less important for salt appetite in ruminants (Weisinger et al., 1996; Blair-West, Denton, McKinley, & Weisinger, 1988). A recent study in double transgenic mice in which expression of the human angiotensinogen gene was controlled by a neuron-specific promoter (synapsin I) and in which the human renin gene was also expressed, showed that these mice had an elevated preference for salt (Morimoto, Cassell, & Sigmund, 2002b). This result suggests that neurally generated Ang plays a role in the generation of salt appetite. However, an increased preference for salt was also observed in double transgenic mice expressing the human renin gene and in which the human angiotensinogen gene was under the control of a glial-specific promoter (Morimoto,

Cassell, & Sigmund, 2002c). Thus, Ang derived in the brain from glial angiotensinogen may also play a role in salt appetite in mice. Circulating Ang II also stimulates a salt hunger by a direct influence on the brain (Thunhorst & Fitts, 1994; Weisinger et al., 1987), probably by an action at one of the forebrain CVOs (Fitts, Starbuck, & Ruhf, 2000a, 2000b).

16. Memory

Central infusions of Ang IV facilitate memory retention and retrieval in rats in passive avoidance paradigms (Braszko et al., 1988; Wright et al., 1993). Moreover, chronic infusions of the more stable analogue of Ang IV, Nle^1-Ang IV, improved performance in rats in the spatial learning task, the Morris water maze (Pederson, Harding, & Wright, 1998). In two rat models of memory deficit, induced by either scopolamine or bilateral perforant pathway lesion, the AT_4 receptor agonists reversed the performance deficits detected in the Morris water maze paradigm (Wright et al., 1999; Pederson et al., 1998). We have shown recently that both Ang IV and LVV-H7 dose-dependently inhibited the catalytic activity of IRAP in vitro (Albiston et al., 2001). We therefore propose that the AT_4 ligands, Ang IV and LVV-H7, facilitate memory and enhance learning by binding to IRAP and inhibiting its enzymatic activity.

17. Blood–brain barrier

Mice in which the angiotensinogen gene had been deleted show an impairment in blood–brain barrier function (Kakinuma et al., 1998). This effect does not occur in mice in which the renin gene has been deleted (Yanai et al., 2000). The damage to the blood–brain barrier in angiotensinogen gene knockout mice may be restored by treatment with Ang II or Ang IV. This effect of Ang II or Ang IV is not mediated by either AT_1 or AT_2 receptors.

18. Concluding summary

Angiotensinogen, renin and ACE are synthesised within the brain, as are AT_1, AT_2 or AT_4 receptors. Angiotensinogen synthesis occurs predominantly in glia, however how and where it is processed to Ang peptides is unknown. Ang peptides generated within the brain may act on AT_1 receptors as neurotransmitters or neuromodulators in neural pathways influencing the cardiovascular system and fluid and electrolyte balance. AT_1 receptors mediating these functions are found in the ventrolateral medulla, nucleus of the solitary tract, lamina terminalis and hypothalamic supraoptic and paraventricular nuclei. Angiotensinergic neural pathways within the brain may have important homeostatic functions, particularly related to the control of arterial pressure, fluid and electrolyte homeostasis and thermoregulation. The AT_4 receptor, which is identical to IRAP, may play a role in memory.

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