Biochemical Pharmacology 78 (2009) 933–940

Contents lists available at ScienceDirect

Biochemical Pharmacology

journal homepage: www.elsevier.com/locate/biochempharm

Commentary

The biochemical pharmacology of renin inhibitors: Implications for translational medicine in hypertension, diabetic nephropathy and heart failure: Expectations and reality

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ARTICLE INFO

Article history:
Received 3 March 2009
Accepted 18 May 2009

Keywords:
Renin
Prorenin
Direct renin inhibitors (DRI)
Angiotensin I-converting enzyme (ACE)
ACE inhibitors (ACEi)
Angiotensin II (AngII)
Angiotensin II receptors (AT1R, AT2R)
Angiotensin receptor blockers (ARBs)
Nitric oxide (NO)
Hypertension
Diabetic nephropathy (DN)
Chronic heart failure (CHF)
Juxtaglomerular apparatus (JGA)
Plasma renin activity (PRA)
Atrial natriuretic peptide (ANP)
Plasma renin activity (PRA)

ABSTRACT

The renin–angiotensin–aldosterone system (RAAS) plays a dominant role in the pathophysiology of hypertension, *Diabetes mellitus* (DM), chronic kidney disease (CKD) and chronic heart failure (CHF). Therefore, drugs that block key components of the RAAS such as ACE inhibitors (ACEi) and angiotensin receptor blockers (ARBs) have gained wide clinical use for these indications. Despite progress, the morbidity and mortality of patients treated with ACEi or ARBs remain high. Small molecules that directly inhibit renin (DRI) and are orally active have also been developed and one such drug, aliskiren, was introduced into clinical use for treatment of hypertension in 2007. Further clinical trials aimed to expand the therapeutic use of aliskiren are in progress for CKD–DM and CHF. In this review we analyze and review the translational medicine prospects of aliskiren in respect to the biochemical pharmacology of the RAAS, the marketed RAAS modulators and the new emerging science regarding the role of prorenin, renin and renin receptors in cardiovascular biology and disease. The information already gained with aliskiren, raises questions regarding the advantages of DRIs as monotherapy compared to marketed ACEis and ARBs, their potential added value in combination with other RAAS modulators and other unproven benefits in relation to prorenin and renin receptor biology. This review will also indicate basic and clinical research needs that are critical to determine whether DRIs can provide meaningful added medical benefits over contemporary medicines that regulate the RAAS, and the need to identify patients that are more likely to benefit from DRIs and any possible long term adverse effects.

1. Introduction

Although renin, the first and rate-limiting component of the renin–angiotensin–aldosterone system (RAAS) was discovered over a century ago, the physiological and pathophysiological aspects of this system are still not fully elucidated. According to the classic paradigm, renin is secreted from the renal juxtaglomerular apparatus (JGA) into the circulation, where it acts on angiotensinogen yielding inactive angiotensin I (AngI). AngI is converted to angiotensin II (AngII) in the lungs by angiotensin converting enzyme (ACE) a dipeptidyl carboxypeptidase (Fig. 1) [1]. However, additional members of the RAAS and their biosynthetic pathways have been determined in the last decade. For instance, in addition to AngII, a wide spectrum of bioactive angiotensin peptides, such as angiotensin III (AngIII), angiotensin IV (AngIV), and angiotensin 1–7 (Ang 1–7), have been identified (Fig. 1) [2,3]. The latter is synthesized by ACE2, a new RAAS member ACE homologue insensitive to ACE inhibitors (ACEi) [4,5]. At least 4 receptors interact with these angiotensin peptides, AT1, AT2, AT4 and Mas (Fig. 1) [6,7]. The canonical biological actions of AII are mediated primarily through the AT1 and AT2 receptors [1] known to belong to the 7-transmembrane, G protein-coupled (GPCR) receptors. In humans, most of the biological activities of AII are mediated through the AT1 receptors, which are ubiquitously expressed in the vasculature, kidney (the JGA and mesangial cells) and heart. Stimulation of AT-1 receptor activates phospholipase A2, C, D, resulting in increased cytosolic Ca^{++}, IP3 and inhibition of adenylate cyclase. In contrast, activation of AT2 receptor results

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doi:10.1016/j.bcp.2009.05.018

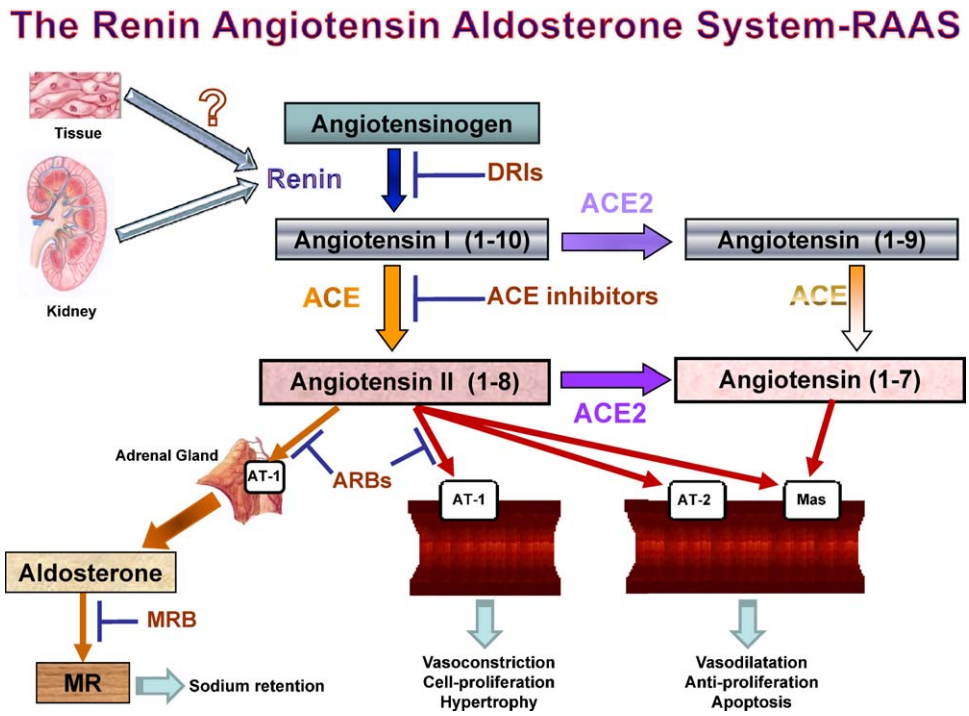

Fig. 1. The renin angiotensin-aldosterone system. ACE: angiotensin converting enzyme, ACE2: angiotensin converting enzyme-2, ARBs: angiotensin receptor blockers. AT-1, angiotensin receptor type-1, AT-2, angiotensin receptor type-2, AT-4, angiotensin (3–8) receptor type-4, MR: mineralocorticoid receptor, MRB: mineralocorticoid receptor blockers. Modified from Staessen et al. [42].

in increased nitric oxide (NO) and bradykinin levels, leading to elevated cGMP concentrations and vasodilation [1]. The Ang 1–7 peptide binds to the Mas receptors, which mediate vasodilation and antiproliferative actions, most likely via an NO dependent mechanism [1,8]. AngIV biology is still poorly understood [1].

The discovery of the renin receptor has added intriguing dimensions to the RAAS complex biology. Renin, considered until recently to serve the sole biological action of rate-limiting enzyme in activation of the RAAS, has turned out to also be a ligand to a protein termed the renin/prorenin receptor (RPR), which binds renin and prorenin about equally regardless of their biological activities. RPR is a transmembranal receptor, abundantly expressed in human mesangial cells, heart, brain, visceral adipose tissue and vascular smooth muscle cells of coronary arteries and kidney arteries [1,9,10]. Prorenin represents 70–90% of the total circulating renin in normal subjects and up to 95% in diabetic patients [1,10,11]. Prorenin, a catalytically inactive zymogene, binds to the RPR and induces an increase in the catalytic efficiency of Angiotensinogen conversion to AngI, which contributes to local production of AngII and its systemic levels (Fig. 2) [12]. In addition, binding of pro (renin) to its receptors initiates an intracellular signal associated with activation of mitogen-activated protein kinase (MAPK), ERK1 and ERK2, and phosphorylation of heat shock protein 27 (HSP27), leading to enhanced synthesis of DNA, plasminogen activator inhibitor-1 (PAI-1), collagen-1, fibronectin and transforming growth factor-β1 (TGF-β1), which are known to mediate vascular fibrosis/remodeling in various disease states [10,13–18]. These recent discoveries might have importance for the potential pharmacology of direct renin inhibitors (DRIs) (*vide infra*). It is well established that the RAAS is inherently involved in cardiovascular and renal diseases, as well as in stroke [19–21]. Traditionally, AngII, has been considered to be the major bioactive effector of the RAAS-induced hemodynamic and inflammatory changes in several organs including heart, kidney, brain, and vasculature [22,23]. Circulating or locally produced AngII promotes stimulation of extracellular matrix synthesis, hypertrophy, induction of chemokines, generation of reactive oxygen species, apoptosis, and proliferation of vascular smooth muscle cells (VSMC), accompanied by the inhibition of nitric oxide (NO) generation (Fig. 3) [22,24,25]. However, increasing evidence has demonstrated that aldosterone *per se*, beyond its effects on renal sodium handling, is also an important mediator of both cardiovascular and kidney injury (Fig. 3) [26–31].

2. Therapeutic rationale for RAAS modulators

The role of AngII and aldosterone in some cardiovascular diseases [1,27,30,31] have lead to the development of several classes of RAAS inhibitors: (1) ACE inhibitors, which block the conversion of AngI to AngII; (2) angiotensin II receptor type 1 (AT1) blockers (ARBs), and (3) mineralocorticoid receptor blockers (MRB) that inhibit aldosterone action via the MR receptor. Although, it is generally accepted that ACE inhibitors, ARBs and MRB reduce the morbidity and mortality from diverse cardiovascular and renal conditions [32–37], their overall efficacy is limited, leaving substantial unmet medical needs. The limitations of ACEi and ARBs are attributed in part to the interruption of AngII negative input on renin release resulting in compensatory renin release and increased plasma renin activity (PRA) (Fig. 4) [38,39]. Moreover, ACEi produce an increase in plasma AngI levels, which can be converted in the tissues to AngII by ACE independent pathways such as chymase, an enzyme resistant to ACEi [40,41]. In view of the belief that insufficient suppression of the RAAS by ACEi or ARBs (inherent to the negative feedback loop of renin release) does not sufficiently fulfill unmet medical needs, efforts have persisted to develop DRIs. Although potent and selective DRI compounds have been developed [42], none realizes clinical requirements owing to limited oral bioavailability [43]. However, in 2007, aliskiren, a potent and selective renin inhibitor, of still very low oral availability (<3%), but long duration of action (half-life of about 40 h), was approved for clinical use in treating hypertension [42]. The addition of aliskiren to the arsenal of RAAS inhibitors provided

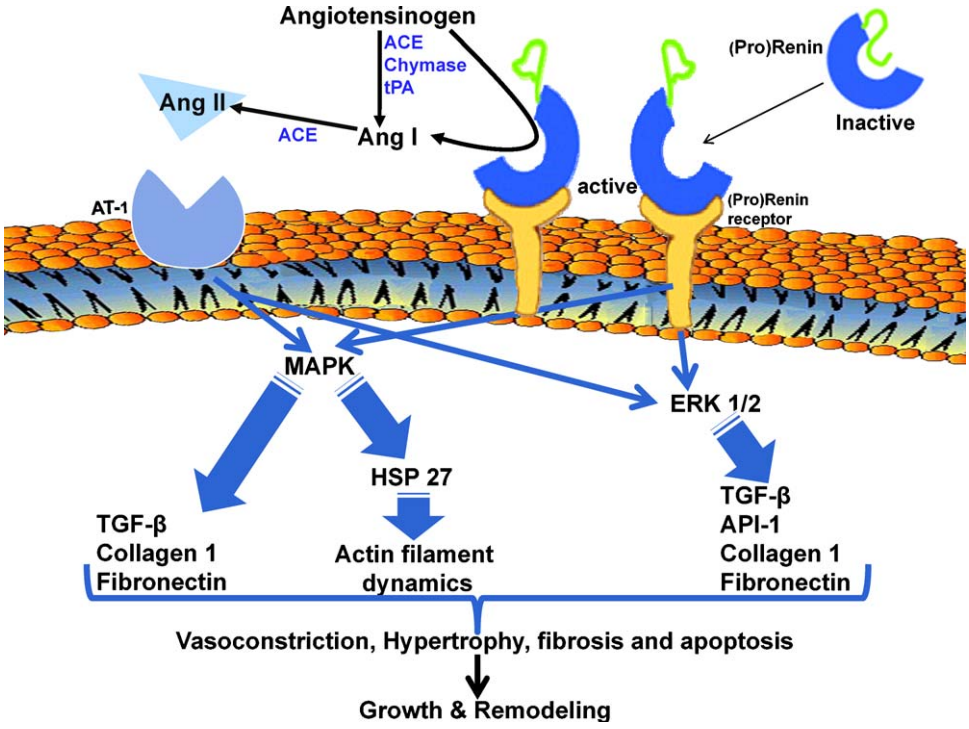

Fig. 2. Biochemical actions of (pro)renin and angiotensin II type 1 receptors. ACE: angiotensin converting enzyme, ERK/1, 2: extracellular signal regulating kinase 1/2, MAPK: mitogenic-activated protein kinase, Hsp-27: heat shock protein 27, PAI-1: plasminogen activator inhibitor-1, tPA: tissue plasminogen activator, TGF-β1: transforming growth factor-β1. Modified from Nguyen [98].

for the first time an opportunity to probe the translational medicine perspectives of DRIs with respect to contemporary RAAS modulators—the ACEi, ARBs and aldosterone receptors blockers.

3. Can DRIs/aliskiren play new role in treatment of hypertension?

Hypertension is a common clinical condition, which affects about 25% of the adult population in the Western world and is one of the leading causes of cardiovascular, renal, and cerebral diseases [44]. Despite the availability of multiple drugs in the therapeutic arsenal for hypertension, about one third of patients with high blood pressure fail to reach targeted reductions in blood pressure (BP) even when treated with multiple anti-hypertensive agents [45,46]. In such regimens, RAAS blockade (primarily by ACEi or ARBs) is the 'mainline' management strategy to lower BP [47]. ACEi or ARBs simply cannot sufficiently suppress the RAAS due to the removal of the negative feedback loop induced by AT1 receptors on renin release (Fig. 4). Therefore, the development of selective, orally active DRIs have been considered a rational strategy to enhance the efficacy of ACEi, ARBs and diuretics (e.g., thiazides, which are known to elevate renin); this consideration has been the classical motive for the discovery and development of DRIs in spite of the fact that more that 100 drugs are already marketed to control high BP.

4. Pre-clinical profile of aliskiren in an experimental hypertension model

Studies in experimental animals have demonstrated that aliskiren is highly effective in reducing blood pressure in sodium-depleted normotensive marmosets [48,49]. In these studies, aliskiren was at least as potent as the ARB, valsartan, or the ACE inhibitor, benazepril. In spontaneously hypertensive rats, aliskiren dose-dependently decreased BP. Moreover, and as per clinical forecasts, aliskiren also potentiated the anti-hypertensive efficacy of low doses of ARBs (valsartan) or ACEi (benazeprilat). In these studies, the anti-hypertensive effects of aliskiren were greater and of longer duration than either the ACEi or the ARB [49] (Table 1). Such an advantage, however, has not so far been reproduced in clinical studies.

5. Clinical profile of aliskiren in hypertension

Initial clinical studies [50–56] in normotensive volunteers administered aliskiren (up to 640 mg/day) established satisfactory tolerance [54]. These early studies also established the expected effects on plasma renin activities (albeit at high doses) (Table 1). Moreover, aliskiren induced more profound renal vasodilatation in normal volunteers as compared to that induced by ACE inhibitors [57], which is a potentially important property to distinguish the DRIs from ACEi and ARBs in diabetic nephropathy [58]. Aliskiren

Table 1
Advantages and disadvantages of aliskiren vs. other RAAS inhibitors.

RAAS inhibitors	AngI	AngII	Renin	PRA	PAC	$T_{1/2}$ (h)	Bioavailability	Cough	Diarrhea	Angioedema
ACEIs	↑	↓	↑	↑	↓	2–25[a]	High	++	–	++
ARBs	↑	↑	↑	↑	↓	2–24	High	+	–	+
Aliskiren	↓	↓	↑	↓	↓	40	Low	–	+	–

AngI: angiotensin I; AngII: angiotensin II; PRA: plasma renin activity; PAC: plasma aldosterone concentration, $T_{1/2}$: half-life.
[a] Excluding ramiprilat, which has $T_{1/2}$ of >50 h.

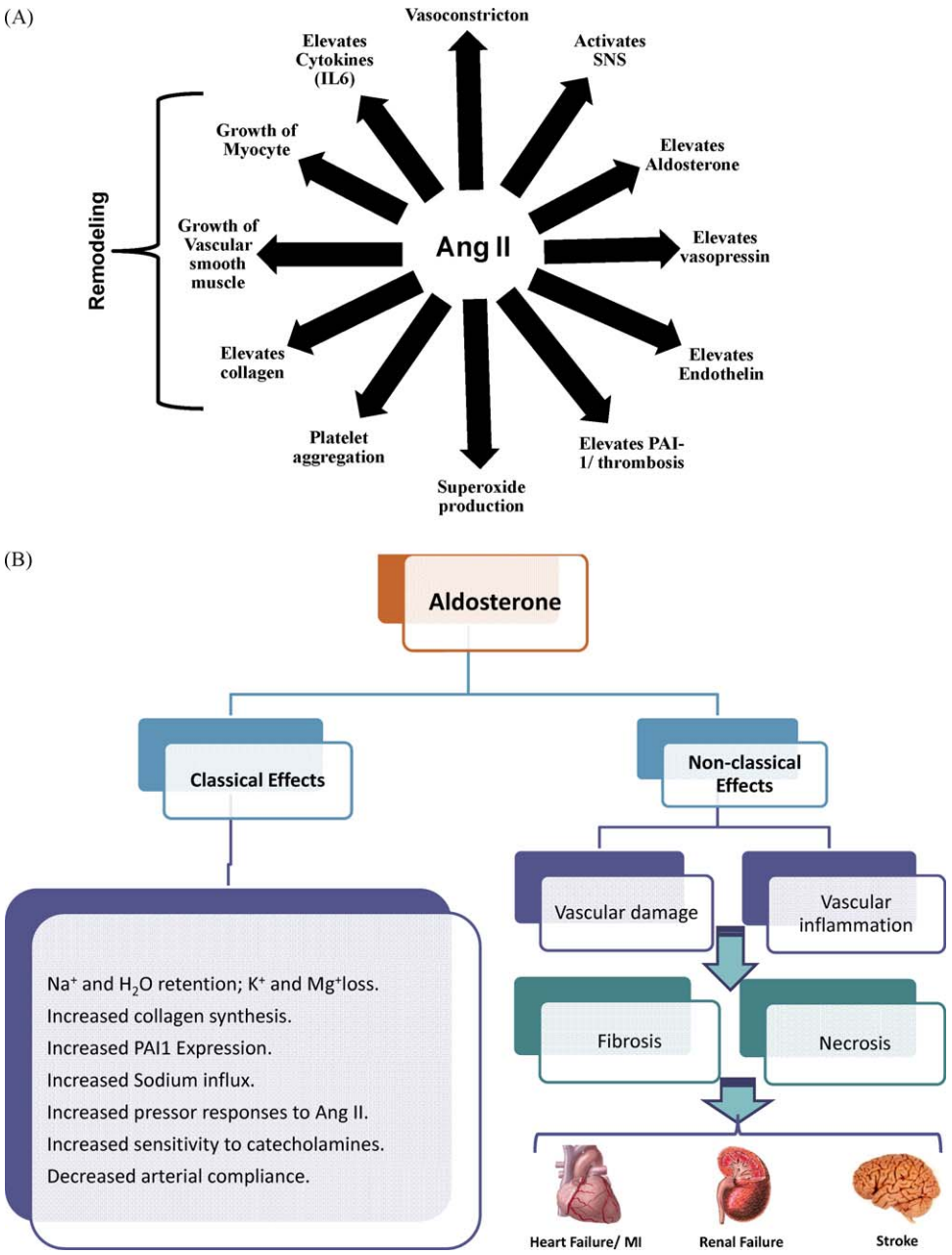

Fig. 3. Deleterious effects of angiotensin II (A) and aldosterone (B). AngII: angiotensin II, plasminogen activator inhibitor-1 (PAI-1), SNS: sympathetic nervous system.

monotherapy in patients with mild to moderate hypertension at doses of 150 mg/day is equivalent to standard doses of ACEi (lisinopril), or losartan (ARB) [50–55].

When administered at higher doses (300–600 mg/day), aliskiren was superior to 150 mg/day of Irbesartan (ARB) in reducing BP [52]. Moreover, when used in combination therapy with maximal doses of ACEi, ARBs, calcium channel blockers (CCBs) and diuretics, aliskiren (150–300 mg for several weeks) improved the reduction in BP as compared with monotherapy (Fig. 5) [59].

It should however be emphasized that a combination of ACEi and ARBs could yield similar reductions in BP over a combination of ACEi and aliskiren or ARBs and aliskiren. Furthermore, considering the unknown potential adverse effects of supplementation of chronic DRIs, the risk vs. benefits of a combination of DRIs with contemporary RAAS modulators awaits further post-marketing experience and pharmacovigilance. One such unknown may be associated with the significantly higher reactive plasma renin and prorenin [56], which even though it may lack enzymatic activity, can still bind and signal through the RPR receptor, a signaling pathway of still unknown implications. Moreover, like other RAAS blockers, which acutely decrease aldosterone levels but fail to act as anti-aldosterone compounds on a chronic basis (aldosterone escape), it is likely that the same phenomenon exists for renin inhibitors. Taking into account these factors concerning the pharmacology of DRIs, one may query the rationale for using such a new combination, namely, aliskiren with classic RAAS inhibitors, in hypertensive patients if the similar efficacy can be achieved with suitable standards of care (ACEi and ARBs)? In this regard, withdrawal of aliskiren from patients with hypertension did not cause rebound in BP, an advantage that needs confirmation in clinical trials. Moreover, a moderate anti-hypertensive effect (possibly due to continuous suppression of renin) seems to last several weeks after drug cessation [52]. Unfortunately, the full efficacy of DRIs might not be realized via aliskiren pharmacology owing to limited tolerance (see Table 1) that capped aliskiren dosage to 300 mg/day. Thus, it is possible that DRIs with improved

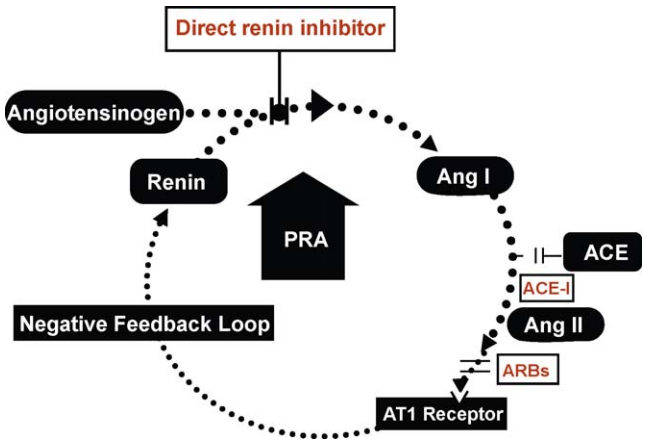

Fig. 4. Direct renin inhibitor neutralizes the compensatory rise in plasma renin release/activity induced by the removal of the angiotensin II negative feedback on the juxtaglomerular cells by ACEIs and ARBs. AngI: angiotensin; ACE: angiotensin converting enzyme; ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; AT1: type 1 angiotensin II receptor; PRA: plasma renin activity.

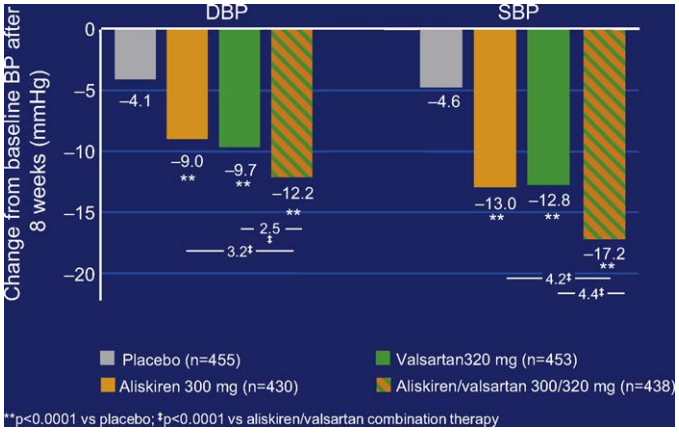

Fig. 5. Effects of aliskiren or valsartan given as monotherapy or in combination on diastolic and systolic blood pressure in patients with mild-to-moderate hypertension. BP: blood pressure; DBP: diastolic blood pressure; SBP: systolic blood pressure (based on data from Oparil et al. [59]).

tolerance may prove to be more effective and safe over aliskiren considering the unique effects of aliskiren in reducing cardiovascular risks (e.g., atherosclerosis, dyslipidemia) and improved NO release [60–62].

In summary, it appears at this time that when taken as monotherapy for treatment of high BP, aliskiren does not provide a greater reduction in BP than ACEi or ARBs. This conclusion is supported by a recent meta-analysis of available clinical studies [63]. With regard to the combination of aliskiren with ACEi or ARBs, preliminary clinical studies in hypertension have suggested the possibility that such a combination can "push the efficacy envelope", however the very limited additional efficacy that such a combination might realize does not exceed that of ACEi combined with ARBs [64], while leaving the tolerance, safety and end-organ protection of prolonged use of aliskiren (alone or in combination) in BP management to be demonstrated. It is however noteworthy that a combination of aliskiren with CCBs was associated with lower rates of edema than that found with the latter drug alone [54].

6. Can DRIs/aliskiren play new role in treatment of diabetic nephropathy?

Diabetic nephropathy (DN) is a common complication of *Diabetes mellitus* (DM), and is currently the leading cause of end-stage renal disease (ESRD) in the Western world, reaching 'epidemic' proportions [65].

The RAAS is thought to play a central role in the pathogenesis of DN [66–68]. Evidence supporting a role of the RAAS in DN is based on large prospective, randomized, clinical trials showing the beneficial effects of ACEi, ARBs and MRBs in slowing the progression of DN to ESRD [20,21,69]. These findings are intriguing considering that in most diabetic patients PRA is not elevated or is even suppressed [67,70]. It has been suggested that in DN a local intrarenal activation of RAAS leads to increased local generation of AngII [71]. The discovery of the RPR pathway (*vide supra*) may indicate that this mechanism may in fact be the previously unrecognized source of intrarenal activation of AngII [68,72–74]. Indeed, it was demonstrated that patients with diabetes have high circulating prorenin levels. Furthermore, increased serum prorenin has been proposed as a biomarker that predicts the onset of microalbuminuria in DM patients [72,75]. Experimental models of DM further support new roles for RPR in renal physiology and disease pathology via prorenin synthesis in the collecting tubules that may not be subjected to negative feedback inhibited by AngII [68,73].

Preliminary studies with aliskiren in DN seem to be more promising with respect to the possibility that DRIs might possess unique benefits in DN surpassing the ACEi or ARBs. In experimental studies in hypertensive diabetic (streptozotocin) rats (transgenic, engineered to express the mouse renin gene, mRen-2), aliskiren demonstrated equal efficacy to ACEi (perindopril), at lesser antihypertensive efficacy indicating a more direct and prominent renal protective action in reducing albuminuria, fibrosis and glomerulosclerosis [76]. Using the same experimental model, aliskiren efficacy as reno-protective agents was confirmed while shedding further light on possible mechanisms of action, including: suppression of TGF-β, collagen I and prorenin receptor expression in glomeruli, tubuli and cortical blood vessels [77]. Thus, it appears that DRIs may have a mechanistic novel effect that could convey advantage over ARBs and ACEi in DN management.

The experimental models used so far provide good congruency to clinical reality. In a small clinical study with DM patients, aliskiren significantly reduced urinary albumin/creatinine ratio as well as 24-h systolic BP [78]. The AVOID (Aliskiren in the Evaluation of Proteinuria in Diabetes), study in patients with DM with nephropathy and hypertension extended the exploration on the potential role of aliskiren as adjunct treatment to standard care [79]. In this study, aliskiren added to standard care with ACEi for 3 months each, reduced overall urinary albumin/creatinine ratio by 20% and in about a quarter of patients almost 50%—twice as many compared with placebo [79]. Interestingly, BP was only minimally reduced (1–2 mmHg) in the aliskiren treated group, indicating that aliskiren may have direct, BP-independent renal protective effects. Overall, early experimental and clinical reports indicate the possibility that DRI/aliskiren might convey unique renal benefits beyond those of traditional RAAS modulators. Further studies are needed to confirm the long-term safety and efficacy of aliskiren/DRIs as preferred adjunct treatment in the management of DN in DM patients [80].

7. Can DRIs/aliskiren play new role in treatment of chronic heart failure (CHF)?

Activation of the RAAS in patients with CHF is well documented and also the therapeutic and prophylactic benefits from ACEi, ARBs and MRB [81,82]. In fact, these RAAS modulators won a 'corner stone' status in management of all CHF stages as well as other cardiac diseases. In fact, it has already been shown that combination of contemporary RAAS modulators add medical

benefits over monotherapy with any RAAS modulators, albeit at the expense of an increase in specific adverse events [83,84].

The undisputed success of the ACEi and ARBs in the prevention and treatment of CHF poses the question of whether aliskiren/DRIs might still have any potential role in CHF management. The rationale for the expectation for preferred combination of DRIs with other RAAS modulators has been explained *vide supra*, i.e., in amelioration of the increase in PRA as the result of omission of AngII negative control on renin release. In experimental models (double transgenic rats, dTRG [85]) of cardiac stress and injury, aliskiren improved cardiac function (systolic and diastolic performance), preserved structure (cardiac hypertrophy and left ventricular wall thickness) and reduced biomarkers of cardiac stress and failure such as ANP. In mice subjected to cardiac ischemia, aliskiren, at a dose that did not affect systemic BP, improved systolic and diastolic left ventricular function and ameliorated cardiac hypertrophy, lung weight, and left ventricular dilatation, compared with placebo treated mice. In addition, aliskiren suppressed ischemia induced activation of inflammation signaling pathways (MAP kinase P38, ERK1/2, AKT) and apoptosis (bax and bcl-2). Such data support the notion that aliskiren shares actions of other RAAS modulators possibly due to lowering AngII in improving cardiac function in ischemic conditions, possibly separate from BP lowering pharmacology [86].

Data from clinical studies on the effects of DRIs in patients with CHF are limited and incomplete [87]. "Older DRIs", enalkiren and remikiren were tried in patients with CHF and found to perform favorably to preserve cardiac function (e.g., cardiac index, left ventricular filling pressure, systemic vascular resistance and pulmonary artery and capillary wedge pressure [88,89]). More recently, it has been reported [90] that aliskiren equals ACEi (ramipril) short term efficacy in CHF patients. While the above studies were done in small groups of patients they follow the pattern seen in hypertension and DN studies. In the only combination study to day of aliskiren and other RAAS inhibitors, the Aliskiren Observation of Heart Failure Treatment (ALOFT) study [91] the addition of aliskiren significantly decreased circulating levels of the BNP (a biomarker of heart failure) and improved ventricular dysfunction [87,91]. Urinary aldosterone excretion was also reduced by aliskiren. These findings indicate that addition of aliskiren to current treatment of CHF may have some favorable functional and neurohumoral effects [91]. It is however important to note that there are still no clinical outcome data showing any benefits for a combination of aliskiren in CHF nor are there data to indicate that a aliskiren combination with other RAAS modulators could provide a better benefit/risk management profile.

8. Pharmacokinetic and interaction between aliskiren and other drugs

The absorption, distribution, metabolism, excretion, and interaction of aliskiren with other drugs that do not necessarily affect the RAAS, has been evaluated both experimentally and clinically [92–95]. Studies investigating the disposition of oral doses of [14C]aliskiren in rats, marmosets and humans demonstrated that excretion of an oral dose occurred almost exclusively (>90%) in the feces, mainly as unchanged aliskiren. A small proportion of the absorbed dose was excreted in the form of oxidized metabolites, probably derived from oxidation by cytochrome P450 (CYP). However, no interaction of aliskiren with cytochrome P450 isoenzymes was found in human liver microsomes *in vitro*, suggesting a low potential for clinically significant drug interactions of aliskiren. Indeed, aliskiren showed no clinically significant increases in exposure during coadministration with a wide range of potential concomitant medications. For instance, no clinically relevant pharmacokinetic interactions have been observed between aliskiren and the CYP substrates celecoxib, digoxin, lovastatin or warfarin, or the CYP inhibitor cimetidine, in healthy volunteers [93,94]. Animal and human studies indicate that aliskiren is a substrate for the efflux transporter P-glycoprotein, which may play a role in the hepatobiliary/intestinal excretion of the drug [96]. However, the lack of pharmacokinetic interaction between aliskiren and the P-glycoprotein substrate digoxin indicates that aliskiren does not inhibit P-glycoprotein activity). Nevertheless, coadministration of ketoconazole (200 mg twice-daily) with aliskiren resulted in an approximate 80% increase in plasma levels of Aliskiren [96]. Additional concern is the fact that coadministration of aliskiren and furosemide significantly reduces the later blood concentrations, but had a minor effect on aliskiren pharmacokinetics [97]. It is noteworthy to indicate that cyclosporine increases blood concentrations of Aliskiren.

9. Could biomarkers that identify patients that have a higher likelihood of response to DRIs vs. poor or low responders improve translational medicine perspectives of aliskiren/DRIs?

As indicated in previous sections, the overall efficacy of aliskiren has not differentiated itself from contemporary RAAS modulators-ACEi and ARBs. One important aspect in reference to more successful translational medicine is whether or not a more specific patient population can be identified for DRIs treatmet. One consideration regarding such a possibility could be patients that display unusual high responses in plasma renin and plasma renin activities as a result of treatments with drugs that increase plasma renin activity such as ACEi, ARBs, MRB and diuretics. Systematic retrospective analysis of all studies with aliskiren to probe individual responses vs. comparators (in any of the indications pursued so far) might provide further insights into this option. In addition, candidate gene profiling might also help identify patients who are poor or high responders to DRIs allowing for genotypic screening for targeted drugs for the most likely responders while omitting those who will probably have no particular benefits.

10. Summary and perspectives in overall translational medicine

The introduction of renin inhibitors into clinical practice as part of the already substantial armamentarium of RAAS modulators is clearly a triumph of modern drug discovery and development. Advances in enzymology, medicinal chemistry, crystallography, molecular modeling and advances in the understanding of chemical–biological interactions of small molecules with large proteins have overcome what appeared to be insurmountable technical and scientific hurdles over several decades. Ironically, by the time the first potent, selective and oral DRI was launched for clinical use, the expected medical benefits from renin inhibition seem to be questionable. This position is based on early (2 years) clinical experience with aliskiren monotherapy and preliminary studies of its use in combination with other RAAS inhibitors (aimed to 'boost efficacy') in treating hypertension, chronic kidney disease (CKD) and heart failure. Aliskiren appears to primarily match contemporary RAAS inhibitors, alone or in combination for all the above clinical indications. However, new science regarding the RPR and its signaling pathways, new data regarding the role of local renin production under different regulatory principles (no negative feedback by AngII) and limited clinical information on potential unique renal protective effects in DN, may distinguish DRIs from other RAAS. Such a forecast will be largely dependent on improved understanding of the cellular and organ specific biology of the renin and RPR as well as the outcome of large clinical studies.

Acknowledgements

The authors are grateful to Niroz Abu-Salah for her help in preparing the figures, and Prof. Raymond Coleman for his editing assistance.

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