Introduction

Hypertension, a major risk factor for cardiovascular and renal diseases, is on the rise in India. According to World Health Report 2002, cardiovascular diseases (CVDs) would be the commonest cause of morbidity and mortality in India by 2020. Several prevalence studies in hypertension which have been conducted in different regions of India, have reported alarming figures. The prevalence of hypertension has been reported to be as high as 45% (1997) in urban Delhi, 51% in Jaipur (2003) and 37% in South India (2000). Uncontrolled hypertension predisposes to cardiovascular, cerebrovascular and renal disease and therefore an all out effort to control hypertension immaculately is required. These rising statistics indicate that hypertension in India is not well controlled or treated despite the presence of different pharmacological agents.

The renin-angiotensin system (RAS) plays a pivotal role in the homeostatic control of arterial pressure, tissue perfusion, and extracellular volume leading to the development of hypertension. Dysregulation of the RAS can result in the pathogenesis of hypertension, cardiovascular and renal disorders. Owing to this, blockade of the RAS with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers has become an important therapeutic approach in cardiovascular and renal medicine.

Abstract

The importance of the renin angiotensin system (RAS) in blood pressure and electrolyte regulation has been well established. High RAS activity results in over-activation of the angiotensin AT1-receptor by its substrate, angiotensin II (AII), leading to increases in BP and direct growth-promoting effects on tissues that result in end-organ damage. The antihypertensive therapies, such as ACE inhibitors and angiotensin AT1-receptor blockers (ARBs) have proved to be successful treatments for hypertension, heart failure, and other related cardiovascular and renal disorders. However, these compounds do not completely inhibit the RAS as a result of AII formation by indirect pathways and compensatory feedback mechanisms, resulting in renin release. Thus renin inhibition has been identified as the preferred pharmacologic approach to blockade of the renin-angiotensin system. The advantages of inhibiting renin in the RAS have been recognized for almost half a century; however major advances in the development of potential clinically effective renin inhibitors have been made only in the past few years with the approval of Aliskiren for clinical use.
angiotensin II receptors (AT1) to increase arterial tone, adrenal aldosterone secretion, renal sodium reabsorption, sympathetic neurotransmission, and cellular growth. The release of renin from the kidney is subject to negative feedback regulation by Ang II.3

Human renin is composed of 340 amino acid residues and contains two glycosylation sites and is formed from the precursor, preprorenin. Renin is a highly specific enzyme for angiotensinogen and the active site of renin appears as a long, deep cleft that can accommodate seven amino acid residues of the substrate, angiotensinogen. Renin activity and subsequent RAS hyperactivation, is a major contributing factor in the pathogenesis of essential and renal hypertension predisposing the patients to end organ damage such as cardiac hypertrophy, renal damage and severe vasculopathy.4

**RAS - Pathophysiological Potential Beyond Hypertension**

Recent research on RAS has indicated that Angiotensin II, the effector octapeptide in RAS, exerts important physiologic and pathologic effects that are not accounted for in the conventional view of RAS. Angiotensin II, is responsible for cardiovascular pathological remodeling, leading to structural and functional changes in the myocardium, kidney and vasculature.5

Studies have also demonstrated that all the important components of RAS may be synthesized in tissues, namely cardiovascular, kidney and adipose. These local angiotensin II generating systems have a major role to play in the angiotensin-induced pathology.6 Ang II exerts short-term hemodynamic effects (increased blood pressure) as well as long-term structural effects (end-organ damage). The oxidative stress, proliferative changes, proinflammatory and prothrombotic stimuli, and vasoconstriction mediated by angiotensin II is responsible for promoting pathological changes in the vascular wall. Clinically, angiotensin II activity can be linked to mechanisms underlying congestive heart failure, left ventricular hypertrophy, plaque rupture, and thrombotic events.7

RAS may also be important in pathophysiology of metabolic syndrome. Activation of the renin-angiotensin system (RAS) in the adipose tissue has been postulated to be an important link between obesity and diabetes.8 The renin-angiotensin system in the adipose tissue modulates adipocyte differentiation and adipose tissue mass.9 Angiotensin II enhances lipogenesis by directly increasing the activity and expression of important lipogenic enzymes, leading to increased triglyceride synthesis and storage and total fat mass. It has been observed that angiotensinogen is significantly increased in adipose tissue of obese subjects.9

Angiotensin II, produced by the visceral adipocytes, may cause insulin resistance and diminish beta cell responsiveness, making obese people more susceptible to diabetes.5 Thus many of the connections between obesity and its cardiovascular, renal, and diabetic consequences could be attributed to the RAS.

**Renin/Prorenin Receptor - New Understanding of its Vascular Pathology**

Newfound data has revealed that renin and prorenin demonstrate vascular effects independent of the action of angiotensin II. The foundation of this new concept is the identification of the renin / prorenin receptor.7 Renin /prorenin receptor was initially identified on mesangial cells and has also been demonstrated to be present in the subendothelium of coronary and renal arteries.10

Both renin and prorenin bind to this receptor with high affinity, with the receptor binding site being different from the renin catalytic sites. Renin receptor mediates pathophysiologic effects in two possible mechanisms.

One of these is linked to the ability of prorenin gaining Ang I-generating activity by binding to the receptor on cell surfaces, without undergoing proteolytic cleavage. Angiotensin I thus produced is acted on by the tissue ACE, producing angiotensin II in immediate proximity to the AT1 receptor at which it exerts its vascular effects.11,12 Interestingly, renin/prorenin binding to the (pro)renin receptor also activates intracellular signaling pathways in an angiotensin-independent manner. Studies in cell cultures have demonstrated that renin binding induces intracellular events, such as activation of mitogen-activated protein (MAP) kinase, which in turn promotes local mechanisms that can result in such potentially adverse effects as cellular hypertrophy, increased fibrosis, and possibly even enhanced production of thrombotic factors.7

(Pro)renin receptor discovery highlights the role of the cell surface in angiotensin II generation and emphasizes the pathophysiological effects of tissue RAS and renin independent of angiotensin II.

**Renin Angiotensin System Blockade**

An enormous contribution to our understanding of the role of the renin-angiotensin system in normal cardiovascular, renal, and endocrine physiology and in the pathogenesis of disease has come from pharmacological interruption of the system. Pharmacological interruption of RAS can be achieved at five major sites, renin release from the juxtaglomerular cells, renin activated cleavage of angiotensinogen, ACE conversion of A-I to A-II, A-II action at AT1 receptors and aldosterone action at the mineralocorticoid receptor.13

Blockade of RAS with ACE inhibitors and angiotensin II type 1 receptor blockers (ARB) have proved to be successful therapeutic options in maximizing the cardiovascular and renal benefits of these agents in the treatment of hypertension. Numerous clinical trials have demonstrated the favourable effects of ACE inhibitors and ARBs in treating hypertension. They have been reported to decrease clinical events in high-risk hypertensive patients, improving left ventricular dysfunction, decreasing clinical events after myocardial infarction and reducing morbidity and mortality in congestive heart failure. Apart from the antihypertensive effects, ACE inhibitors and ARBs have also been found to exert renal protective effects in diabetic nephropathy and other chronic renal diseases.14

However, ACE inhibition and ARBs may not achieve complete blockade of RAS pathway.

**Limitations of ACE inhibitors and ARBs**

Although ACE inhibitors are effective antihypertensive agents, they do not block ACE independent pathways, leading to increase in Ang II levels. Non-ACE converting enzymes such as chymase primarily found in kidneys regulate these pathways and this may affect the antihypertensive response in some patients; about 40% of Ang I is converted to Ang II by non-ACE pathways.15
It has been observed that during chronic ACE inhibitor treatment, serum Ang II concentrations, which are initially suppressed by treatment, return almost to baseline levels. This ‘escape’ from ACE inhibition reflects the reflex rise in renin release from the kidney following interruption of normal Ang II feedback inhibition, which increases synthesis of Ang I. This “escape phenomenon” observed with ACE inhibitors is thought to be a major cause of treatment failure in heart failure patients.16

ACE also influences bradykinin degradation and leads to increased circulating and tissue levels of substance P. Although the increased levels of bradykinin and substance P that occur with ACE inhibition may contribute to BP lowering, they are also responsible for adverse effects such as cough and angioedema.11 Likewise, chronic use of ARBs has been shown to increase circulating levels of Ang I, II, III and IV. Ang II and IV are cleaved from Ang II by aminopeptidases. Though part of the beneficial effects of AT1 receptor antagonists are thought to be mediated through increased stimulation of unblocked AT2 receptors, deleterious effects such as impaired fibrinolysis secondary to elevated plasma and tissue plasminogen activator inhibitor 1 levels, due to stimulation of AT4 receptors by Ang IV, is also possible. The rise in Ang II levels in the face of the use of these drugs may also be a potential explanation for limiting the therapeutic benefit of these drugs in providing adequate protection against heart attack as was reported from SCOPE study.13

Interestingly, chronic suppression of RAS with ACE or ARB stimulate a reactive increase in plasma renin activity as they disrupt the short feedback loop by which Ang II normally inhibits renin release from the kidney. Thus, reactive increase in plasma renin activity could potentially reduce some of the blood pressure lowering effects of ACE and ARBs. Renin may also exert direct vasoconstrictor effect unrelated to downstream consequences. Pre-treatment plasma renin activity is an independent risk factor for myocardial infarction in hypertensive patients and for microvascular complications in diabetes.16,17

Another issue with ACE inhibitors and with ARBs is that they may not provide effective inhibition of the RAS at the tissue level, reflecting the limited effect of these agents to influence autocrine and paracrine tissue-based systems.

Renin - An Attractive Target for Optimal RAS Blockade

In view of the inadeacies of ACEI and ARBs, direct renin inhibition may be a more rewarding approach in inhibiting the RAS. As renin catalyses the first and rate-limiting step of the RAS pathway, inhibition of renin will block the RAS in its entirety.16

Renin unlike ACE, is highly selective to angiotensinogen, hence renin inhibition for treatment of hypertension is likely to be safe with a low adverse effect profile. As a result of direct renin inhibition, there is a suppression of the reactive rise in plasma renin activity, in contrast to that observed with ACE inhibitors and ARBs. Renin inhibition offers advantages over ACE inhibition and angiotensin receptor blockade by prompting complete blockade of the RAS, without the escape phenomenon. Other potential advantages include reduction of angiotensin II generated through non-ACE pathways (which may be particularly important in heart failure) and inhibition of tissue renin/prorenin (nephropathy and retinopathy).

The differential mechanism of action may therefore provide an opportunity to facilitate blood pressure reduction, and even reduce the toxic effect of Angiotensin II. A renin inhibitor may prove to be more beneficial in preventing vascular injury associated with high blood pressure. Renin inhibition offers significant promise as a renoprotective antihypertensive agent, due to their capability to attenuate the activity of RAS without a reactive increase in plasma renin activity (PRA) or other components of RAS.16

Renin inhibitors hold great promise in hypertensive patients with progressive vascular disease or patients with greater risk for kidney or cardiovascular disease progression.

Renin Inhibition - Potential in Cardiovascular Diseases

Activation of the renin-angiotensin system (RAS) is significant in the pathogenesis of cardiovascular disease and specifically coronary atherosclerosis. There is strong evidence that the RAS has effects on the mechanisms of action of atherosclerosis, including fibrinolytic balance, endothelial function, and plaque stability. Pharmacological inhibition of the renin could thus provide a beneficial effect in cardiovascular diseases.18

The role of local cardiovascular and renal tissue and even intracellular systems in angiotensin-induced pathology has directed the focus of researchers towards effective renin inhibition. Renin inhibition may prove beneficial in cardiovascular diseases by gaining access to the tissue sites of renin formation, and influencing the formation and action of angiotensin. Though there are alternate pathways to renin cleavage namely, tonin and cathepsin, these systems are not thought to be of any great physiological importance. The theory that more effective blockade of tissue A-II formation may occur with renin inhibition has been confirmed by a number of studies in which a 50 % greater rise in renal perfusion has been observed with intravenous renin inhibition than with ACE inhibition, despite similar lowering of BP.13

Renin Inhibition- Potential in Diabetes

Activation of RAS is a key step in the progression of diabetic kidney disease. Also it has been observed that, the increase in prorenin exceeds substantially the increase in diabetes as compared to other diseases and prorenin levels in type II diabetes correlate with severity of proteinuria and retinopathy.16,17

Renin inhibitors may provide protection over other RAS inhibitors, by interfering with the enhanced catalytic activity of renin and prorenin after the binding of these molecules to the renin/prorenin receptor or by interfering with the binding of these molecules to their receptor. The well established effect of renin inhibitors on interaction of renin/prorenin with its receptor may be potentially useful in patients with diabetes mellitus, in whom prorenin levels are increased and are a powerful predictor of microvascular complications. Renin inhibitors, due to their effect on (pro)renin receptors modulate vasoconstriction, hypertrophy, atherosclerosis and fibrosis in target organs including kidney, heart and blood vessels, thereby providing an important therapeutic option in diabetes.10

Combination of renin inhibitors with ACE inhibitors or ARBs may maximize renin-angiotensin system (RAS) blockade with subsequent increase in the antiproteinuric and nephroprotective effects of each drug class. Trials are ongoing to evaluate the effect of this combination in achieving optimum RAS blockade.
Development of orally active renin inhibitors was very tough and challenging due to major hurdles like low bioavailability, poor gastrointestinal absorption, large interindividual variation in BP lowering and development costs. However new promising renin inhibitors have been developed using molecular modeling and X-ray determination of the crystallographic structure of active renin site. The first representative of this class is aliskiren, a potent renin inhibitor. Animal models have demonstrated that aliskiren provides dose-dependent rapid (within 15 min) BP lowering effects which persisted for more than 25 hours after a single dose. Aliskiren also reduced or prevented albuminuria and left ventricular hypertrophy, in animal models of hypertension and end-organ damage, suggesting protection of the heart and kidneys. 19

The low bioavailability of aliskiren coupled with is high potency to inhibit renin and a long plasma half-life makes it suitable for once-daily dosing. The once-daily administration of aliskiren in hypertensive patients lowers BP as strongly as standard doses of established angiotensin II type 1 receptor blockers, hydrochlorothiazide, angiotensin converting enzyme inhibitors or long-acting calcium channel blockers. 20

Aliskiren combined with losartan was reported to reduce proteinuria significantly greater than the placebo group by Hans Parving and his group. 21 They concluded that Aliskiren may have renoprotective effects that are independent of its blood pressure lowering effects in patients with hypertension, type II diabetes and nephropathy. With the availability of direct rennin inhibitor, now there are at least four possible combinations of use of various RAAS system inhibitors: ACEI + ARB, DRI + ACEI, DRI + ARB; DRI + ACEI + ARB and all of these with or without aldosterone inhibitors which have also been documented to reduce proteinuria as well as cardiac fibrosis.

Conclusion

Renin inhibition offers substantial promise for cardioprotection and renoprotection, due to the fact that they not only provide effective blood pressure reduction, but also an opportunity to attenuate RAS activity without an increase in plasma renin activity or other angiotensin products.

References


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