

Review Article

Update on the Renin-Angiotensin System

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Abstract

The physiological and pathophysiological actions of the renin-angiotensin system (RAS) extend far beyond its role as a regulator of cardiovascular homeostasis. The "classical" RAS has evolved into a complex system with multiple pathways and counterbalancing axes which are pivotal to the function of most organ systems in the body. The discovery of "local" RAS's which began with the characterization of a brain RAS now includes a diverse array of tissues: liver, kidney, heart, lungs, reproductive organs, adipose tissue, pancreas, spleen, adrenal and the eye. This review describes the classical RAS as a framework upon which the newest discoveries in the RAS are described. These include the discovery of new enzymatic pathways by which novel angiotensinergic signaling molecules are formed, the expanding number of angiotensin receptor subtypes and molecules that transduce their increasing array of cellular responses. This new understanding is leading to the development of new drugs that can mimic or promote the axes of the RAS that counteract the classical axis that causes its pathophysiological actions.

Keywords

- Renin-angiotensin system
- Angiotensin peptides
- Angiotensin receptors
- (pro) Renin receptor
- Peptidases

ABBREVIATIONS

AP: Aminopeptidase; Ang: Angiotensin; Ang I: Angiotensin I; Ang II: Angiotensin II; Ang III: Angiotensin III; Ang IV: Angiotensin IV; Ang (1-7): Angiotensin (1-7); ACE: Angiotensin Converting Enzyme; ARB: Angiotensin Receptor Blocker; AGT: Angiotensinogen; AT₁R: Angiotensin type 1 receptor; AT₂R: Angiotensin type 2 receptor; AT₄R: Angiotensin type 4 receptor; BK: Bradykinin; GPCR: G Protein Coupled Receptor; HRP: Handle Region Peptide; KO: Knockout; PKC: Protein Kinase C; (P)RR: (Pro) Renin Receptor; ROS: Reactive Oxygen Species; RAS: Renin-Angiotensin System

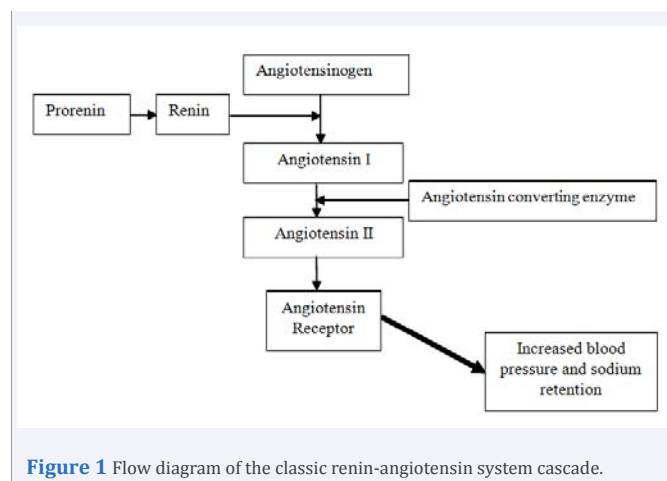
THE CLASSIC RENIN-ANGIOTENSIN SYSTEM

The renin-angiotensin system (RAS) is a potent short term regulator of systemic blood pressure, as well as fluid and electrolyte homeostasis. The classic RAS is a cascade comprised of several different components (Figure 1). The key components are: 1) the systemically circulating enzyme renin and its precursor, prorenin, derived from the juxtaglomerular cells of the renal afferent arterioles; 2) angiotensinogen (AGT), a high molecular weight protein, released from the liver, which is the only substrate of renin and is the precursor for the decapeptide angiotensin (Ang I); 3) angiotensin-converting enzyme (ACE), a dipeptidyl carboxypeptidase, which converts Ang I into the active hormone of the system, Ang II; and 4) the Ang II receptor located in arterioles, the adrenal gland and circumventricular regions of the brain. In this classical system these Ang II receptors caused vascular smooth muscle cells in resistance vessels to contract,

thereby reducing the arteriolar lumen and increasing resistance to blood flow thereby increasing blood pressure. The receptor behavior was that of a G protein coupled receptor (GPCR) using G_q protein to activate phospholipase C, which ultimately increased cytoplasmic calcium which then promoted shortening of myofilaments. In the adrenal glomerulosa, this cytoplasmic calcium mobilization promoted secretion of aldosterone. And, in the circumventricular organs of the brain, Ang II receptor stimulation activated the sympathetic nervous system and stimulated vasopressin/antidiuretic hormone release from the posterior pituitary.

It is generally accepted that the stimuli for renin release into the bloodstream are low blood pressure in the renal artery, hyponatremia, and sympathetic nervous system activation of β_1 adrenergic receptors. Angiotensinogen, constitutively released into the blood stream by the liver, is a circulating α -2 macroglobulin, a member of the serpin family of proteins. However, AGT does not appear to have significant serine protease inhibitory capacity. While the stimulated release of renin from the kidney into the bloodstream is the major influence for the production of Ang II, circulating levels of AGT, which approximate or slightly exceed the Km of renin, have long been thought to also regulate production of Ang II. Recently, it was shown that the Km of AGT for renin varies with redox state. In conditions of oxidative stress, a disulfide bond forms between cys18 and cys138 in AGT which makes it more readily converted to Ang I by renin [1].

This change in affinity of AGT for renin may explain the difficulty in determining the significance of plasma AGT levels



on Ang I formation. The hepatic synthesis of AGT is increased by hormones that activate nuclear receptors for glucocorticoids, estrogen, thyroxine, as well as plasma membrane receptors for Ang II. Numerous pathological conditions such as inflammation alter the synthesis of AGT [2].

In the classical RAS cascade, prorenin (which is also constitutively expressed) is converted to renin via proteolytic and nonproteolytic activation [3].

Renin then converts the circulating plasma protein AGT, into Ang I and other weakly active peptides. Previously, prorenin has been thought to be inactive but increased levels in the plasma and vitreous of diabetic patients with retinopathy have suggested otherwise [4-8].

Angiotensin I generally is not considered to be biologically active. Once Ang I is formed in the bloodstream it is quickly converted into the octapeptide Ang II by the abundance of ACE on the luminal side of the vascular endothelium [9] as well as circulating ACE that has been shed into the bloodstream [10]. Angiotensin converting enzyme is also known as kininase II because of its ability to metabolize bradykinin (BK) [11,12], to inactive peptides. In the classic RAS there is a single Ang II receptor, which for the most part mediates the same effects as the angiotensin type-1 (AT₁R) Ang II receptor subtype. These effects include elevation of blood pressure, stimulation of aldosterone synthesis and release, and induction of thirst and salt appetite. The primary signaling system for the effects of Ang II employed G_q to activate phospholipase C, which generated inositol trisphosphate which then caused the release of calcium (Ca⁺⁺) into the cytoplasm from the endoplasmic reticulum, promoting the contraction of myofilaments of vascular smooth muscle cells. The mobilization of Ca⁺⁺ to the cytoplasm in zona glomerulosa cells of the adrenal cortex stimulated exocytosis of aldosterone into the bloodstream. As the stimulation of aldosterone synthesis and release is such an integral component of the RAS, occasionally this system is referred to as the renin-angiotensin aldosterone system.

NEWER CONCEPTS OF THE RENIN-ANGIOTENSIN SYSTEM

In recent years there has been a substantial expansion of our

knowledge of the RAS with the discovery of new components and peptides (Figure 2) whose function complements, antagonizes or differs from the classic effects of the RAS. These include the recognition that the des-Asp1 fragment of Ang II, known as Ang III, acts in a manner similar to Ang II [13].

The identification of two Ang II receptor subtypes; AT₁R and AT₂R, [14], whose functions for the most part appear to be antagonistic [15-17], akin to the opposing effects of epinephrine on α1 and β2 adrenergic receptors in vascular smooth muscle. The discovery of an AT₄R for the des-Asp1, des-Arg2 Ang II (Ang IV) [18], now known to be the enzyme insulin regulated aminopeptidase (IRAP) [19]. The discovery of a homolog of ACE, ACE-2 a monocarboxypeptidase that acts primarily to metabolize Ang II to Ang (1-7) [20-22], but also forms Ang (1-9) from Ang I [20]. Ang (1-9) can then be converted to Ang (1-7) by ACE.

The identification of the Mas protein as the receptor for Ang (1-7) and characterization of its functional antagonism of the AT₁R Ang II receptor subtype [23].

Discovery of additional alternative enzymatic pathways of formation of angiotensin peptides such as chymase conversion of Ang I to Ang II [24], neutral endopeptidase (neprilysin), thimet oligopeptidase, prolyl endopeptidase, and neurolysin mediated conversion of Ang I to Ang (1-7) see review [25], aspartyl aminopeptidase conversion of Ang I to Ang (2-10) [26].

Discovery of a receptor for renin and prorenin that increases the catalytic activity of renin and unmasks the catalytic activity of prorenin on AGT [27].

Angiotensin II receptor subtypes

Discovery of the two major subtypes: In the 1980's several drug companies were developing antagonists to Ang II receptors in order to reduce the pressor actions of Ang II in people with hypertension (HTN). There had been hints that different subtypes of Ang II receptors existed. These hints were based on different relative potencies of Ang II and Ang III to elevate blood pressure and to stimulate aldosterone secretion [13].

The second was documentation of the differential effects of the sulfhydryl reducing agent, dithiothreitol (DTT), on the inhibition of angiotensin receptor binding in the vasculature versus enhancing angiotensin receptor binding in the adrenal gland and brain. Until 1989, it was generally thought that the classic RAS exerted its physiological effects via a single angiotensin receptor. In 1989 two distinct subtypes of Ang II receptors were identified [28,29].

The Ang II receptor antagonist losartan was shown to bind preferentially to a receptor subtype of Ang II that caused constriction of vascular smooth muscle while showing little affinity for Ang II receptors in adrenal medullary area [28]. Other Ang II receptor antagonists, CGP-42112A (Ciba Geigy) and PD 123319 (Parke Davis), showed high affinity for adrenal and uterine Ang II receptor binding sites, but little ability to inhibit the vasoconstrictor actions of Ang II or to bind to liver Ang II receptor binding sites [28-30]. Of note, CGP-42112A is now known to be an AT₂R agonist [31]. These two Ang II receptor subtypes were subsequently identified as G protein-coupled receptors and were named AT₁R and AT₂R [32].

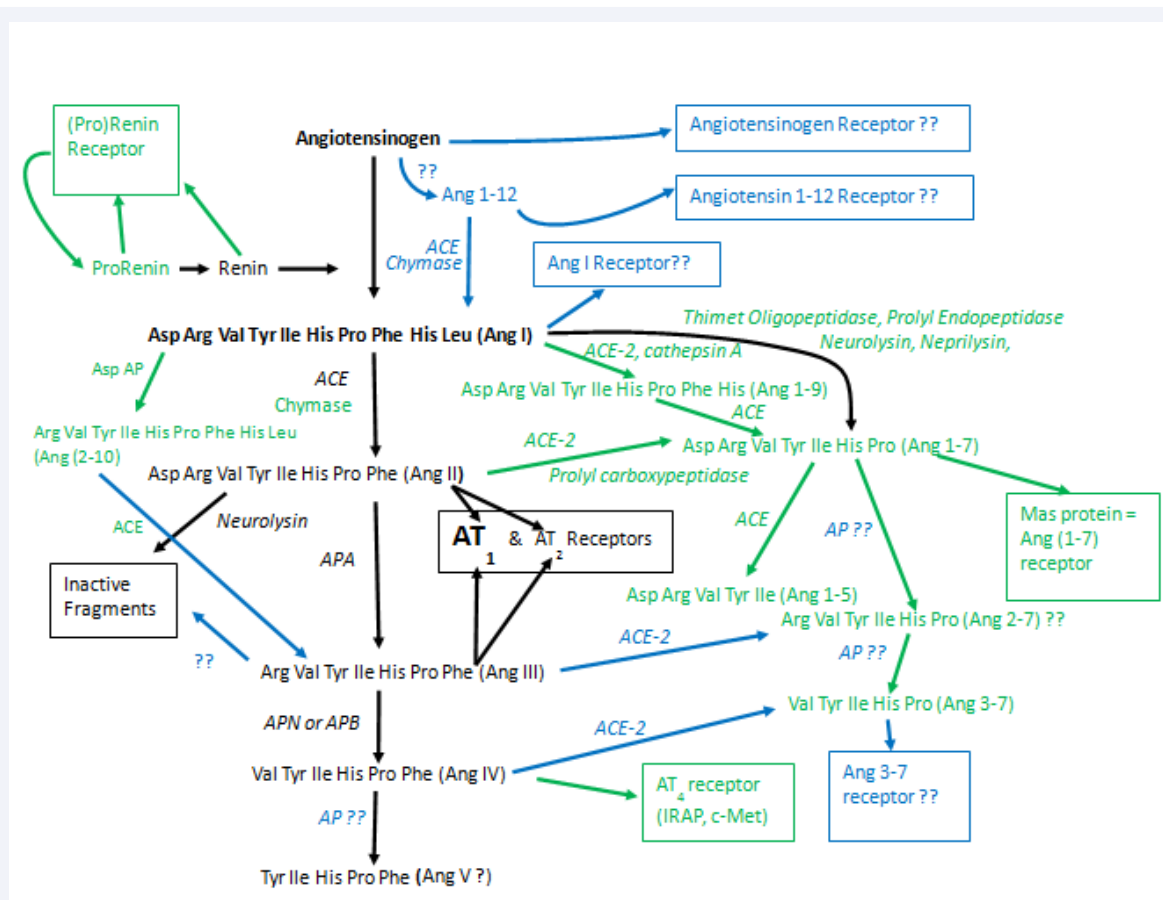


Figure 2 Flow diagram of the current renin-angiotensin system cascade. Ang, Angiotensin; ACE, Angiotensin converting enzyme; APA, Aminopeptidase A; APN, Aminopeptidase N; APB, Aminopeptidase B; Asp AP, Aspartyl aminopeptidase; IRAP, Insulin-regulated aminopeptidase; AT₁R, Angiotensin type 1 receptor; AT₂R, Angiotensin type 2 receptor. Black text and lines delineate the classical RAS cascade. Green text and lines delineate newer pathways of the RAS. Blue text and lines delineate hypothetical components and pathways of the RAS.

- AT₁ receptor subtype:** As noted above, the AT₁R subtype mediates the classic, acute Ang II responses of vasoconstriction, aldosterone synthesis and release, as well as dipsogenesis and salt appetite. Angiotensin II elevates blood pressure by causing the release of vasopressin from the posterior pituitary, noradrenaline and adrenaline via sympathetic nervous system activation, and endothelin-1 [33]. Chronic Ang II elevation is reported to cause fibrosis and other pathophysiological alterations in AT₁ receptor containing organs as well as pathophysiological alterations of the vasculature [30,34-43].

It is now known that Ang II, is proinflammatory [44] and promotes many different inflammatory processes in the vasculature, heart, brain, liver, kidney and lung [45-47]. These effects are modulated in a non-hemodynamic manner [44,48]. Ang II also functions as a growth factor and immune-modulator influencing cell proliferation, apoptosis and tissue fibrosis [49]. Additionally, it causes extracellular matrix remodeling, regulates expression of numerous inflammatory genes and activates other cell signaling pathways such as the Rho kinase system [50] and mTOR [51].

Stimulation of the AT₁R by Ang II increases expression of many inflammatory mediators in a variety of cell types. In macrophages, there is an increase in C-C chemokine receptor type 2 (CCR2) and monocyte chemoattractant peptide (MCP)-1 [52]. Stimulation of the AT₁R by Ang II increases maturation, antigen uptake and migration in dendritic cells; increases activation, proliferation and production of chemokines/cytokines in T lymphocytes; increases expression of toll-like receptor (TLR)-4, reactive oxygen species (ROS) and apoptosis in mesangial cells, and increases expression of TLR-4 and increases in chemokines and cytokines in vascular smooth muscle cells [53].

Other inflammatory events include the proliferation and chemotaxis of vascular smooth muscle and endothelial cells, increased transcription of vascular endothelial growth factor (VEGF), [54,55] production of ROS [56,57] production of pro-inflammatory cytokines such as interleukin (IL)-6, IL-1α, and C-reactive protein [58]. Additionally, endothelial adhesion molecules such as selectins, vascular cell adhesion molecule (VCAM) and intercellular adhesion molecules (ICAMs) are induced [59]. It has been noted that AT₂R is also up-regulated in injured tissue and during pathological processes [60].

Angiotensin II is also involved in wound healing and

Table 1: List of renin-angiotensin system components, primary sources and functions.

Component	Source*	Functions*
Pro-renin	Kidney, constitutive release	Conversion of Angiotensinogen (AGT) to angiotensin (Ang I) (when bound to the prorenin receptor [(P)RR]), signaling via renin receptor
Renin	Pro-renin via proconvertase, cathepsin B	Conversion of AGT to Ang I, signaling via renin receptor
Angiotensinogen	Liver, adipose tissue (in obesity)	Substrate for renin and prorenin precursor of Ang I
Ang I (Ang 1-10)	AGT via renin or prorenin. Cathepsin G, tonin AGT via Ang 1-12	Weak vasoconstrictor, precursor of Ang II
Ang II (Ang 1-8)	Ang I via angiotensin converting enzyme (ACE) Ang I via chymase, cathepsin G AGT via cathepsin G, tissue-type plasminogen activator (t-PA), tonin, trypsin, chymotrypsin	AT ₁ R binding: vasoconstrictor, mitogenic, hypertrophic, aldosteronogenic and aldosterone-releasing, antinatriuretic, dipsogenic, halophilic, antidiuretic (via increased antidiuretic hormone release), proinflammatory, pro-oxidative stress, profibrotic, and prothrombotic AT ₂ R binding: vasodilation, antiproliferative, pro-apoptotic, prenatal development,
Ang III	Ang 2-10 via ACE Ang II via aminopeptidase A (APA)	Effects are generally the same as Ang II on AT ₁ R and AT ₂ R
Ang IV	Ang III via APN, APB Ang II via dipeptidyl peptidase I or III	Cell proliferation, inflammation, neuronal development, Nitric oxide (NO) synthesis, neuropeptide metabolism,
Ang 1-12	AGT via cathepsin G, t-PA, tonin, trypsin, chymotrypsin	uncertain
Ang 2-10	Ang I via APA or aspartyl AP	Antagonism of the actions of Ang II and Ang III
Ang 1-9	Ang I via ACE-2	Substrate for formation of Ang (1-7) via ACE, activates bradykinin to increase NO formation
Ang 1-7	Ang I via ACE-2 & ACE, neprilysin, neurolysin prolyl endopeptidase & thimet oligopeptidase Ang 1-9 via ACE, neprilysin Ang II via ACE-2, prolyl endopeptidase, prolyl carboxypeptidase	Vasodilatory, NO-releasing, anti-inflammatory, antifibrotic, antithrombotic, antiproliferative
Ang 2-7	Ang III via ACE-2 (hypothesized)	unknown
Ang 1-5	Ang 1-7 via ACE	unknown
Ang 3-7	Ang 1-7 via AP, Ang IV via ACE-2 (hypothesized)	Neuromodulatory: learning and memory, blood pressure regulation

*See text for citations for pathways and functions

tissue repair [61], it has profibrotic effects leading to excess accumulation of extracellular matrix material [62]. Studies suggest a role for AT₁R activation in the promotion of the atherosclerotic process [63]. Evidence also suggests that Ang II plays a role in autoimmune disease such as multiple sclerosis and in cognitive changes associated with aging [64]. Agonistic autoantibodies to the AT₁R have been shown to contribute to the pre-eclamptic hypertension of pregnancy [65].

The primary transduction pathway of the AT₁R is coupling to the G protein Gq with activation of the phospholipase-C cascade resulting in activation of protein kinase C (PKC) and release of Ca⁺⁺ into the cytoplasm from the smooth endoplasmic reticulum. The AT₁R also activates MAP kinases either directly via PKC, via transactivation of the epidermal growth factor (EGF) receptor, or via scaffolding of β-arrestin with MAP kinases [66-68]. The AT₁R also signals directly through the ERK1/2 MAP kinase pathway causing phosphorylation of a variety of proteins and activation of transcriptional regulators [69]. This is mediated via formation of transforming growth factor beta (TGF-β), proinflammatory cytokines and the formation of ROS [46,70,71] as well as via β-arrestin scaffolding [72].

- **The AT₂ receptor subtype:** From its initial discovery the AT₂R has been an enigma and cause of confusion. As noted above, initial efforts to develop an antagonist

of “the angiotensin II receptor” employed two different approaches. The approach taken by Ciba-Geigy (now Novartis) and Parke-Davis (now part of Pfizer) focused on radioligand binding assays to screen for compounds that competed with Ang II for its receptor. These assays used either human uterus or rodent tissue membrane binding assays in which DTT was added to protect the radio-iodinated Ang II from degradation. In 1989 reports from both DuPont-Merck and Ciba-Geigy described how DTT and other sulfhydryl reducing agents inactivated the AT₁R while protecting and even possibly enhancing the ability of the AT₂R to bind Ang II [28,29,73]. Both Ciba-Geigy and Parke-Davis succeeded in developing ligands for the AT₂R, however, they were ineffective as antagonists of the pressor actions of Ang II. The lead compounds developed by these companies, CGP42112A (Ciba-Geigy) and PD123319 (Parke-Davis) are still known by these names today, while the DuPont-Merck compound DUP-753 went on to become losartan and Cozaar®. Although CGP42112A and PD123319 were unsuccessful as therapeutic agents, they have been widely used by the research community to study the RAS. CGP42112A, originally thought to be an AT₂R antagonist, serves as an AT₂R selective agonist, and PD123319 serves as an AT₂ receptor-selective antagonist.

Initial attempts to determine the functionality of the AT₂R were largely unsuccessful. It did not appear to cause any of the major physiological actions ascribed to Ang II, e.g. elevation of blood pressure, generation of thirst or sodium appetite, aldosterone release, sodium retention. Attempts to link it to known signaling pathways of G protein-coupled receptors (GPCR) were also unsuccessful. With the cloning of the AT₂R in 1993 [74,75] it was clearly shown to be a member of the GPCR family, however, its behavior differed significantly from most other GPCRs in that guanosine triphosphate or its stable analogs did not affect its affinity for agonist ligands [75,76].

The earliest definitive demonstration of functionality of the AT₂R showed that it opened a potassium (K⁺) channel that hyperpolarized neurons grown in a primary cell culture system [77]. Subsequent studies showed that AT₂R mediated stimulation of protein phosphatase activity was required to activate the K⁺ channels [78]. Since protein phosphatases oppose the actions of protein kinases, this was the first indication that the effects of AT₂R stimulation could antagonize the effects of AT₁R stimulation. The mutual antagonism of AT₁ and AT₂Rs was further documented by studies showing that the AT₂R antagonized the mitogenic effects of AT₁R stimulation of neo-intimal cells [16]. These studies also showed that transfected AT₂Rs in cultured vascular smooth muscle cells inhibited the AT₁R mediated increase in MAP kinase activity.

It is now well established that the actions of the AT₂R oppose those of the AT₁R [79-83] and there is an increasing interest in the potential therapeutic value of AT₂R stimulation. Indeed, it can be argued that part of the beneficial actions of angiotensin receptor blockers (ARBs), the "sartans", as AT₁R selective antagonists, arise from the fact that there is an increased stimulation of AT₂Rs. This arises from the loss of negative feedback inhibition of renin release from the kidney, mediated by AT₁R stimulation. When the AT₁Rs on the juxtaglomerular cells of the kidney are blocked, there is an increase in renin release with subsequent increases in the formation of Ang I and Ang II. The increased levels of circulating Ang II would then lead to a selective increase in AT₂R stimulation.

The ability of the AT₂R to counteract the actions of the AT₁R has stimulated interest in the development of AT₂R-selective agonists. While CGP42112A and p-aminophenylalanine⁶ Ang II are AT₂R selective agonists [31,76], they are peptides that are not good drug candidates because they are not orally bioavailable. Development of non-peptide agonists of AT₂Rs has been undertaken and an orally active AT₂R-selective agonist, compound 21, is now being investigated as a possible therapeutic agent to reverse pathologies mediated by AT₁Rs [84-86].

ACE-2/Ang-(1-7)/Mas axis

Several years ago a homologue of ACE, called ACE-2, was identified [20,21]. It is found in the plasma membranes of cells of virtually all organs as an ectoenzyme and is shed into the plasma and urine in an active soluble form [87]. Angiotensin converting enzyme-2 is highly expressed in cardiac blood vessels and tubular epithelia of the kidneys [88,89]. It has also been identified in testis [20,90,91], lung [92,93] and has recently been described in the brain [94]. This enzyme hydrolyzes

Ang I into Ang (1-9) [20,22] and Ang II into Ang (1-7) [21,95]. Thus ACE-2 is effectively an inhibitor of the formation of Ang II by stimulating alternative pathways for Ang I metabolism and as a metabolic inactivator of Ang II. Angiotensin (1-9) has been shown to prevent cardiomyocyte hypertrophy after myocardial infarction [96], enhance the ability of bradykinin (BK) to generate nitric oxide (NO) and arachidonic acid [97] and also serve as a precursor of Ang (1-7) via conversion by ACE [20,21] or neprilysin [22]. ACE-2 can convert bioactive Ang II into Ang (1-7) which has vasorelaxing effects via its receptor Mas [23]. It has been suggested that ACE-2 is a physiologically important modulator of blood pressure [98]. It is not established whether ACE-2 converts Ang III into Ang (2-7) and Ang IV into Ang (3-7) whose physiological significance is still uncertain. Additionally, ACE-2, in contrast to ACE, does not metabolize BK [20]. Bradykinin dilates blood vessels via stimulation of NO and cGMP and also by the release of the vasodilators prostaglandin (PG) E₂ and prostacyclin [99]. However, bradykinin also induces inflammation and increased vascular permeability [100,101]. Enhancement of ACE-2 activity in the lung has been shown to reverse pulmonary hypertension and bleomycin induced inflammatory damage [42]. Of note, membrane bound ACE-2 has been identified as the receptor for severe acute respiratory syndrome (SARS) virus [102,103]. In addition to ACE-2, another carboxypeptidase, prolyl carboxypeptidase has been shown to form Ang (1-7) from Ang II in the kidney under acidic conditions [104].

Angiotensin (1-7) acts as a major biologically active peptide product of the RAS [105]. As noted above, it is formed by the direct conversion of Ang II by the enzyme ACE-2 [21,106], prolyl carboxypeptidase (angiotensinase C) [107], and prolyl endopeptidase [108], or from Ang (1-10) via conversion to Ang (1-9) by ACE-2 and then to Ang (1-7) by ACE [20], and by direct conversion to Ang (1-7) by neprilysin [109], thimet oligopeptidase and neurolysin [110] and prolyl endopeptidase [111]. The receptor for Ang (1-7) has been identified as the Mas protein [23]. Mas protein displays a G protein-coupled receptor motif and is encoded by the Mas oncogene [112]. It was once proposed to be the Ang II receptor [113], however, the pharmacological characteristics of this receptor did not properly match the profile of the Ang II receptor. Angiotensin (1-7) can induce cardiovascular changes, promoting the release of PGs from vascular endothelial and smooth muscle cells [114,115], release of nitric oxide (NO) [116,117], vasorelaxation [23], inhibition of vascular wall cell growth [118], and attenuation of Ang II-induced vasoconstriction [119]. It is neuroprotective in an animal model of stroke [120], reducing ischemia induced inflammation [121]. Its effects are basically antagonistic to the effects of Ang II binding to AT₁R and it is generally recognized as being a counter-regulator of AT₁R mediated effects, akin to the AT₂R. Additionally, Ang (1-7) is reported to have weak antagonistic effects at the AT₁R [122].

An interesting adjunct to the ACE2/Ang (1-7)/Mas axis is the discovery of a novel Ang II analog in the bloodstream with high affinity and efficacy for the mas receptor, angiotensin (Pro¹,Glu² Ang II) [123]. Angiotensin reportedly binds with higher affinity than Ang (1-7) at the Mas receptor [123]. Of note, commercial antibodies used to measure plasma Ang II, which are directed at the C-terminal domain of Ang II do not distinguish

between angiotensin and Ang II, thus casting into doubt the significance of plasma Ang II-like immunoreactive material measurements.

(Pro) Renin and other receptors

Additional receptors have also been identified, one being the (pro)renin receptor ((P)RR) [27,124]. It is now becoming clear that (P)RR is a multifunctional protein that is also involved in the control of intracellular and extracellular pH via its interaction with the V-ATPase, MAP kinase signaling, Wnt/beta catenin signaling as well as by its ability to activate prorenin to form Ang I from AGT and to enhance the affinity of renin for AGT [124]. Renin has profibrotic actions that appear to be independent of Ang II formation which may be mediated through the (P)RR-ERK1/2 pathway [125]. (Pro) Renin receptor knockdown with SiRNA decreases mRNA for and protein expression of the proinflammatory mediators TGF β and fibronectin, and mRNA for plasminogen activator inhibitor-1 (PAI-1) in cultured glomerular cells from nephritic rats [126]. The (P)RR is found in a variety of tissues and may be critical to local formation of Ang II in tissues in which the concentration of renin is low, e.g. brain [127,128]. As noted previously, AGT can exist in two different conformations in plasma depending upon the redox state [1] and oxidative stress. Oxidized AGT forms a sulfhydryl bridge (cys 18-cys 138) that has more than a 10-fold increase in affinity for (P)RR bound renin. (P)RR has been linked to renal disease and hypertension via increased Ang II formation in the kidney [43] and brain [127] [128]. However, the physiological significance of the (P)RR for the RAS has been questioned [124,129].

A putative receptor for des Asp¹, des Arg² Ang II (Ang IV) known as the AT₄R has been shown to be the enzyme insulin-regulated aminopeptidase (IRAP) [19], also known as oxytocinase or vasopressinase (E.C. 3.4.11.3). This receptor may play a role in regulation of the central nervous system (CNS), extracellular matrix, glucose metabolism, as well as modulation of oxytocin and vasopressin metabolism and release [130-137]. The AT₄R is reported to have vasorelaxant effects via activation of NO synthase [138], however, it is also reported to have proinflammatory, prothrombotic activity [139]. A second subtype of AT₄R has been reported to be the c-met receptor for hepatocyte growth factor [140]. Ang IV competes with hepatocyte growth factor for binding to c-met thereby inhibiting its actions [141].

The peptide fragment Ang (3-7) is reported to have neuromodulatory effects when administered into the brain [142-144], however no specific receptor for this fragment has been identified. Similarly, the Ang (2-10) fragment of Ang I is reported to have effects that are antagonistic to those of Ang II at the AT₁R, but no receptor for Ang (2-10) has been described, see review [26].

An additional binding site for Ang I, Ang II and Ang III has been reported in mouse, rat and human brain tissue [145-147]. This binding site has recently been identified as a membrane-bound variant of neurolysin [148]. While the function of neurolysin includes metabolism of Ang I and Ang II [149-151], the possibility of additional functionality of the protein has not yet been explored.

Tissue renin-angiotensin systems

In addition to the classical circulating RAS, tissue-specific RAS's have been well documented. The presence of a local system suggests tissue specific functions. To be identified as having a complete tissue specific RAS, the following criteria must be met: 1) mRNAs for all components necessary for biosynthesis of a biologically active product (e.g., Ang II) are present, 2) a biologically active product is synthesized, 3) receptors for the biologically active angiotensin are present, 4) the biologically active product in the tissue is regulated, independently of the systemic RAS, and 5) reduction or elimination of the action of the product produces a physiological response. Depending on the tissue, the local enzymes responsible for cleavage of AGT or Ang I into Ang II may be different from those found in the classical cascade referred to as renin-independent or ACE-independent pathways. These are described in the next section. This is a most important concern in view of the fact that some tissue RAS's have little or no ability to synthesize renin and may depend on angiotensin-forming enzymes other than renin [25] or may be able to use prorenin to synthesize Ang I via the (pro)renin receptor [152].

Locations of tissue-specific RAS's include the brain [153,154], heart [155], pancreas [156,157], kidney [43], adrenal gland [158], blood vessels [159], reproductive tracts [160,161], lymphatic system [162,163]; adipose tissue [164]; bone marrow [165] and eye [6,166,167]. For comprehensive reviews of tissue RAS's see [168,169]. The RAS also acts as a modulator of hormone functions as evidenced in the adrenal gland. Angiotensin II is one of the most important physiological stimulators for the secretion of aldosterone [170,171]. The importance of aldosterone in the pathogenesis of cardiovascular diseases, including hypertension, has been well documented [172,173]. Ang II also stimulates the release of epinephrine from the adrenal gland [174,175].

Alternate pathways for angiotensin peptide metabolism

Over the past few years, a number of alternative pathways of the RAS have provided additional cascades for this system (Figure 2). These involve enzymes not generally considered to be part of the RAS. The zinc metallopeptidase, neprilysin (EC 3.4.24.11), converts Ang I into Ang (1-7) [22]. Similar to ACE, neprilysin also converts Ang (1-9) into Ang (1-7). Neurolysin is an endopeptidase that acts as the soluble and membrane associated Ang II binding protein in the RAS. It hydrolyzes Ang I to Ang (1-7) and Ang II to Ang (1-4) and (5-8), but is better known for its role in metabolizing neurotensin and BK [176]. It has been identified in the CNS [177] and is associated with neurons expressing neurotensin [178]. Other enzymes that are involved in angiotensin peptide metabolism are thimet oligopeptidase (EC 3.4.24.15.) and prolyl endopeptidase (EC 3.4.21.26) These enzymatic processes appear to be tissue-specific with neprilysin being primarily responsible for Ang (1-7) production in the circulation and vascular endothelium; whereas the other enzymatic pathways, e.g., ACE-2, prolyl endopeptidase and prolyl carboxypeptidase may be more active in tissues such as the brain [179] and kidney [180,181].

Other enzymes that can contribute to the RAS cascades

via conversion of Ang I to Ang II or angiotensinogen to Ang II include: cathepsin G (E.C. 3.4.21.20) [182,183], a membrane bound protein expressed on neutrophils, which may play a role in the production of potent vasoactive proteins and chemo-attractants in inflammation [184] and tonin [185] (see review [25]). Chymase (E.C. 3.4.21.29), forms α and β , which is found in the heart, kidney, vascular smooth muscle and in the secretory granules of mast cells is also able to generate Ang II from Ang I [182]. The literature suggests that alternate pathway Ang II production is important in both physiological and pathological processes [24,186]. Chymase mediated Ang II formation may also be important in diabetic nephropathy [187], vasoproliferative diseases [188,189] and in myocardial infarction [189].

Intracellular “intracrine” renin-angiotensin system

An intracellular RAS has also recently been identified [190-193]. It is characterized by RAS components inside the cell along with the intracellular synthesis of Ang II [194,195]. Numerous studies have shown the presence of functional intracellular RAS's [196,197]. However, the physiological role and involvement in pathophysiological processes have not yet been clearly identified [191,198,199]. It has been recently shown to have blood pressure elevating, sodium retention and prothrombotic effects mediated by AT₁Rs in rodent models [193,200,201].

CURRENT UNDERSTANDING OF THE RAS

Our understanding of the RAS has evolved dramatically since Tigerstedt and Bergman's seminal observation that a pressure raising substance “eine drucksteigernde Substanz” which they called renin, was secreted into the bloodstream from the kidney in 1898 [202]. In what might be an incredible turn of events, this initial characterization of renin as a hormonal substance was verified with the discovery of a receptor for renin [203] now known as the (pro)renin receptor [27,204], although the functional significance of renin is still primarily based upon its enzymatic activity leading to the formation of the pressor hormone Ang II.

Perhaps the greatest change in our understanding of the RAS is that it is not all bad. While the predominant receptor of the system, the AT₁ receptor, mediates a host of pathophysiological actions ranging from elevation of blood pressure to stimulation of inflammatory cytokines and promotion of fibrosis, there are two other arms of the RAS that act to counteract the actions of Ang II at the AT₁ receptor. The first arm is that of the AT₂ receptor which is now recognized to have the opposite effects of the AT₁ receptor. Indeed, initial concerns that selective AT₁ receptor antagonists, the ...sartans, might have harmful effects because they would block the inhibitory feedback on renin release from the kidney mediated by the AT₁ receptor [205] leading to elevated levels of blood Ang II never materialized. Suddenly the AT₁ receptor blockers gained an additional therapeutic effect: to increase AT₂ receptor stimulation by Ang II. Currently there is considerable interest in development of AT₂ agonists as therapeutic agents based upon their ability to protect against stroke [206], myocardial infarction induced damage [207] and renal damage [208] in rodent models of cardiovascular disease. Additionally a naturally occurring variant of Ang II angiotensin A (Ala¹ Ang II) [209] has been discovered to have greater affinity

for the AT₂ receptor than for the AT₁ receptor. This variant may be generated by a specific decarboxylase to reduce the pathophysiological actions of Ang II [209].

The other beneficial arm of the RAS is that of the ACE-2/Ang (1-7)/mas axis. Although the initial report of Ang (1-7) as an active hormone of the RAS indicated it to have AT₁ receptor-like actions [210], it is now well established that Ang (1-7) exerts actions at its own receptor mas [23] which are largely antagonistic to the actions of Ang II at the AT₁ receptor [211]. Key to this arm of the RAS is the enzyme ACE-2 (also initially characterized under the name ACEH [21]), which forms Ang (1-7) from Ang II, thereby simultaneously inactivating the AT₁ receptor agonist and forming the mas agonist. Initially identified as an Ang I metabolizing enzyme [20] it is now known that Ang II is the preferred substrate of ACE-2 [22]. When ACE-2 was first discovered Millennium Pharmaceuticals developed an effective small molecule inhibitor of ACE-2, MLN-4760 with a subnanomolar inhibition constant [212]. However, the drug was never developed in view of the ability of ACE-2 to counter the pathophysiological actions of Ang II at the AT₁ receptor. In contrast to the ACE-2 inhibitor MLN-4760, agents have been discovered that enhance the activity of ACE-2 [213] lowering blood pressure in an animal model of hypertension and improving cardiac function in an animal model of diabetes [214]. Most recently, an antiparasitic agent, diminazene, was also found to enhance ACE-2 activity and attenuate experimental pulmonary hypertension in rats [215].

The new direction of research aimed at understanding the beneficial arms of the RAS with the goal of developing novel therapeutic agents is something that was not even imaginable 20 years ago, this begs the question: Where will the RAS lead us in the next 20 years?

METHOD OF LITERATURE SEARCH

A search of the entire PubMed database was conducted using various combinations of the key words, *renin, prorenin, angiotensinogen, angiotensin, AT₁, AT₂, AT₄ receptors, mas, ACE, ACE2, intracellular, signaling*, including various combinations of the different RAS components. A Google search using the same variations of these words was also performed to identify any scientific publications related to these words such as PhD dissertations or abstracts not published but presented at scientific meetings.

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