Renin-angiotensin-aldosterone System Blockers, Hypertension and Clinical Outcomes

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Abstract

The renin-angiotensin-aldosterone system (RAAS) plays a key role in the physiology of blood pressure control and the pathophysiology of hypertension (HTN). Fortunately, RAAS blocking agents have been available to treat HTN since the 1970s and newer medications are being developed. In this review, we will refresh our current understanding of the RAAS pathway, examine anti-hypertensive medications affecting the RAAS, evaluate recent studies that help provide a better understanding of RAAS blockade on clinical outcomes and review newer RAAS blocking agents and RAAS modulation in clinical practice.

Key words: Advances, hypertension, outcomes, RAAS system, RAAS blockers

Introduction

The renin-angiotensin (Ang)-aldosterone system (RAAS) consists of a group of enzymes and peptides whose main function is to control blood pressure (BP) by regulating vasoconstriction, sodium reabsorption and body fluid homeostasis.

Historical Perspective

Our knowledge of the RAAS started in 1898 when Tigerstedt and Bergman showed that renal extract from rabbits increased BP when infused and named it as renin.[1] In 1934, Goldblatt demonstrated that renal artery constriction caused renal ischemia and induced hypertension (HTN) in dogs. Later, in 1939–1940, Braun-Menende in Argentina and Page and Helmer in the USA simultaneously discovered a pressor substance capable of causing renal HTN. This was originally named hypertensin in Argentina and angiotenin in the USA and later renamed as angiotensin to give credit to both groups.[1] The discovery of captopril, an orally active Ang-converting enzyme inhibitor (ACE-I) in 1980 and Ang receptor blockers (ARBs) in 1998, went on to revolutionize medical care.[3]

Current Understanding of the RAAS Pathway

The modern view of the RAAS began with the concept that this was a lifesaving system, which raised BP in case of an acute hemorrhage. RAAS raises BP beginning with the release of renin into the bloodstream.[4] This circulating renin cleaves hepatic angiotensinogen and generates Ang I, which is converted to Ang II by pulmonary ACE. Ang II causes smooth muscle cell vasoconstriction, stimulates the sympathetic nervous system, and promotes renal retention of salt and water. Moreover, in the adrenal glands, Ang II stimulates the release of aldosterone, which enhances tubular sodium reabsorption in the kidney and increases the effective circulating plasma volume [Figure 1].[4]

In the heart, kidney, and brain, Ang II is also produced by non-ACE pathways namely chymases, cathepsin G, kallikrein-like enzymes and endopeptidases.[2] Ang II acts by binding to the G protein-coupled receptors type 1 (ATR1) and type 2 (ATR2). The ATR1 receptor mediates the more deleterious effects of Ang II - that is, vasoconstriction and cardiac and vascular hypertrophy. The ATR2 receptor regulates opposing effects. In addition to the conversion of AI to Ang II, ACE inactivates two vasodilator peptides, bradykinin and kallidin.[4]
ACE2 and (Pro)Renin Discovery

Recently, ACE2 discovery represents a paradigm shift in RAAS understanding [Figure 3]. ACE2 is a carboxypeptidase whose main function is to degrade Ang II to generate Ang 1–7. Although ACE2 can also degrade Ang I to generate Ang 1–9, its catalytic efficiency is 400-fold higher with Ang II. Therefore, its main effect is the degradation of Ang II to Ang 1–7. Ang 1–7 exerts opposite peripheral actions to those of Ang II by binding predominantly to the Mas1 receptor (Mas1R). The most prominent effect of Ang(1-7) is the inhibition of the AII-induced vasoconstriction apart from its antiarrhythmogenic, antithrombotic, and growth inhibitory effects [Figure 2].

The identification of ACE2 provided evidence that the RAAS had two pathways with opposite effects: The classic ACE/Ang II/AT1R and the new ACE2/Ang 1–7/Mas1R (and AT2R) pathway [Figure 3]. Accordingly, the current scientific opinion is that what is critical in CVD development is an imbalance between ACE-Ang II and ACE2-Ang 1–7. ACE2 is regarded as the central regulator of the RAAS. Changes in ACE2 level/activity can enhance Ang II detrimental actions and negate Ang 1–7 protective effects [Figure 3].

The final entry in our understanding of the RAAS is the (pro)renin receptor [(P)RR], which is a specific receptor for both renin and its inactive precursor prorenin. When (pro)rennin binds to (P)RR, it results in the degradation of angiotensinogen to Ang I and also activates mitogen-activated protein kinases. These mechanisms, independent of Ang II generation, have adverse consequences in terms of organ damage and progression of cardiovascular disease. RAAS is targeted at different places by the existing antihypertensive therapies. ACEIs and ARBs block the feedback loop and increase plasma renin activity (PRA) [Figure 4]. This increase in PRA may limit the organ protection offered by these drugs. The whole RAAS is therefore upregulated although Ang II is blocked. Direct renin inhibitors (DRI) target the RAAS at its point of activation, resulting in the reduction of PRA. Hence, the production of Ang I decreases resulting in less substrate available for conversion to Ang II. In doing so, DRI produces effective overall RAAS suppression.

Figure 1: The activation of systemic renin-angiotensin-aldosterone system cascade for blood pressure control. Journal of Diabetes Research Volume 2016, Article ID 8917578

Figure 2: Renin-angiotensin-aldosterone system. J Diabetes Metab 3:171
Circulating and Tissue Renin-Ang-Aldosterone System

The observation that many tissues were capable of synthesizing the RAAS led to another paradigm shift in RAAS understanding: RAAS is not anymore only a circulating hormonal system but also a tissue system widespread in cardiovascular organs. ACE and Ang II receptors were identified in all the relevant target tissues including the heart, kidney, blood vessels and adrenal glands, where they have not only endocrine but also paracrine and autocrine effects [Table 1].

Agents that Block the RAAS: Their Effects on CVD and Renal Disease

ACE Inhibitors

Oral ACE inhibitors, the oldest category of RAAS inhibitors, were commercially released over 30 years ago in the early 1980s. The introduction of ACE inhibitors heralded major changes in the way HTN and cardiovascular disease was treated. They are categorized into three subgroups according to their mode of metabolism: Active compounds that are metabolized to form inactive metabolites (e.g., captopril); prodrugs that require hepatic metabolism (e.g., enalapril maleate, fosinopril, perindopril, quinapril, ramipril, and trandolapril); and active compounds that are excreted unchanged (e.g., lisinopril). However, ACEIs also differ within these groups in their bioavailability, protein binding, lipid solubility, affinity to the ACE binding site, duration of onset, half-life and potency. ACEIs have proved to be highly successful in the treatment of HTN-related target organ damage, including left ventricular hypertrophy, heart failure, postmyocardial infarction left ventricular remodeling, renal insufficiency and diabetes with proteinuria. The most common reported adverse reactions ascribed to ACEIs include hypotension, renal impairment, hyperkalemia, cough and angioedema.

Table 1: Cellular and tissue effects of Ang II, Ang 1–7, aldosterone, and (pro) renin in normal conditions

<table>
<thead>
<tr>
<th>Tissue</th>
<th>ATII through AT1R</th>
<th>Ang1–7 through MAS1R</th>
<th>Aldosterone through MR</th>
<th>Pro (rennin) through (P) RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiomyocytes</td>
<td>Hypertrophy</td>
<td>Hypertrophy inhibition</td>
<td>Hypertrophy Apoptosis</td>
<td>Hypertrophy Hyperplasia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Oxidative stress</td>
<td></td>
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<tr>
<td>Cardiac fibroblasts</td>
<td>Proliferation</td>
<td>Extracellular matrix production</td>
<td>Anti-proliferative effects</td>
<td>Inhibition of collagen production</td>
</tr>
<tr>
<td>Endothelial cells</td>
<td>Oxidative stress</td>
<td>Inflammation</td>
<td>No production</td>
<td>Anti-inflammatory effects</td>
</tr>
<tr>
<td>Smooth muscle cells</td>
<td>Oxidative stress</td>
<td>Hypertrophy</td>
<td>Anti-proliferative effects</td>
<td>Proliferation Migration</td>
</tr>
<tr>
<td>Macrophages</td>
<td>Inflammation</td>
<td>Anti-inflammatory effects</td>
<td>Inflammation</td>
<td>Oxidative stress</td>
</tr>
<tr>
<td>Heart</td>
<td>Hypertrophy</td>
<td>Fibrosis apoptosis</td>
<td>Antiarrhythmic</td>
<td>Hypertrophy Fibrosis</td>
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<td></td>
<td></td>
<td></td>
<td>Antifibrotic</td>
<td>Proarrhythmicogenic</td>
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<tr>
<td>Vessels</td>
<td>Impaired vascular relaxation</td>
<td>Atherosclerosis</td>
<td>Vasodilation</td>
<td>Impaired vascular relaxation</td>
</tr>
</tbody>
</table>

Figure 3: The new angiotensin (Ang)-converting enzyme 2/Ang 1–7/Mas1R (and AT2R) pathway. Journal of Diabetes Research Volume 2016, Article ID 8917578
Ang II-Aldosterone Escape

The advantages of Ang II reduction by ACE inhibition are substantial but may be compromised in the long term due to “Ang II and aldosterone escape.”[6] Disrupted negative feedback mechanisms cause renin and Ang I concentrations to rise, eventually leading to Ang II escape when non-ACE enzymes such as chymase convert Ang I to Ang II.[6] Similarly, aldosterone escape occurs after long-term ACE inhibitor therapy. Given this scenario, one might expect ACE inhibitors to lose all their efficacy in the long term, but this is not the case. ACE inhibitors also increase concentrations of the vasodilatory peptide bradykinin. Physiologically, bradykinin is regarded to have opposite effects of Ang II, namely it reduces BP, protects the heart and improves arterial function. These bradykinin-mediated effects help counter the “escape” effects and maintain the efficacy of ACE inhibition in the long term.[6]

Ang 1 Receptor Blockers

ARBs prevent the binding of Ang II to AT1 receptors.[2] Vasconstriction, sympathetic stimulation, oxidative stress, release of inflammatory factors and aldosterone release are all reduced by AT1 receptor blockade. Compared with ACE inhibition, selective AT1 receptor blockade has certain distinct advantages, like the absence of Ang II escape by blockade of all Ang II, independent of the site of production.[2] Pure AT1 receptor blockade may, however be a mixed blessing. Ang II increases in response to AT1R blockade allows Ang II to bind to Ang receptors (AT2, AT3, and AT4). AT2 receptor activation causes positive effects
ACEIs and ARBs have been the cornerstone of RAAS inhibition for years and are key therapeutic options in patients with HTN, reducing cardiovascular morbidity and mortality and improving renal outcomes. In the HOPE (Heart Outcomes Prevention Evaluation), MICRO-HOPE (The Microalbuminuria, Cardiovascular, and Renal Outcomes in HOPE), EUROPA (European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease), SOLVD (Studies of Left Ventricular Dysfunction) and Captopril Prevention Project studies. ACEIs were beneficial in reducing rates of death, myocardial infarction, stroke, coronary revascularization, cardiac arrest and complications related to diabetes and heart failure. Both the RENAAL and IDNT trials demonstrated a renoprotective effect of RAAS inhibition in diabetic nephropathy (DN). ACEIs and ARBs are considered to be equally beneficial on the basis of studies such as ONTARGET, which compared telmisartan and ramipril and DETAIL, which compared telmisartan with enalapril and found no difference in progression of diabetic nephropathy.

In patients with HTN and left ventricular hypertrophy, ARB-based therapy, compared with beta-blocker (atenolol)-based therapy with identical BP control, has shown to significantly reduce the composite risk of cardiovascular death, stroke and MI and to decrease the rate of new-onset diabetes (LIFE study).

In patients with chronic heart failure, addition of an ARB to conventional treatment compared with placebo, has been shown to significantly reduce the risk of cardiovascular mortality and hospitalization (CHARM and Val-HeFT studies). In high-risk post-MI patients, ARB therapy has been shown to reduce the risks of all-cause mortality, recurrent MI, sudden cardiac death, revascularization, coronary artery bypass grafting, or all-cause hospital admission to a degree similar to that of ACEI therapy (OPTIMAAL study).

**Mortality Reduction with RAAS Inhibitors In Contemporary Trials of HTN: Are ACE-I and ARB equivalent?**

The most recent meta-analysis of mortality reduction with RAAS inhibition in HTN, published in the European Heart Journal, confirmed a difference between ACE inhibitors and ARBs in terms of mortality reduction in HTN. Overall, there were
76,615 patients from ACE inhibitor trials and 82,383 patients from ARB trials in the meta-analysis. Approximately half of the 158,998 patients were randomized to active treatment (n = 71,401) and half to control (n = 87,597). The relative risk of all-cause mortality fell significantly by 8% (P = 0.036) with RAAS inhibitors. ACE inhibitors were responsible for much of this mortality reduction; 10% (P = 0.004). In contrast, there was no significant relative risk reduction in all-cause mortality with ARBs (P = 0.683). There was a significant difference in treatment effect between ACE inhibitors and ARBs (P = 0.036) [Figure 6].

With regard to cardiovascular mortality, RAAS inhibition was shown to significantly reduce the relative risk of cardiovascular mortality by 7% (P = 0.018). Analysis of nine ARB trials that reported cardiovascular mortality data showed that ARBs were not responsible for this reduction (P = 0.143). Mortality reduction was dominated by the effect of ACE inhibitors, with a relative risk reduction of 12% (P = 0.051) from seven ACE inhibitor trials [Figure 6].

**Dual RAAS Blockade**

The dual blockade strategy comes from the concept called “Ang 2-Aldo escape”. Incomplete blockade of the RAAS with ACEI causes Ang II escape by non-ACE pathways. ARB monotherapy causes lack of negative feedback producing high PRA and consequent increases in AI and AII and AT2R-mediated Aldo escape. Dual blockade would, therefore, provide a more complete blockade of the RAAS. This “maximization approach” however, may induce more adverse effects such as hyperkalemia, symptomatic hypotension or hemodynamically mediated deterioration of renal function. However, the role of dual RAAS blockade in clinical practice is unclear based on large clinical trials both for congestive heart failure (CHF) and chronic kidney disease (CKD).

**Dual RAAS Blockade on Cardiovascular Outcomes**

The valsartan in acute myocardial infarction (VALIANT) study of 14,703 elderly patients with the left ventricular systolic dysfunction, CHF, or both after MI reported similar rates of all-cause mortality, death from cardiovascular events, recurrent MI and hospitalization for heart failure in all three treatment groups (ACEI, ARB, and ACEI/ARB), accompanied by significantly (P = 0.05) more adverse events in the combination therapy group.

Two meta-analyses of patients with CHF or left ventricular dystrophy (CHARM-Added, Val-HeFT, and VALIANT) showed that ACEI/ARB combination therapy significantly increases the risk for adverse events (e.g., HTN, worsening renal function, and hyperkalemia), inducing treatment discontinuation.

The valsartan heart failure trial determined whether valsartan could further reduce morbidity and mortality in patients with heart failure, who were already receiving optimal therapy (including ACEIs in 93% of patients and β-blockers in 35% of patients). The primary end point of mortality was similar for the valsartan and placebo groups, whereas the combined primary end point of morbidity and mortality was significantly reduced (P = 0.009) in patients receiving valsartan plus optimal therapy compared with the placebo group.

Based on this data, dual RAAS blockade could be indicated for the treatment of CHF although hard end point benefits are lacking.

**Dual RAAS Blockade on Renal Outcomes**

In patients with CKD, dual blockade with ACEI/ARB has been shown to reduce BP and proteinuria more effectively than either monotherapy. However, evidence for the benefit of ACEI/ARB combination on hard endpoints in CKD is lacking. In the Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial (ONTARGET), combination therapy with telmisartan plus ramipril produced no greater reduction in the primary end point of death from cardiovascular events, MI, stroke, or hospitalization for heart failure than monotherapy in high-risk patients with cardiovascular disease or diabetes but without heart failure.

The decline of estimated glomerular filtration rate (eGFR) and dialysis requirement was higher with dual RAAS blockade than that of monotherapy group. Combination therapy was associated with an increased risk of hypertension (P = 0.001), syncope (P = 0.03), hyperkalemia (P = 0.001), and acute renal impairment (P = 0.001). However, followup reported that the risks of development and progression of microalbuminuria and macroalbuminuria were lower for those receiving combination therapy (hazard ratio [HR] = 0.88, P = 0.003 and HR = 0.76, P = 0.019, respectively), compared to the ramipril alone. Other metaanalyses have also shown that as compared with ACEI or ARB alone, combination therapy results in 20–30% additional reduction in proteinuria.

The goal of the Veterans Affairs Nephropathy in Diabetes trial (VA NEPHRON-D) was to evaluate whether
combination treatment with ACEI (lisinopril) and ARB (losartan) compared with ARB alone in patients with DN slows the progression of CKD. Patients with diabetes, eGFR of 30.0–89.9 mL/min per 1.73 m² and a UACR of >300 mg/g were included in the study. After 2.2 years, the primary outcome of decrease in eGFR, end-stage renal disease or death occurred in 18.2% in the combination of ACEI/ARB group versus 21.0% in the ARB group \( (P = 0.30) \).\(^{7,14}\) There was increased risk for adverse events in the combination group versus ARB alone, including acute kidney injury (18.0% vs. 11.0%; \( P < 0.001 \)) and hyperkalemia (9.9% vs. 4.4%; \( P < 0.001 \)).\(^{7,14}\) The increased risk for adverse events led to early termination of the trial.

The results of ONTARGET, VA NEPHRON-D confirms that dual RAAS blockade has not shown to be superior to monotherapy in any trial of validated hard renal end points, namely doubling of creatinine, time to dialysis or death. It shows promise in nephrotic syndromes, advanced proinflammatory nephropathy for additional proteinuria reduction. Whether this additional proteinuria reduction translates into meaningful outcomes of CKD is unknown, as proteinuria change is not a validated surrogate end point. Until we know the answer to this question, only those with very high levels of proteinuria should receive combination RAAS blocking therapy with carefully monitoring.

DRI

Renin secretion is the first step of the RAAS cascade.\(^{3,8}\) Inhibition of renin provides an attractive option to inhibit the RAAS from its origin.\(^{4}\) The development of DRI started >30 years ago, but there were issues with potency, bioavailability and cost. At present, aliskiren is the only approved DRI for use in HTN and a significant BP reduction has been demonstrated in patients with essential HTN.\(^{3,8}\) Aliskiren is well tolerated and has a similar dose-dependent BP reduction in hypertensive patients as ARBs.\(^{4}\)

However, several recent studies have shown either no benefit or even harmful effects of aliskiren in certain populations. The Aliskiren in Type 2 Diabetes Using Cardio-Renal Endpoints trial (ALTITUDE) randomly assigned patients with type 2 diabetes and CKD or with cardiovascular disease already on ACEI or ARB to aliskiren or placebo.\(^{7,13}\) Although there was a lower BP in the aliskiren arm, there was no reduction in the primary composite outcome, which included cardiovascular and renal events and mortality.\(^{7,13}\)

In the Aliskiren Trial to Minimize Outcomes in Patients with Heart failure (ATMOSPHERE trial), the addition of aliskiren to enalapril in patients with chronic heart failure was not associated with reduction in adverse outcomes.\(^{7}\) Similarly, no improvement in coronary atherosclerosis in prehypertensive patients (AQUARIUS) or improvement in cardiovascular outcomes in patients hospitalized with heart failure (ASTRONAUT) was seen with aliskiren compared with placebo.\(^{7}\) Given the lack of demonstrated benefit and increased rates of adverse events such as hyperkalemia, hypotension, and renal impairment as seen in ASTRONAUT when combined with ACEIs or ARBs, the current use of aliskiren in combination is limited.\(^{7}\)

Mineralocorticoid Receptor Antagonists (MRA)

MRAs competitively inhibit mineralocorticoid receptors and decrease the number of epithelial sodium channels in the distal renal tubule.\(^{9}\) Spironolactone has long been used for the treatment of HTN; however, it is non-specific for mineralocorticoid receptors and has anti-androgenic and progestational effects. Spironolactone was found to be the most effective add-on antihypertensive drug in treating resistant HTN in the PATHWAY-2 trial.\(^{7}\)

This trial supports the important role of sodium retention in resistant HTN. Eplerenone, an MRA with lower affinity to progesterone and androgen receptors than spironolactone, has been shown to be efficacious and safe in the management of HTN. The third- and fourth-generation MRAs are being developed having the potency of spironolactone and the selectivity of eplerenone.\(^{7}\) Finerenone, a novel nonsteroidal MRA, has a greater affinity to the mineralocorticoid receptor than eplerenone and greater selectivity than spironolactone.\(^{9}\)

The Mineralocorticoid Receptor Antagonist Tolerability Study (ARTS) finerenone (2.5–10 mg per day), decreased albuminuria with lower rates of hyperkalemia compared with spironolactone in patients with CKD and albuminuria.\(^{7}\) The recent Mineralocorticoid Receptor Antagonist Tolerability Study–Diabetic Nephropathy (ARTS-DN) study demonstrated greater reduction in albuminuria with the addition of finerenone to ACEI or ARB in patients with DN compared with placebo.\(^{7}\)

ACE inhibition, AT1R antagonism and MR blockade are some of the most classic therapeutic strategies against CVD. Another classic therapeutic strategy against heart failure is to increase natriuretic peptide levels as they are natriuretic, diuretic and vasodilating and able to inhibit pathologic growth in heart failure.\(^{4}\) These approaches included short-term intravenous infusions of natriuretic peptides or inhibition of neprilysin, which is the enzyme that degrades natriuretic peptides along with bradykinin, adrenomedullin and Ang II. The disappointing effect of neprilysin inhibitor was that neprilysin also degraded Ang II. Therefore, inhibiting neprilysin would increase both natriuretic peptides and Ang II and with it the detrimental effects of AT II. Hence, the combination of an ACEI and a neprilysin inhibitor was tried. Unfortunately, in clinical trials, this combination was associated with bradykinin-mediated angioedema. To overcome this issue, ARNIs were developed, such as LCZ696, which is an association of the ARB valsartan with the neprilysin inhibitor sacubitril.\(^{14}\) In the PARADIGM and the PARAMOUNT trial, this valsartan/sacubitril combination was found superior to enalapril in reducing the risk of death and hospitalization in patients with heart failure.\(^{4}\) This is consistent with experimental models where it showed significantly reduced cardiac hypertrophy and fibrosis with improved ejection fraction.\(^{14}\)
Aldosterone Synthase Inhibitors

Another way of blocking the effects of mineralocorticoid receptor activation is to inhibit aldosterone formation. LCI699 is a potent first-in-class aldosterone synthase inhibitor. In patients with primary hyperaldosteronism, LCI699 (up to 1.0 mg twice a day) caused modest reduction in 24-h systolic BP (SBP) and office SBP compared with placebo. LCI699 significantly lowered office and ambulatory BP in patients with primary HTN, but 20% of the patients on LCI699 developed blunted cortisol release. Due to this non-specificity, the development of LCI699 has been stopped in favor of developing more specific inhibitors.

New Agents for New Targets [Figure 7]

ACE2 Replenishing Strategies

A promising therapeutic strategy in cardiovascular medicine is represented by RAAS modulation. As compared to RAAS antagonism, RAAS modulation combines ACE/AngII/AT1R blockade with the stimulation of ACE2/Ang1-7/Mas1R and AT2R. The latter can be achieved by a series of new therapies that include ACE2 replenishing strategies, Ang 1–7 administration and AT2R agonists. The current therapeutic tools that modulate ACE2 levels/activity include adenoviral ACE2 gene transfer, recombinant human ACE2 (rhACE2), ACE2 activators, oral ACE2 and Ang 1–7 bioencapsulated in plant cells. Both ACE2 gene transfer and the administration of an ACE2 activator have ameliorated diabetic cardiomyopathy. rhACE2 administered intravenously to healthy human subjects was well tolerated and has resulted in sustained reduction in plasma Ang II levels and elevation in Ang 1–7 levels.

Ang 1–7 Administration

Several experimental studies have tested the hypothesis that Ang 1–7 infusion could ameliorate diabetic cardiomyopathy. Ang 1–7 improved all the structural hallmarks of diabetic cardiomyopathy. Ang 1–7 improved cardiac recovery from ischemia/reperfusion and restored the normal vascular reactivity. These effects were completely blocked by the Mas1R antagonist, suggesting that Mas1R was the main receptor mediating Ang 1–7 effects on endothelial cells.

AT2R Agonists

AT2R activation has been currently achieved by compound 21 (C21), which is a non-peptide that acts as a highly selective AT2R agonist and stimulates AT2 receptors. Several studies have shown its efficacy in reducing cardiac tissue fibrosis. C21 was also able to significantly reduce renal fibrosis in experimental models. C21 was able to significantly reduce the expression of several inflammatory mediators.

RAAS Blockade: Renoprotection Versus Renoprevention

While it has been shown that RAAS blockade is cardioprotective, renoprotective and hence being extensively used in clinical practice, its continued use in certain clinical settings could have deleterious effects on the kidneys. For example, continuation of RAAS blockers during episodes of volume depletion - diarrhea, during use of nonsteroidal anti-inflammatory drug, perioperatively during episodes of hemorrhage, and severe infections can precipitate acute kidney injury. Patients not only need to be educated regarding the renal benefits of RAAS blockage in the long term but also to be educated regarding stopping RAAS blockade in the short term during episodes of volume depletion - thereby gaining renoprotection.

Conclusion

The RAAS has been studied for more than a century. The current picture of the RAAS is that of an extremely complex pathway, which has not yet been fully characterized and might hold in store new aspects that have still to be discovered. Certainly, what we do know is that blocking Ang II reduces cardiovascular and renal complications. This is particularly true in diabetes, where Ang II/AT1R pathway is activated, whereas the Ang 1–7/Mas1R is not. Therefore, the aim of new therapies is not only to block ACE/AngII/AT1R-mediated harmful effects but also to augment the activity of potentially beneficial pathways, with the stimulation of ACE2/Ang 1–7/Mas1R and AT2R. Here is another paradigm shift: To move from RAAS inhibition to RAAS modulation.

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