0013-7227/03/$15.00/0
Printed in U.S.A.

Endocrinology 144(6):2179–2183

doi: 10.1210/en.2003-0150

Minireview: Overview of the Renin-Angiotensin System—An Endocrine and Paracrine System

JULIE L. LAVOIE AND CURT D. SIGMUND

Departments of Internal Medicine and Physiology and Biophysics, Roy J. and Lucille A. Carver College of Medicine, University of Iowa, Iowa City, Iowa 52242

Since the discovery of renin as a pressor substance in 1898, the renin-angiotensin (RAS) system has been extensively studied because it remains a prime candidate as a causative factor in the development and maintenance of hypertension. Indeed, some of the properties of the physiologically active component of the RAS, angiotensin II, include vasoconstriction, regulation of renal sodium and water absorption, and increasing thirst. Initially, its affect on blood pressure was thought to be mediated primarily through the classical endocrine pathway; that is, the generation of blood-borne angiotensin with actions in target tissues. More recently, however, it has become appreciated that a local autocrine or paracrine RAS may exist in a number of tissues, and that these may also play a significant role in regulating blood pressure. Some of the difficulties in studying tissue RAS stem from the limitations of pharmacology in not differentiating between RAS products made systemically from those synthesized locally. However, the development of transgenic animals with highly specific promoters to target the RAS to specific tissues provided important tools to dissect these systems. Thus, this minireview will discuss recent advances in understanding the relationship between endocrine and paracrine (tissue) RAS using transgenic models. (*Endocrinology* 144: 2179–2183, 2003)

THE RENIN-ANGIOTENSIN SYSTEM (RAS) is well known for its regulation of blood pressure and fluid homeostasis. Angiotensin II (Ang-II), the final effector of the system, causes vasoconstriction both directly and indirectly by stimulating Ang-II type 1 receptor (AT-1) receptors present on the vasculature and by increasing sympathetic tone and arginine vasopressin release. Chronically, Ang-II regulates blood pressure by modulating renal sodium and water reabsorption directly, by stimulating AT-1 receptors in the kidney, or indirectly, by stimulating the production and release of aldosterone from the adrenal glands, or stimulating the sensation of thirst in the central nervous system (CNS). The enzymatic cascade by which Ang-II is produced consists of renin (REN), an aspartyl protease, which cleaves angiotensinogen (AGT) to form the decapeptide angiotensin I (Ang-I; Fig. 1). Ang-I is then further cleaved by angiotensin-converting enzyme (ACE), a dipeptidyl carboxypeptidase, to produce the octapeptide Ang-II, the physiologically active component of the system. Further degradation (or processing) by aminopeptidase A and N produces angiotensin III (Ang 2–8), and angiotensin IV (Ang 3–8), respectively. The actions of Ang-II results from its binding to specific receptors (AT-1 and AT-2), classified by their differential affinities for various nonpeptide antagonists (1). Both of these cell surface receptors belong to the large family of G protein-coupled receptors although the pathways used are completely different and signal in apparent opposition. For example, AT-1 receptors mediate vasoconstrictor responses whereas AT-2 receptors are thought to mediate vasodilator responses. Comprehensive reviews of AT-1 and AT-2 signaling have been published (2–4). These receptors have a wide tissue-specific distribution, and are both present in the kidney, brain, and adrenal gland. In general, AT-1 receptors are present in adult cardiovascular tissues, whereas AT-2 is highly expressed during fetal development (5).

Pharmacological studies using specific antagonists have determined that most of the physiological actions of Ang-II are mediated by the AT-1 receptor (1). Two subtypes of this receptor, AT-1a and AT-1b, have been identified in the rat (6), mouse (7), and an AT-1b receptor has been reported in humans (8), although it is generally accepted that humans express only one type of AT-1 receptor. These receptor subtypes are pharmacologically indistinguishable and are thought to signal identically, but are the product of different genes (*Agtr1a* and *Agtr1b*) that are differentially expressed and regulated (9, 10). It is this differential expression that most likely distinguishes the function of the two receptor subtypes. The AT-1a is the predominant receptor in most organs, whereas AT-1b is more abundant in the adrenal and pituitary glands (11). Gene-targeting experiments have been useful in identifying the individual role of the AT-1a and AT-1b in the periphery (12, 13) and in the CNS (14). AT-1a receptors are predominantly involved in the regulation of vascular tone and sodium reabsorption in the periphery as well as the pressor response to Ang-II in the CNS, whereas AT-1b receptors are necessary for the dipsogenic response to Ang-II in the CNS. On the other hand, AT-2 receptor function has not yet been fully determined. Recent studies have suggested that it might oppose the actions of the AT-1 receptor with respect to blood pressure and cellular proliferation (15). It has also been suggested that AT-2

Abbreviations: ACE, Angiotensin-converting enzyme; AGT, angiotensinogen; Ang-I and II, angiotensin I and II; AT-1, Ang-II type 1 receptor; AT-2, Ang-II type 2 receptor; CNS, central nervous system; GFAP, glial fibrillary acidic protein; hAGT, human AGT; hREN, human REN; ICV, intracerebroventricular; RAS, renin-angiotensin system; REN, renin; Syn, synapsin.

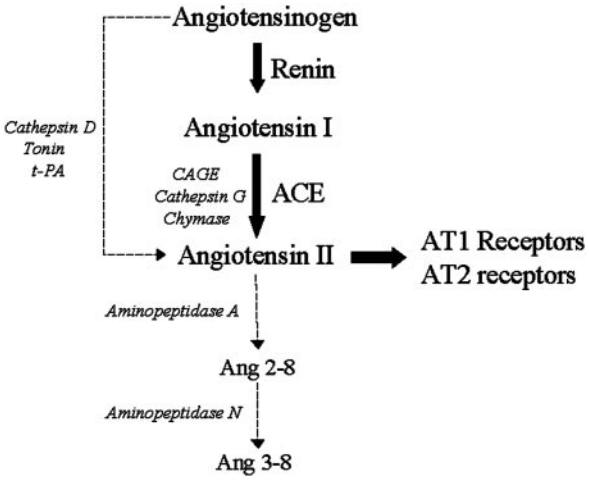

FIG. 1. The REN-angiotensin cascade. The classic cascade of the RAS is shown in *block arrows*. Alternative means for the generation of Ang-II is indicated by *dotted arrows*. Ang 3–8, Angiotensin IV; Ang 2–8, angiotensin III; CAGE, chymostatin-sensitive Ang-II-generating enzyme; t-PA, tissue plasminogen activator.

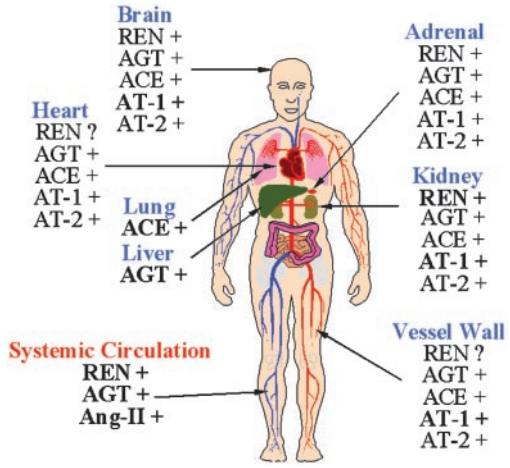

FIG. 2. Expression of the RAS. Sites of expression of the different components of the RAS are shown. Classical sites of synthesis for the endocrine RAS are in *bold*.

receptor stimulation decreases renal tubular sodium reabsorption (16), and AT-2 receptor knockout mice exhibit behavioral changes (17).

Other receptors have been described in relation to the RAS. For instance, an AT-4 binding site has been identified, and in contrast to the other AT receptors does not seem to be a G protein-coupled receptor (18). This receptor binds Ang 3–8 preferentially, has been localized in various mammalian tissues, and has been suggested to cause vasodilatation (18, 19). More recently, the presence of a REN receptor has also been reported in the heart, brain, placenta, kidney, and liver (20). This receptor reportedly binds both REN and prorenin and that binding increases the catalytic activity of REN to cleave AGT while rendering active prorenin.

Local RAS

Tissue RAS exist in tissues that have the capacity for both the local generation and action of Ang-II (Fig. 2). All components of the RAS can be found in the brain (21, 22), heart (21), vasculature (21), adipose tissue (23), gonads (24), pancreas (25), placenta (26), and kidney (21), among others. The intrarenal RAS is hypothesized to regulate systemic blood pressure and aspects of renal function such as blood flow and sodium reabsorption (27), whereas in the brain it may facilitate neurotransmission and stimulate vasopressin release and sympathetic outflow (28, 29). The tissue RAS concept is strongly supported by primary expression data showing all components of the RAS in individual tissues. However, it is important to point out that clinical observations form the basis for the concept and potential importance of tissue RASs. These observations include: 1) the antihypertensive actions of ACE inhibitors are better correlated with inhibition of tissue ACE rather than plasma ACE, and 2) hypertensive patients with normal or even low levels of systemic RAS activity can be effectively treated with inhibitors of the RAS (30, 31).

In some tissues, only some components of the RAS could be found leading some to speculate on the existence of alternate pathways for the production of Ang-II (Fig. 1). For instance, the conversion of Ang-I to Ang-II by the use of enzymes such as cathepsin G, chymostatin-sensitive Ang-II-generating enzyme, and chymase has been reported (32, 33), and a pathway for REN-independent production of Ang-II from AGT has also been reported (34, 35). The physiological relevance of these pathways remains unclear and will not be detailed further in this review.

Transgenic Animal Models of Tissue RAS

Targeting the brain

There has been substantial interest in the brain RAS on the basis of evidence implicating its contribution to the hypertensive state in many animal models such as the spontaneously hypertensive rat, deoxycorticosterone acetate (DOCA) salt-hypertensive rat, and Dahl salt-sensitive rat (36, 37). In the spontaneously hypertensive rat, acute and chronic intracerebroventricular (ICV) injection of an ACE inhibitor, angiotensin receptor blocker, or antisense oligonucleotides to AT-1 receptors or AGT mRNA attenuates the development of hypertension (38, 39). In double transgenic hypertensive mice expressing both human REN (hREN) and human AGT (hAGT) systemically, we have reported a significant decrease in blood pressure after ICV injection of losartan, an angiotensin receptor blocker (40, 41).

To better assess the role of primary production of REN and AGT in the brain and distinguish between the effects of glial and neuronal production of Ang-II, we developed transgenic mice expressing hAGT and/or hREN driven by either the synapsin I (SYN I) promoter, a neuronal promoter, or the glial fibrillary acidic protein (GFAP) promoter, a glial promoter. Transgene expression in the GFAP-hAGT mice was evident mainly in astrocytes in the brain, but hAGT could also be detected in cells in the subfornical organ, which also costained with microtubule-associated protein-2, a neuronal marker (42). When GFAP-hAGT mice were crossed with mice expressing hREN systemically, a 15-mm Hg increase in blood pressure was observed. In addition, these double transgenic mice exhibited a preference for saline when pro-

vided with a choice between tap water and saline. These results are in accordance with studies done in transgenic rats expressing an antisense RNA against AGT mRNA driven by the GFAP promoter, TGR(ASrAOGEN), where a significant decrease in blood pressure was observed (43). We also produced transgenic mice expressing hREN under the control of the GFAP promoter (GFAP-hREN; Ref. 44). These transgenic mice expressed hREN in the brain, specifically in glia, with some ectopic expression in lung and adipose tissue, but no detectable plasma hREN. When these mice were crossed with GFAP-hAGT mice, the double transgenic animals had an increase in blood pressure, an increase in drinking volume, and an increase in salt intake. The increase in blood pressure observed was reversed by ICV injection of losartan, whereas the same dose given IV proved ineffectual. This suggests that the observed increase in blood pressure was due to the local production and action of Ang-II in the brain. This pressor effect may be mediated by an increase in sympathetic activity because hexamethonium, a ganglionic blocker, caused a greater fall in blood pressure in the double transgenic mice than in negative littermates.

We also produced SYN I-hAGT transgenic mice, which express the transgene solely in neurons in the brain, and at low levels in the kidney and heart, but exhibit no detectable plasma hAGT (45). A pressor response was observed in these mice after ICV, but not iv injection of purified recombinant hREN, which could be prevented by pretreatment with ICV losartan, indicating the pressor response was AT-1 receptor dependent. Accordingly, when the SYN I-hAGT mice were bred with SYN I-hREN mice, which also show a neuronal-specific expression pattern in the brain, they were moderately hypertensive and exhibited increased drinking volume and salt preference (44). Both the GFAP and SYN models clearly demonstrate that local production of Ang-II within the brain has numerous physiological effects regulating blood pressure, and water and electrolyte homeostasis.

We and others (46, 47) have reported an altered form of REN mRNA derived from the utilization of an alternative transcription start site in the brain. If translated, this mRNA would encode an intracellular (nonsecreted) and constitutively active form of the protein, suggesting the possibility of an autocrine intracellular pathway of Ang-II production in the brain. Because the physiological relevance of this pathway remains unknown, we are currently studying the regulation of blood pressure and fluid homeostasis in new transgenic models expressing this intracellular form of REN driven by either the GFAP or SYN I promoters.

Targeting the kidney

In kidney, REN is expressed primarily in juxtaglomerular cells where it is stored in dense core secretory granules and released into the interstitium in response to a variety of physiological cues. From there, REN finds its way to the systemic circulation, where it can act as part of the endocrine RAS. AGT is expressed in proximal tubule cells of the kidney and exhibits polarized secretion through the apical membrane into the tubular lumen (48, 49). In the lumen, REN either filtered from the circulation, transported from the renal interstitium, or made in the tubules directly processes AGT to Ang-I. In the tubular fluid, Ang-I is rapidly converted to Ang-II by the high concentration of ACE on the brush border membrane of the proximal tubule.

To test whether an intrarenal RAS could influence blood pressure independent of changes in circulating Ang-II, we produced a kidney-specific model resulting from proximal tubule-specific expression of the AGT gene. We produced transgenic mice expressing hAGT driven by the kidney androgen-regulated protein promoter, which is expressed specifically in the renal proximal tubule and is highly responsive to androgen (50). Elevated concentrations of hAGT were observed in urine, reflecting its elevated production in proximal tubule cells and its release into the tubular lumen, but no hAGT was detected in the systemic circulation. Double transgenic male mice expressing kidney androgen-regulated protein-hAGT and a systemically expressed hREN (expressed in juxtaglomerular cells of the kidney) had increased blood pressure but normal circulating Ang-II levels (51). The increase in blood pressure could be induced in the female double transgenic mice by treatment with testosterone, with the increase in blood pressure paralleling the induction of the androgen-responsive transgene. Given the high concentration of hAGT in the urine, we presumed there was a high concentration of Ang-II in proximal tubular fluid, and perhaps further in the fluid along distal portion of the nephron. This would be consistent with measurement showing that the level of Ang-II in tubular fluid cannot be accounted for from filtration of circulating Ang-II (27, 52). Ang-II has direct effects on sodium transport in the early nephron by stimulating sodium-hydrogen exchange in proximal tubule and indirect effects in the late nephron by regulating synthesis of epithelial sodium channels by aldosterone both of which may occur through Ang-II binding to luminal AT-1 receptors (53). This supports the hypothesis that hypertension in these mice may be caused by alterations in sodium or fluid homeostasis, perhaps through alterations in these transport mechanisms. Such affects appear to be a common underlying mechanism causing high blood pressure in a number of human genetic syndromes (54).

Conclusion

The recent demonstration that local RAS exist and are physiologically active in many tissues points to the importance of the tissue or paracrine pathway of Ang-II generation and action. It is this duality of the RAS, both tissue and endocrine systems, working simultaneously, which has made the system extremely complex, and why after over 100 yr of study there are still secrets to discover. As new technologies emerge and new tools are brought to bear on the problem, we will undoubtedly learn more about how this complex system works *in vivo*. For example, our laboratory has demonstrated that the absence of hAGT in the liver, induced by the use of the Cre-loxP recombinase system to generate a tissue-specific knockout of AGT, causes a loss of circulating hAGT, directly demonstrating that extrahepatic sources of AGT do not significantly contribute to the circulating pool of AGT (55). Moreover, infection of double transgenic mice containing hREN and a floxed hAGT transgene with an adenovirus encoding cre-recombinase reduces blood

pressure significantly (56). We are thus currently using cre-recombinase in conjunction with cell-specific promoters to study the role of the different tissue RASs.

Acknowledgments

Received January 30, 2003. Accepted February 6, 2003.

Address all correspondence and requests for reprints to: Curt D. Sigmund, Ph.D., Departments of Internal Medicine and Physiology & Biophysics, 3181B Medical Education and Biomedical Research Facility, Roy J. and Lucille A. Carver College of Medicine, University of Iowa, Iowa City, Iowa 52242. E-mail: curt-sigmund@uiowa.edu.

This work was supported by an American Heart Association Heartland Affiliate Postdoctoral Fellowship (to J.L.L.). We gratefully acknowledge research support from the Carver Trust.

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