

REVIEW

Efficiency and specificity of RAAS inhibitors in cardiovascular diseases: how to achieve better end-organ protection?

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RAAS, a major pharmacological target in cardiovascular medicine, is inhibited by pharmacological classes including angiotensin converting enzyme (ACE) inhibitors (ACEIs), angiotensin-II type 1 blockers (ARBs) and aldosterone receptors antagonists, in addition to the recently introduced direct renin inhibitors (DRIs). However, currently used RAAS inhibitors still cannot achieve their desired effects and are associated with certain drawbacks, such as adverse side effects, incomplete blockage of the system and poor end-organ protection. In this review, we discuss the efficiency and specificity of the current RAAS inhibitors and propose some recommendations for achieving better treatments with better end-organ protection.

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INTRODUCTION

The renin-angiotensin-aldosterone system (RAAS) is one of the major pharmacological targets in cardiovascular medicine. With respect to cardiovascular adverse remodeling and associated morbidity, RAAS acts as a 'non-specific amplifier' of risk factors such as hypertension and insulin resistance and as a 'local amplifier' by directly inducing deleterious cardiac and vascular remodeling.^{1,2}

In its cardiovascular endocrine view, the plasma renin concentration, which is tightly regulated, is the rate-limiting step for angiotensin-II (Ang-II) generation from its circulating substrate, angiotensinogen (AGT). AGT, which is secreted primarily by the liver, circulates at concentrations approximately equal to or lower than the Michaelis constant (K_M) for renin and has an estimated plasma half-life of several hours, as a result of renin activity.³ AGT has no acute regulatory properties, but its basal expression may participate in the long-term regulation of RAAS activity.⁴ Angiotensin converting enzyme (ACE), which produces Ang-II from the renin-produced decapeptide angiotensin-I (Ang-I), is a non-rate limiting enzyme that is abundantly expressed on almost all endothelial cells and has a soluble form that circulates in the plasma. Ang-II exerts its cardiovascular effects through the G-protein coupled receptor angiotensin-II type 1 receptor (AT1R) and, to a lesser extent, through the less abundant angiotensin-II type 2 receptor (AT2R). Thus, RAAS is an unusual endocrine system because the key point of regulation is not the release of the active form of the hormone, but that of an enzyme. Indeed, the high specificity of the response relies on the high selectivity and efficiency of renin toward AGT. In addition, the Ang-I produced by renin is not an active

hormone; instead, it is a precursor that requires further processing. This multi-step regulated signal generation opens the possibility that downstream peptides might be produced through proteolytic cleavage by other proteases. Indeed, neither the complete blockade of plasma renin nor the complete inhibition of ACE (or even their combination) leads to the complete disappearance of plasma Ang-II, thus indicating that a 'leak' exists somewhere and that other enzymatic pathways are accessible, as was shown 40 years ago.⁵

EXTENDED RAAS: FROM AN ENDOCRINE TO A PARACRINE ANGIOTENSIN SYSTEM

Numerous tissues, including the brain, kidney, heart, ovary, pancreas and the vascular wall, have been shown to express a functional paracrine angiotensin system. This function usually refers to the ability to produce and respond to Ang-II independently of kidney renin.⁶ Beyond circulating renin and ACE, numerous enzymes have been shown to participate in the local tissue angiotensin system. Indeed, to date, at least 18 peptidases have been shown to participate in angiotensin peptide generation and metabolism⁷ (Figure 1). In such a system of proteases, 'competition' between proteolytic pathways may occur, as has recently been shown for ACE and ACE2 competing for Ag-I in the kidney.⁸

Tissue analysis of RAAS has also revealed the existence of other active peptides, including Ang-(1-7) and Ag-IV, which act through their specific receptors Mas1 and IRAP, respectively (Figure 1). In addition, specific receptors for renin have also been discovered. Consequently, numerous reviews have been recently published that emphasize the new aspects of RAAS, including renin receptors,

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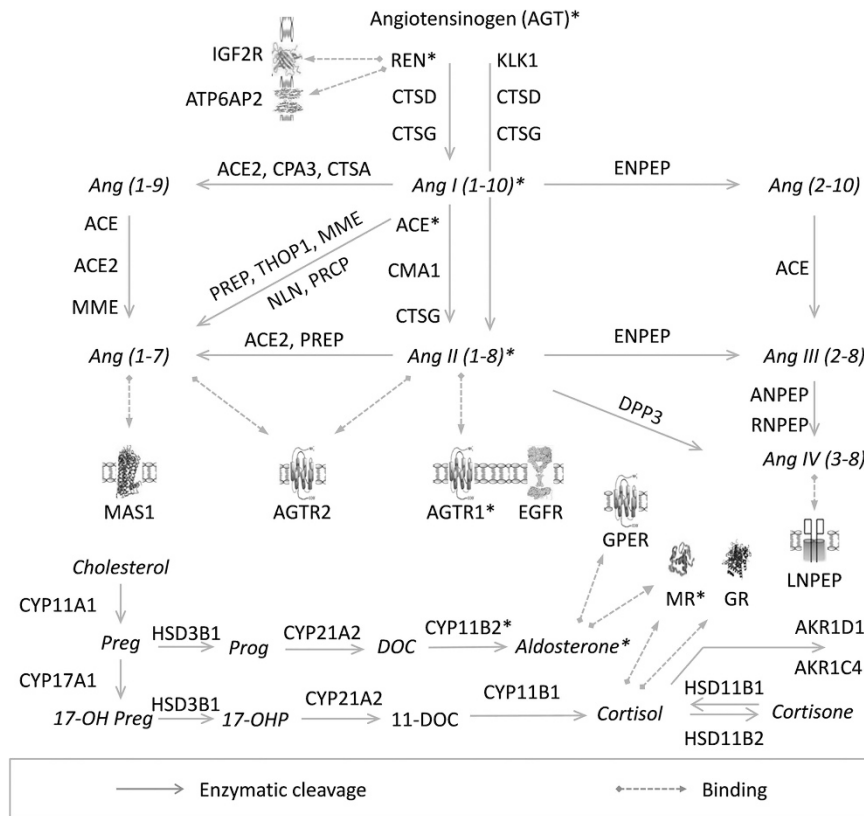


Figure 1 ExtRAAS components. Proteins are represented by the corresponding official gene symbols. Metabolites are represented in gray italics. Classical RAAS components are labeled with an asterisk (*). ACE, angiotensin-I converting enzyme; ACE2, angiotensin-I converting enzyme type 2; AGTR1, angiotensin-II type 1 receptor; AGTR2, angiotensin-II type 2 receptor; AKR1C4, aldo-keto reductase family 1, member C4; AKR1D1, aldo-keto reductase family 1, member D1; Ang, Angiotensin; ANPEP, alanyl-aminopeptidase; ATP6AP2, prorenin/renin receptor; CMA1, chymase 1; CPA3, carboxypeptidase A3; CTSA, cathepsin A; CTSD, cathepsin D; CTSG, cathepsin G; CYP11A1, cytochrome P450, family 11, subfamily A, polypeptide 1; CYP11B1, cortisol synthase; CYP11B2, aldosterone synthase; CYP17A1, cytochrome P450, family 17, subfamily A, polypeptide 1; CYP21A2, cytochrome P450 enzyme, family 21, subfamily A, polypeptide 2; DOC, 11-deoxycorticosterone; DPP3, dipeptidyl-peptidase 3; ENPEP, glutamyl aminopeptidase (aminopeptidase A); GR, glucocorticoid receptor; HSD11B1, hydroxysteroid (11-beta) dehydrogenase 1; HSD11B2, hydroxysteroid (11-beta) dehydrogenase 2; IGF2R, insulin-like growth factor 2 receptor; KLK1, tissue kallikrein; LNPEP, leucyl/cystinylaminopeptidase; MAS1, MAS1 proto-oncogene; MME, membrane metallo-endopeptidase; MR, mineralocorticoid receptor; NLN, neurolysin (metallopeptidase M3 family); PREP, prolylendopeptidase; Preg, progesterone; 17-OHP, 17-OH progesterone; REN, renin; RNPEP, arginyl aminopeptidase (aminopeptidase B); THOP1, thimetoligopeptidase 1. The figure was adapted from Nehme *et al.*⁹¹

bioactive peptides, new enzymatic pathways and new cellular mechanisms.⁹

As the synthesis and secretion of adrenal aldosterone are highly dependent on Ang-II stimulation and contribute to the overall cardiovascular effects of RAAS activation, aldosterone is often considered part of the system. Aldosterone participates in these actions through its mineralocorticoid receptor (MR), thus inducing salt retention and directing cardiac and vascular actions. However, from a systemic view, including aldosterone in the system brings together the entire mineralo- and gluco-corticoids pathways. Indeed, cortisol can stimulate MR in the absence of 11-beta-hydroxysteroid dehydrogenase type 2. In addition, HSD11B1 has been shown to induce a metabolic syndrome with high blood pressure and high AGT in lipid storage tissues in mice.¹⁰ Moreover, glucocorticoids have been shown in several instances to increase tissue RAAS gene transcription and to be associated with hypertension, vascular remodeling and an increased cardiovascular risk.¹¹

THE EFFICIENCY OF CURRENT RAAS PHARMACEUTICALS

As RAAS is involved in local tissue homeostasis, RAAS inhibitors exert cytoprotective molecular effects in the target tissues, thus providing greater end-organ protection. In fact, Ang-II and aldosterone are the

most studied effectors of RAAS; therefore, the pharmacological inhibition of RAAS has been currently targeted through (1) the inhibition of Ang-II generation through ACE inhibitors (ACEIs); (2) the inhibition of Ang-II actions through AT1R blockers (ARBs); (3) the inhibition of the generation of Ang-I from AGT through direct renin inhibitors (DRIs); or (4) a combination of Ang-II and aldosterone receptor antagonists (ARAs).

Angiotensin-II inhibitors

ACEI and ARBs are the most commonly used RAAS inhibitors in the treatment of cardiovascular diseases, such as hypertension, heart failure, myocardial infarction, chronic kidney disease (CKD) and diabetes.¹² In fact, RAAS inhibitors are considered the cornerstone for the treatment of hypertensive patients at high risk for vascular disease.¹³ Indeed, ACEIs and ARBs have been shown to exert effects beyond blood pressure control, decreasing cardiovascular mortality and morbidity.¹⁴

ACEIs. ACEIs were first introduced into clinical practice in 1981 and were primarily used for the treatment of refractory hypertension. However, the importance of these reagents expanded as a result of

their beneficial effects in decreasing morbidity and mortality in congestive heart failure, myocardial infarction, diabetes mellitus, chronic renal insufficiency and atherosclerotic cardiovascular disease.¹⁵ ACEIs are considered first-line treatment agents and are recommended for ventricular systolic dysfunction and high cardiovascular risk patients,¹⁶ owing to their advantage of more favorable side effects than those of sympathetic blockers, beta blockers and diuretics.¹⁷ In fact, ACEI's not only prevent Ang-II production; but also prevent the degradation of bradykinin, a potent vasodilator peptide,¹⁸ thus explaining ACEI's superior effects in the treatment of certain conditions, such as renal artery stenosis and hypertension in patients with type 2 diabetes.¹⁹ However, the ACE-independent generation of Ang-II has been shown to be more active than its ACE-dependent generation in certain tissues under specific conditions,²⁰ thus potentially leading to important clinical issues, because intracellular chymase-mediated Ang-II formation is unaffected by ACEIs.²¹ Indeed, it has been shown that treatment of mice with ACEI does not suppress Ang-II levels in the left ventricle interstitial fluid, despite a marked inhibition of ACE.²¹ However, a combination of chymase and ACE is better than ACE inhibition alone in decreasing Ang-II levels and adverse cardiac remodeling. This finding may provide a basis for boosting the efficacy of Ang-II inhibition and preventing 'ACE inhibitor escape', in which the plasma Ang-II concentration returns to pretreatment levels, despite substantial ACE inhibition.²² Similarly, the ACE-independent generation of Ang-II is the predominate pathway in diabetic kidneys, but not in normal kidneys, thus potentially explaining the greater renal protection of ARBs compared with ACEI in human diabetic nephropathy.²³ Furthermore, a meta-analysis on the Prospective Epidemiological Study of Myocardial Infarction (PRIME) has shown that ACEIs are associated with both cardiovascular death and stroke event risks after adjustment for classic risk factors (age, smoking, total cholesterol, high-density lipoprotein (HDL) cholesterol, systolic blood pressure and diabetes).²⁴ Similarly, monotherapy treatment with ACEI or ARB decreases the risk of all-cause mortality and cardiovascular death, but not the risk of MI or ischemic stroke.²⁵ This finding may be because patients with a previous history of cardiovascular disease with advanced organ damage possess a high incidence of cardiovascular events.²⁶ Therefore, it is recommended that these patients receive complex therapy with RAAS inhibitors, dietary changes and other therapies, such as statin, that may aid in the correction of other risk factors.²⁷

ARBs. ARBs were first introduced in 1995 as a class of RAAS-based antihypertensive agents that can overcome ACEI deficiencies, such as 'ACE inhibitor escape', ACE-independent Ang-II generation, and the specific adverse effects associated with ACEIs.²⁸ Although ARBs do not show superior benefits over ACEIs in the treatment of cardiovascular diseases, such as hypertension,¹⁶ heart failure,²⁹ atherosclerosis¹⁶ and diabetes, they represent a good alternative, owing to their high tolerability.³⁰ Indeed, ARBs have been shown to be comparable to ACEIs in decreasing primary and secondary cardiovascular outcomes, including all-cause mortality, cardiovascular mortality, myocardial infarction, stroke, hospitalization and end-stage renal failure. In addition, a combination therapy using both compounds has been shown to be more effective than either compound alone in decreasing hospitalization but not mortality.^{31,32} However, several recent clinical trials and meta-analyses have shown that combination therapy using ACEI and ARBs for the treatment of hypertension and heart failure may lead to adverse effects, such as hypotension, hyperkalemia and renal dysfunction.^{33–38} However, a post hoc analysis of the

ONTARGET trial has shown that the increase in residual renal risk may be specific to patients with normo-albuminuria, although the treatment is also beneficial to those with micro-albuminuria and macro-albuminuria.³⁹ Indeed, the small number of patients with a decreased glomerular filtration rate and macro-albuminuria in the ONTARGET trial (2.4%) may exhibit masked beneficial effects of combination therapy. Similarly, other studies have shown that monotherapy with either ACEI or ARB confers greater protection against all-cause death, cardiovascular death and renal protection in a subgroup of patients with normal glomerular filtration rate and normo-albuminuria compared with patients with micro-albuminuria, macro-albuminuria or low glomerular filtration rate or the overall population. However, these therapies are harmful in low-risk populations and are associated with a higher mortality with dual therapy than with monotherapy in normo-albuminuria.^{39–41} However, a network meta-analysis of randomized trials comprising 43 256 participants with diabetes and kidney disease has shown that mono- or combination therapies using ACEIs and ARBs are the most effective strategies against end-stage kidney disease, despite borderline increases in the estimated risks of hyperkalemia or acute kidney injury in combination therapy.³² In addition, Tobe *et al.*³⁹ have shown that combination therapy is superior to monotherapy in subgroups at high risk for renal outcomes, such as patients with diabetic nephropathy or macro-albuminuria or in hypertensive patients with left ventricular hypertrophy, normo-albuminuria or micro-albuminuria.^{39,42} In fact, these side effects may be the result of non-specific local RAAS inhibition in certain tissues that possess a RAAS-dependent homeostasis, such as the kidney. Therefore, better understanding of the global organization of extrRAAS in normal and diseased tissues is necessary to achieve more specific and efficient treatments with fewer side effects.

AT1R activation exerts negative feedback on renin, thereby decreasing its activity. Consequently, ARBs have been shown to induce plasma renin activity, thus leading to compensatory increases in both Ang-I and Ang-II that may restore AT1R stimulation in the long term.⁴³ In addition, the produced Ang-II may stimulate pro-fibrotic AT2R and prothrombotic AT4R,^{43,44} a result consistent with findings from studies showing that ARB administration to high risk cardiovascular patients may increase MI despite significant decreases in blood pressure.⁴⁴ However, a recent systematic review on adult patients with diabetes mellitus has found comparable effects between ACEIs, ARBs and their combination on major cardiovascular and renal outcomes, including cardiovascular mortality, myocardial infarction, stroke and end-stage renal disease.⁴⁵

DRIs. DRIs were approved for the treatment of hypertension in 2007, under the generic name Aliskiren.⁴³ The potential advantages of Aliskiren include unique plasma renin activity reduction capacity, long terminal elimination half-life and hepatic elimination.⁴⁶ However, its potential limitations include modest side effects, decreased gastrointestinal absorption with a high fat meal and large reactive increases in renin secretion.⁴³ Mono- and combination therapies using Aliskiren have been shown to be comparable or inferior to ACEI and ARB in decreasing blood pressure and protecting against end-organ damage in patients with hypertension, chronic heart failure, type 2 diabetes and CKD.^{47–52} In contrast, other studies have not found an effect of Aliskiren on the incidence of major cardiovascular events and mortality in patients with heart failure and type 2 diabetes.^{45,53–55} Interestingly, a recent study has shown that treatment with Aliskiren decreases oxidative stress and restores decreased baroreflex sensitivity but also normalizes blood pressure and reverses left ventricular hypertrophy when used in combination with L-arginine in

renovascular hypertension.⁵⁶ The importance of this class of inhibitors lies in its ability to directly target the most proximal and rate-limiting step in RAAS, the conversion of AGT to Ang-I, thereby potentially overcoming the increase in plasma renin that results from ACEIs and ARBs administration and the deficiency of ACEIs in blocking the ACE-independent pathways involved in Ang-II generation.⁴³ However, Aliskiren has been shown to induce a higher reactive rise in plasma renin compared with ACEIs and ARBs, which may lead to activation of fibrotic signaling pathways by the renin receptor that are completely independent of renin proteolytic activation and Ang-II production.^{57,58} Furthermore, similar to combination therapy with ACEIs and ARBs, dual RAAS blockade with Aliskiren in heart failure and diabetic patients cause adverse events, such as hypotension and hyperkalemia.^{38,46,51,54,59,60} In addition, a combination of Aliskiren and Enalapril has been found to lead to a higher risk of hypotensive symptoms than Enalapril alone in patients with heart failure, and it also leads to higher risks of elevated serum creatinine and potassium levels.⁵⁵ This risk may be because proximal blockade of RAAS might decrease the production of protective angiotensin peptides, such as Ang-(1-7).⁴³

AT2R agonists. Despite the well-known protective effects of AT2R on cardiovascular end-organ damage,^{61,62} no AT2R agonist has been introduced into clinical practice to date. Nonetheless, several pre-clinical studies have shown the beneficial effects of AT2R agonists and have proposed them as an adjunct to protect against end-organ damage, together with the decrease in blood pressure induced by other RAAS inhibitors.^{61,63}

Angiotensin-(1-7) agonists

Alterations in the systemic and tissue levels of Ang-(1-7) have been found to be associated with different cardiovascular diseases, including hypertension, myocardial disease, CKD and hepatic cirrhosis.⁶⁴

Ang-(1-7) is considered the main antagonist of AT1R-mediated Ang-II actions.⁶⁵ Ang-(1-7) is formed from Ang-I or Ang-II through several alternative enzymes and pathways (Figure 1). Ang-(1-7) exerts its effects mainly through the Mas receptor (MasR) and AT2R (Figure 1), thereby leading to Ang-II/AT1R-antagonistic effects, such as vasodilation, cell growth inhibition and anti-inflammatory effects.⁶⁶ Thus, RAAS tissue effects result from the balance between the vasoconstrictor/proliferative and the vasodilator/antiproliferative actions of Ang-II and Ang-(1-7), respectively.⁶⁴

Although Ang-(1-7) is known to be the major protective arm of RAAS in local tissue homeostasis, few data are available on its clinical effects on end-organ damage in hypertension and other cardiovascular diseases. Nonetheless, several studies have shown that an Ang-(1-7) agonist, AVE 0991, can be used for the treatment of atherosclerosis.^{67–69} In addition, a recent study has shown that the combination of Ang-(1-7) along with losartan (an ARB) induces greater atheroprotective effects, as compared with the use of either molecule alone.⁷⁰

In fact, Ang-(1-7) is cleaved by ACE, thus generating the Angiotensin-(1-5) (Ang (1-5)) peptide,⁷¹ whose biological activity remains unknown. Thus, an increase in ACE activity may lead to increased Ang-II production concomitant with Ang-(1-7) degradation.⁶⁴ Therefore, the beneficial effects of ACE inhibitors in cardiac and kidney diseases are also attributed to the inhibition of Ang-(1-7) degradation by ACE.⁷² Indeed, elevations in Ang-(1-7) levels after treatment with ACEIs may contribute to the beneficial effects seen in cardiac dysfunction and ventricular remodeling after myocardial infarction.⁷³

These findings pave the way for the development of new combination strategies that use Ang-(1-7), along with other currently used RAAS inhibitors, for the treatment of cardiovascular diseases and protection against end-organ damage in hypertensive patients.⁷⁴

New Angiotensin peptides

Ang-(1-7) is thought to be produced primarily by the highly potent enzyme ACE2, which generates Ang-(1-7) directly from Ang-II or indirectly from Ang-I through an Ang-(1-9) intermediate.⁷⁵ Interestingly, Ang-(1-9) has recently been shown to exert several beneficial cardiovascular effects that are independent of Ang-(1-7)/MasR activation via AT2R in hypertensive rats, including reduced cardiac hypertrophy, fibrosis, oxidative stress and improved cardiac and endothelial function.⁶⁴ In contrast, another study in rats has shown that Ang-(1-9) may indirectly induce AT1R, thus leading to enhanced venous thrombosis.⁷⁶

A recent study has identified an altered Ang-II octapeptide, Ang-A,⁷⁷ which can be used as an indicator of renal failure, showing higher levels in the plasma of patients with end-stage renal disease compared with healthy individuals.⁷⁸ Ang-A is an Ang-II agonist that acts through both AT1R and AT2R with equal affinity to Ang-II.⁷⁸ Interestingly, it may establish another arm of RAAS as a precursor for the recently discovered peptide alamandine, which is also produced from Ang-(1-7) by ACE2.⁷⁹ Alamandine has been shown to produce several beneficial cardiovascular effects that resemble those produced by Ang-(1-7), including vasodilation, antifibrosis and antihypertension. Alamandine mediates its effect through the activation of its own specific receptor, member D of the Mas-related G-protein-coupled receptor (MrgD).⁷⁹

Corticosteroids

Several clinical data have indicated that MR blockade confers benefits of decreasing blood pressure and preventing end-organ damage and improving survival hospitalization.^{80–84} In addition, there is growing evidence that aldosterone has an important role in the pathogenesis of heart failure beyond its sodium retention properties. Indeed, MR blockade using eplerenone is associated with lower cardiovascular morbidity and death in post-myocardial infarction patients, independently of early potassium-sparing or diuretic effects.⁸⁵ Similarly, the major antihypertensive effect of eplerenone in hypertensive patients is mediated via mechanisms other than those involving electrolyte and fluid transport.⁸⁶ Furthermore, spironolactone, another MR inhibitor, decreases intra-ventricular pressure, carotid dispensability and fibrosis in congestive heart failure patients, independently of blood pressure, and reverses carotid intima-media thickness in patients with CKD.⁸⁷ Finally, plasma aldosterone concentration is correlated with left ventricular mass and left ventricular concentric geometry in CKD patients, thus suggesting that aldosterone may have a role in inducing a concentric geometry of the left ventricle and increasing the left ventricular mass in hypertensive patients with early CKD.^{88,89}

Despite the importance of aldosterone in MR activation, MR is bound and activated by cortisol, which is present in 100–1000× concentrations in the circulation, as compared with that of aldosterone.⁹⁰ In fact, in VSMC and cardiomyocytes, MR is predominantly occupied by cortisol at high concentrations in a tonic inhibitory mode.⁸² However, in atherosclerotic lesions and during heart failure, the cortisol-MR complex is activated by elevated ROS generation, thus mimicking the effects of aldosterone on blood vessels and the heart.⁸² Therefore, the antagonistic effects of MR blockers are likely to result from blocking cortisol-mediated MR activation, independently of aldosterone levels.

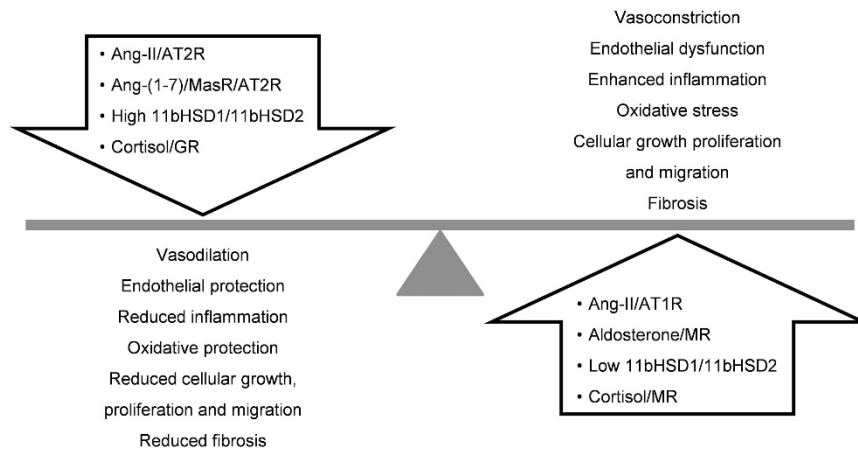


Figure 2 Tissue extRAAS components play key roles in tissue homeostasis. ExtRAAS pathways exert antagonizing effects at the tissue level that balance each other, thereby maintaining tissue homeostasis. A change in extRAAS component expression may shift the balance in one direction, thus possibly leading to tissue physiopathology.

CONCLUSION AND FUTURE DIRECTIONS

Tissue RAAS acts through two opposite arms at the paracrine level: the pro-inflammatory/pro-fibrotic/vasoconstrictive arm and the anti-inflammatory/anti-fibrotic/vasodilator 'protective arm' (Figure 2). Several studies have shown that end-organ damage due to alterations in extRAAS expression results from an increase in the pro-inflammatory arm, concomitantly with a decrease in the protective arm. However, in clinical practice, little focus on the protective-arm has been taken into consideration. Thus, to achieve more efficient treatment with higher protection against end-organ damage in cardiovascular diseases, RAAS pharmacological targeting should be performed by decreasing the harmful effects of the pro-inflammatory arm and inducing the beneficial effects of the protective-arms.

Although monotherapy with ACEI and ARB result in comparable beneficial effects in the different cardiovascular diseases, combination therapies results in higher risks of renal failure in patients with chronic heart failure. Thus, the beneficial effects of combined ACEI and ARB treatment must be balanced against the potential harms, on the basis of the pathophysiological condition in question. Indeed, the extensive inhibition of RAAS by using combination therapy for the treatment of hypertension and heart failure may interfere with the RAAS-dependent homeostasis of normal kidneys. However, ACEI and ARB treatment may restore RAAS to normal in participants with diabetes and kidney disease. In line with these results, we have shown, using transcriptomic data, that the transcripts coding for the Ang-II, Ang-(1-7) and Ang-IV generating enzymes are highly expressed and coordinated in normal kidney tissue,⁹¹ thus indicating that angiotensin metabolism is tightly regulated, both at the transcriptional and functional levels. Therefore, a balance in the system should be maintained in the kidney to preserve tissue homeostasis.

Despite the clear benefits of RAAS inhibitors, residual risks, such as renal and cardiovascular risks, remain high. Thus, careful interpretation of the efficiency of these treatments is crucial, and further studies are needed to elucidate the mechanisms for residual cardiovascular events. Indeed, a careful interpretation should include three main factors: stage of the disease, concurrent diseases and tissue non-specific effects of the RAAS inhibitors on other organs.

Finally, the complexity of the system is increasing with the discovery of new peptides and pathways. Therefore, these molecules warrant further studies to elucidate their clinical importance and the manner

in which they participate in the final effects of RAAS at the local tissue level.

In conclusion, RAAS is a ubiquitous system that is locally expressed in diverse tissue types. Therefore, the systemic targeting of the system for the treatment of a certain pathophysiological condition may affect the organization of extRAAS in other tissues and consequently lead to adverse side effects. We have recently established the transcriptional atlas of tissue RAAS, which includes the expression maps of 37 RAAS genes in 23 normal human tissues.⁹¹ This atlas needs to be extended to include maps for each tissue under different pathophysiological conditions, to provide a better view of the tissue-specific expression of the system. By identifying the tissue-specific characteristics of extRAAS organization, more specific and efficient treatments with fewer side effects may be achieved.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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