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REVIEW

Update on tissue renin–angiotensin systems

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Abstract Angiotensin (Ang) II is not only generated in the circulation by renin and angiotensin-converting enzyme (ACE) but also is produced locally in numerous organs including kidney, vessels, heart, adrenal gland, eye, testis, and brain. Furthermore, widely distributed mast cells have been shown to be a production site. Local Ang II production process is commonly termed the result of a "tissue" renin–angiotensin system (RAS). Because pharmacological experiments do not easily allow targeting of specific tissues, many novel findings about the functional importance of tissue RAS have been collected from transgenic rodent models. These animals either overexpress or lack RAS components in specific tissues and thereby elucidate their local functions. The data to date show that in most tissues local RAS amplify the actions of circulating Ang II with important implications for physiology and pathophysiology of cardiovascular diseases. This review summarizes the recent findings on the importance of tissue RAS in the most relevant cardiovascular organs.

Keywords Renin · Angiotensin · Transgenic animals · Gene targeting · Angiotensin receptor · Renin–angiotensin system · Transgenic

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Introduction

Since its discovery in 1898 [1] and subsequent work thereafter spanning more than half a century, the renin–angiotensin (Ang) system (RAS) was thought to be a hormone system by which the kidney influences systemic cardiovascular regulation. Reacting to changes in renal perfusion pressure, tubular salt content, and the renal sympathetic nerve activity, the juxtaglomerular (JG) cells of the kidney release active renin into the circulation. In the blood, the aspartyl protease proteolytically cleaves the liver-borne angiotensinogen (AOGEN) to form the inactive decapeptide Ang I. The angiotensin-converting enzyme (ACE) further removes two C-terminal amino acids thereby generating Ang II. ACE is a sessile zinc-containing metalloproteinase on endothelial cells. The pulmonary endothelium is a particularly rich source of ACE (Fig. 1). Ang II has two receptors, AT1 and AT2, expressed in many cardiovascular and other tissues. Both receptors belong to the G-protein-coupled receptor class with seven transmembrane domains. The AT1 receptor confers most classical actions of the peptide such as vasoconstriction, aldosterone release from the adrenal zona glomerulosa, salt retention in the renal proximal tubules, and stimulation of the sympathetic nervous system via receptors in the brain. In rodents, which carry two isoforms of the AT1 receptor, AT1A and AT1B, the AT1A receptor mediates most of these actions.

In addition to the classical RAS components, several new participants have been discovered in recent years. A homolog of ACE, ACE2, was discovered and shown to degrade Ang II yielding Ang-(1-7) (Fig. 2) [2, 3]. Santos et al. discovered that the *Mas* proto-oncogene is a receptor for this peptide and that the ACE2–Ang-(1–7)–Mas axis is counter-regulating the abovementioned cardiovascular actions of the classical RAS [4, 5]. Furthermore, a protein has recently been discovered,

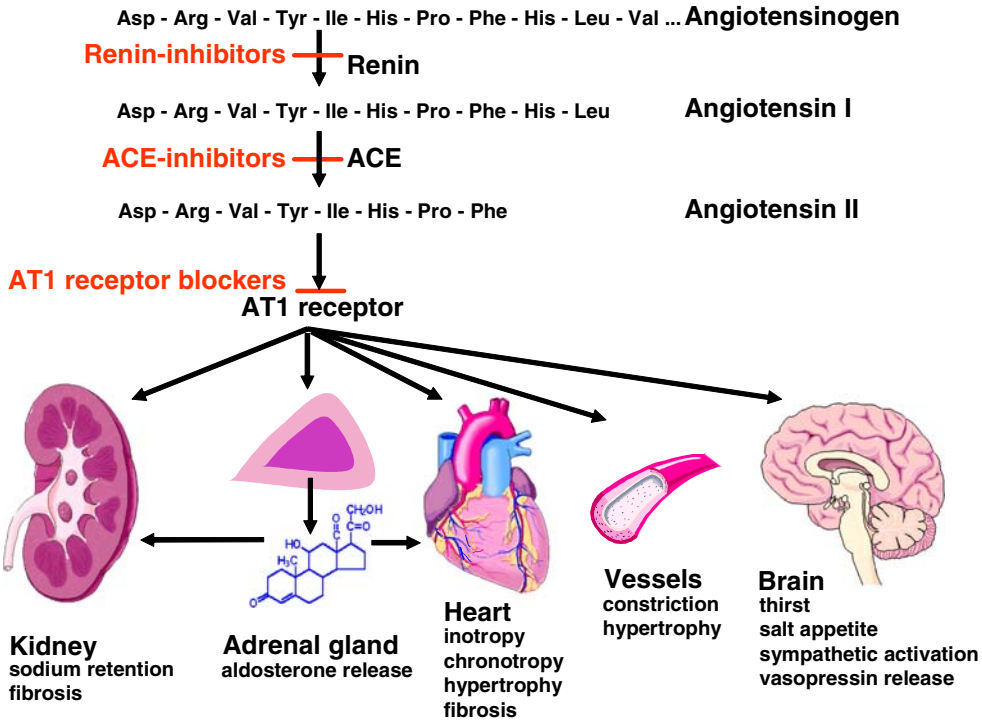

Fig. 1 The classical renin–angiotensin system (RAS). The components of the classical RAS, their interactions, the sites of intervention by clinically approved drugs (in *red*), and the main effects of the RAS in different cardiovascular organs are shown

which binds and activates renin and prorenin in tissues, the (pro)renin receptor or (P)RR [6, 7]. The physiological role of these new RAS components is not completely resolved, but, as outlined below, they probably exert considerable impact on local Ang II generation and effect mediation in tissues.

The RAS has been a therapeutic target for cardiovascular diseases since the discovery of the ACE inhibitor captopril about 30 years ago [8]. Later, antagonists for the AT1 receptor were developed [9] and joined the ACE inhibitors as very efficient antihypertensive agents (Fig. 1). Very recently, inhibitors of the rate-limiting enzyme in the RAS, renin, were approved for clinical use [10]. The efficiency of these drugs is partially based on the fact that they not only inhibit the classical RAS in the circulation but also local RAS in tissues [11–14]. In this short update, we will only summarize the data of the last decades and will add some novel aspects, which are mostly based on experiments with transgenic animal models with altered RAS components in single tissues.

Kidney

The first place to surmise a tissue RAS is the kidney because the kidney is the source of the initiating enzyme of the cascade,

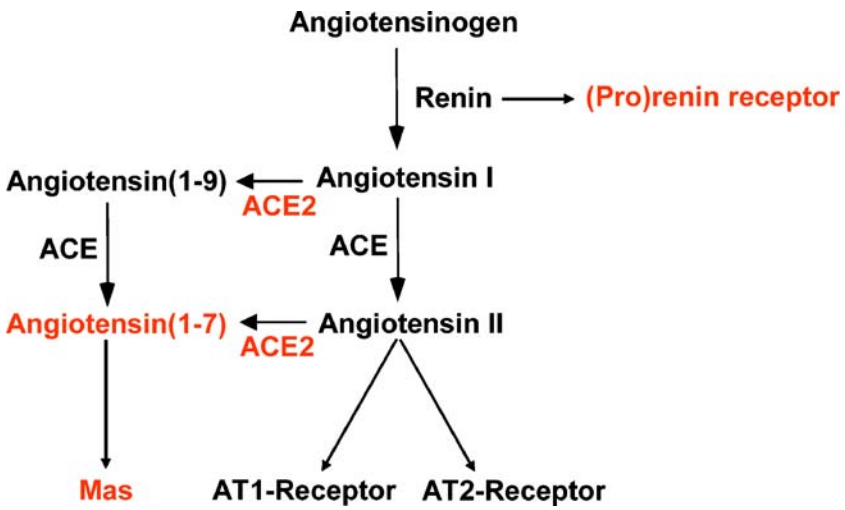

Fig. 2 The new renin–angiotensin system (RAS). The newly discovered components of the RAS, such as angiotensin-(1-7), ACE2, Mas, and (P)RR are shown in *red*

renin. When the substrate AOGEN and the second enzyme ACE were found to be expressed within the kidney, a local generation of Ang II with physiological importance became a foregone conclusion [15, 16]. Furthermore, early studies detected renin and its messenger RNA (mRNA) [17] outside of the JG cells in the proximal tubules and even in the collecting duct. At these sites, renin is not primarily implicated in the regulation of circulating Ang II levels. Intrarenal Ang II generation is very effective and, under positive feedback control at these renal sites, causes higher local concentrations of the peptide than in the circulation [18–20]. Ang II has numerous functions within the kidney. Besides effects in renal development [21], knockout mice lacking AT1 receptors have shown that Ang II regulates glomerular blood flow, tubular sodium reabsorption, and renin secretion. The local RAS in the kidney may be of high relevance for blood pressure regulation as an amplifier of circulating Ang II actions. In elegant experiments, Crowley et al. [22, 23] showed that AT1 receptors in the kidney are relevant for baseline blood pressure regulation and even more importantly for hypertension induced by Ang II infusion. Bilaterally nephrectomized mice transplanted with one kidney lacking AT1A receptors hardly reacted to chronic Ang II infusion with a blood pressure increase, in contrast to mice lacking AT1A receptors in all tissues except in a transplanted kidney. These mice developed the same increased blood pressure levels as wild-type (transplanted control) mice. Furthermore, the local kidney RAS may be pivotal for renal damage caused by hypertension. We recently showed that mice lacking intrarenal AOGEN synthesis developed less hypertensive damage in the kidney than control mice [24]. Accordingly, mice generating more renal Ang II, either by a transgenic human RAS [25] or by local overexpression of rat AOGEN [26], develop high blood pressure and ample renal injury.

Müller, Luft, and their associates recently shed light on mechanisms involved in Ang II-induced target-organ damage. Using our double-transgenic rat model expressing the human RAS [27], they found that Ang II elicits an inflammatory and immunological response, which leads to interstitial fibrosis, glomerulosclerosis, albuminuria, and finally renal failure [28, 29]. The novel (P)RR protein is implicated in renin- and prorenin-mediated organ damage, both related to and independent of Ang II [6]. The (P)RR is able to activate bound prorenin, thereby facilitating local Ang II generation, but also initiates extracellular-related kinase signaling on its own. The (P)RR has been implicated in the pathogenesis of hypertensive and diabetic kidney damage. Ichihara and coworkers have presented compelling evidence involving a peptide inhibiting the interaction of prorenin with (P)RR. They found that their "decoy" peptide could blunt renal damage induced by diabetes and hypertension [30, 31]. Nevertheless, these data require confirmation in the light of the fact that (P)RR has additional essential functions in cellular physiology [7, 32].

Vascular wall

Almost 40 years ago, Ganten et al. [33] were able to show that renin can be released from splanchnic vessels. Further studies detected AOGEN mRNA and protein in the vessel wall and documented the local generation of Ang II [34]. By direct action on AT1 receptors in vascular smooth muscle cells, Ang II increases vascular tone and blood pressure. However, this classical concept has recently been challenged by the use of T-lymphocyte-deficient mice, which showed a blunted pressor response to low-dose Ang II infusion. These findings by the Harrison laboratory suggest that immune cells may be involved in the local actions of the peptide on vascular tone [35]. Moreover, these mice did not develop the vascular dysfunction and damage normally observed after Ang II infusion. When these data can be confirmed, we will have to accept the fact that the effects of Ang II on the vascular wall are partially mediated by AT1 receptors on T-cells and probably other immune cells. By personal communication, we know that the Müller–Luft laboratory has made similar observations in mice lacking dendritic cells (personal communication).

ACE2, its product Ang-(1-7), and Mas have all been found in the vascular wall [36]. The postulate that (P)RR is responsible for uptake of renin from the circulation into the vessel wall was supported by us in experiments employing a transgenic rat model overexpressing this protein in vascular smooth muscle cells. These (P)RR transgenic animals showed an increased accumulation of prorenin in vessels and elevated blood pressure [37, 38]. Ang-(1-7) is generated in the vascular wall from Ang II by ACE2 and interacts with Mas on endothelial cells [4, 39]. As we could recently show using Mas-deficient mice, this interaction improves endothelial function and reduces blood pressure [40]. Thus, the ACE2–Ang-(1-7)–Mas system is counteracting the classical RAS in the vessel wall. Moreover, using an animal model overexpressing the AT1 receptor only in endothelial cells, Ramchandran et al. [41] demonstrated that Ang II can also act as a vasodilator, when interacting with AT1 on these cells. A similar effect had already been shown for AT2 receptors earlier. Thus, the net cardiovascular effect of angiotensin metabolism in the vascular wall depends on the relative expression of classical and novel components of the RAS in endothelial and smooth muscle cells.

Heart

Local Ang II production in the heart has been observed about 20 years ago [42, 43]. While cardiac AOGEN and ACE expression was unequivocally shown, the expression of renin is disputed. In bilaterally nephrectomized pigs, cardiac renin activity was reduced to minute amounts,

which argues against local renin expression [44]. Probably, (P)RR or other renin binding proteins are responsible for the uptake of the enzyme from the circulation into the heart where it initiates Ang II generation [45]. Another source of renin may be mast cells which carry and release renin from their granules and which invade the heart in particular after myocardial infarction. Mast-cell-derived renin was found to be pivotal for activating a cardiac RAS leading via AT1A receptors to increased local norepinephrine release via cardiac neurons. The result was malignant rhythm disturbances [46].

Cardiac fibroblasts and myocytes express AT1 and AT2 receptors. Ang II was found to exhibit growth-promoting effects in the heart more than 30 years ago [47]. Furthermore, in the heart [48], these effects were thought to be most relevant by inducing hypertrophy and fibrosis. An interplay between AT1 and AT2 receptors in the heart has been described [49]. However, recent evidence suggests that this paradigm must be revised [50]. In the experiments with transplanted AT1A-deficient kidneys already mentioned above, the extent of cardiac hypertrophy correlated solely with the blood pressure of the transplanted mice and not with the presence or absence of AT1A receptors in the heart [23]. Moreover, in most transgenic animal models with increased generation of Ang II locally in the heart, either by overexpression of AOGEN, ACE, or a protein releasing the peptide, no hypertrophy was detected, as long as the animals remained normotensive [51–53]. However, in some cases, increased fibrosis and an augmented hypertrophic response to increased afterload was reported [51, 52]. The same was true for some, but not all, transgenic rat and mouse models overexpressing the AT1 receptor in cardiomyocytes [54, 55]. Some cardiac AT1 overexpression models developed cardiac hypertrophy, if an interaction with the epidermal growth factor receptor (EGFR) was possible [56–58]. Furthermore, in hypertensive mice lacking local AOGEN generation in the heart, cardiac hypertrophy and fibrosis was attenuated [24]. How can these data be reconciled into a “unifying theory” about Ang II and cardiac hypertrophy? Probably, locally produced Ang II alone is not sufficient for hypertrophy but it maybe for fibrosis induction. Pressure-induced cardiac hypertrophy appears to require an interaction between Ang II and the EGFR. In this pathway, AT1B or AT2 receptors may compensate for the absence of AT1A. This role of the cardiac RAS may explain the therapeutic effectiveness of RAS inhibitors in the amelioration of hypertensive end-organ damage often exceeding their efficacy in blood pressure control in patients.

Another component of the classical RA(A)S, aldosterone, has gained therapeutic interest in particular in cardiac diseases. Mineralocorticoid receptor antagonists turned out to decrease the risk after myocardial infarction [59, 60]. The underlying pathophysiological mechanisms, however, are not yet completely understood.

Brain

The concept of tissue RAS in general was coined after the discovery of local Ang II generation in the brain [61, 62]. However, the identity of the synthesizing enzyme as being true renin is still under discussion and other enzymes have been postulated to be responsible for Ang II generation in the brain [63].

Due to the blood–brain barrier, most Ang II receptors, which are expressed at multiple sites in the brain, cannot be reached by circulating Ang II. To activate these sites, Ang II needs to be synthesized from locally expressed AOGEN by brain-derived ACE and renin. Exceptions are the circumventricular organs (CVO), where a fenestrated endothelium allows the sensing of the hormonal status in the circulation including the systemic Ang II levels by AT1 receptors expressed there in high amounts. Activation of these receptors leads to increases in blood pressure, thirst, and salt appetite.

However, there is now increasing evidence that the transduction of the signals from the CVO to physiological outputs such as release of vasopressin or activation of the sympathetic nervous system requires a local RAS in areas of the brain inside the blood–brain barrier. Concordantly, transgenic mice with increased Ang II generation only in the brain became hypertensive and exhibited increased salt appetite [64–66]. Even more convincing were studies in which Ang II generation was specifically decreased in the brain. Transgenic rats expressing an antisense RNA against AOGEN only in astrocytes, TGR(ASrAOGEN), were suitable tools for studying this issue [67]. The animals showed reduced blood pressure, sympathetic nervous system activity, and vasopressin release, as well as a blunted response to increased circulating Ang II [67–69]. In a more sophisticated approach, the groups of Sigmund and Davisson generated mice expressing human AOGEN in the whole brain except the subfornical organ (SFO). The investigators locally injected an adenovirus, which deleted the AOGEN transgene [70]. These animals showed a blunted pressor response to intracerebroventricular human renin infusion, indicating that the SFO is of pivotal importance for the central pressor effect of Ang II. When in transgenic animals carrying human renin and human AOGEN, the local expression of AOGEN in the SFO was ablated in the same way; water intake decreased. This observation provides evidence that this brain region is also essential for the drinking control exerted by Ang II [71].

Adrenal gland

Forty years ago, renin and later its mRNA was discovered in the adrenal gland [72, 73]. The gland already begins to express renin in high amounts during embryogenesis in parallel to the kidney [74]. In contrast to the heart (see above), adrenal renin concentration is even upregulated after bilateral nephrectomy, indicating independence of the adrenal RAS from the systemic one [75]. The functions of the adrenal RAS may include modulation of aldosterone secretion in conjunction with the circulating Ang II. This conclusion is supported by the drastically altered steroidogenesis in TGR(mREN2)27 rats with a stimulated adrenal RAS in the presence of normal plasma Ang II levels [76, 77]. Interestingly, the adrenal gland expresses also a cytoplasmic form of renin called renin A [78, 79]. When the renin A isoform is overexpressed in transgenic rats, aldosterone synthesis is stimulated [80]. The adrenal RAS may serve as an amplification system for the effects of the circulating RAS on steroidogenesis because Ang II can induce renin release from adrenocortical cells [81]. Furthermore, a role of Ang II in adrenal development is implicated by the early embryonic expression of renin in this organ [82], but as yet no conclusive evidence was provided. However, growth-promoting, but probably not proliferative, effects of the locally generated Ang II are of major importance for the adjustment of the size of adrenal glomerulosa to physiological needs [83].

Conclusions

The local generation of Ang II has been demonstrated for all tissues relevant for cardiovascular control. These tissue RAS play important roles in the functional regulation of the respective organs mostly conveying and amplifying the effects of circulating Ang II. Thereby, they modulate cardiovascular parameters and influence—mostly accelerate—the pathogenesis of cardiovascular diseases. Thus, tissue RAS form the basis for the understanding of the extraordinary therapeutic efficiency of drugs inhibiting the RAS, such as ACE inhibitors, AT1 antagonists, and the newly developed renin inhibitors.

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