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COMMENTARY

Combining drugs to optimize the therapy of hypertension: experimental evidence derived from animal models

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Hypertension is widely known to promote renal disease and this is associated with complex pathophysiological mechanisms including enhanced renal sympathetic activity and the hyperactivation of the renin–angiotensin–aldosterone system (RAAS). Increased sympathetic nervous system stimulation activates renin release, sodium reabsorption, vasoconstriction, and decreased renal blood flow.[1] Abnormal activation of the RAAS and increased renin secretion lead to increased angiotensin II production, which in turn activates multiple intracellular signaling pathways (Figure 1) that result in increased blood pressure and a variety of functional and structural alterations of the cardiovascular system.[2]

The study by Tiradentes *et al.*[3] used the two-kidney one-clip (2K1C) hypertension model, which resembles human severe hypertension and is clearly dependent on renin–angiotensin–aldosterone system (RAAS) activation.[2] The authors took advantage of a very interesting physiological approach to show that the combination of aliskiren (a renin inhibitor) and L-arginine (a substrate for nitric oxide, NO, synthesis) effectively lowers blood pressure in 2K1C hypertensive rats in association with improved renal function and reduced renal sympathetic nerve activity (RNSA).[3] Although a clear mechanistic link between reduced RNSA and drug effects is not provided in this study, the authors concluded that RNSA contributes to renovascular hypertension, and that combining aliskiren and L-arginine reduces RNSA, improves renal dysfunction and lowers blood pressure.[3] This study provides experimental evidence that may contribute to the improved understanding of hypertensive mechanisms and therapeutic approaches.

Aliskiren has recently been approved for the therapy of hypertension with the idea that inhibiting renin activity could provide substantial additional protection, at least to some patients, as compared with other traditional antihypertensive drugs. Indeed, direct renin inhibitors, by interfering with the initial steps in the RAAS cascade (conversion of angiotensinogen to angiotensin I), could provide a complete blockade of the RAAS.[4] As monoterapy, aliskiren 150, 300 and 600 mg once a day lowered blood pressure in mild-to-moderate hypertensive patients and

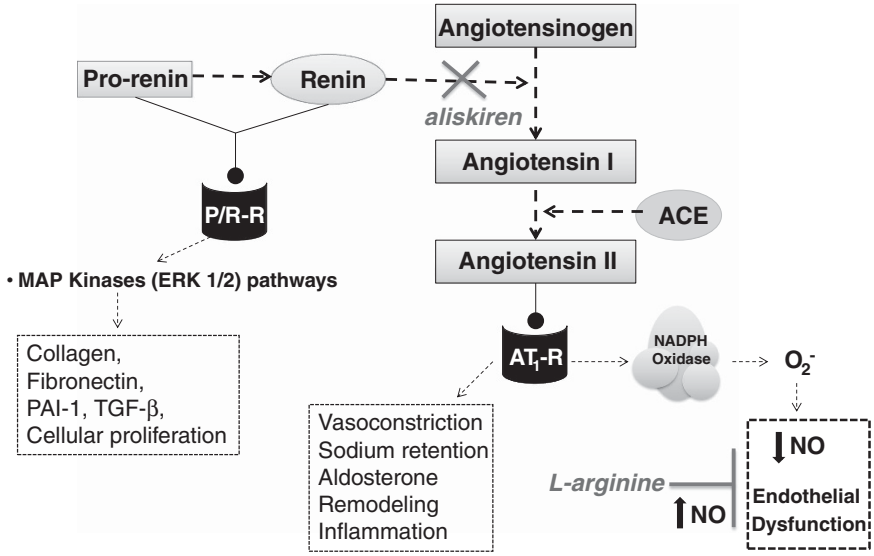

Figure 1 Signaling pathways involved in the pathophysiology of hypertension. Activation of the renin angiontensin aldosterone system (RAAS) is commonly found in different animal models of hypertension. Increased angiotensin II concentrations increase blood pressure by activating hypertensive mechanisms and promotes cardiovascular inflammation and remodeling. Although aliskiren inhibits renin activity, thus decreasing the overall activity of the RAAS and angiotensin II concentrations, both renin and prorenin can bind to receptors and activate a variety of profibrotic pathways, therefore limiting the responses to aliskiren. Angiontensin II activation of AT_1R also increases NADPH oxidase activity, a major contributor to superoxide formation in hypertension. L-arginine is a substrate for nitric oxide (NO) formation, and therefore can replenish NO bioavailability, which is impaired by increased oxidative stress in hypertension. ACE, angiotensin converting enzyme; AT_1R, angiotensin II type 1 receptors; NADPH, nicotinamide adenine dinucleotide phosphate oxidase; P/R-R, prorenin and renin receptors. A full color version of this figure is available at *Hypertension Research* online.

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this drug is apparently as effective as angiotensin receptor blockers.[5] However, althouigh the inhibition of RAAS is often used in the therapy of hypertension and its complications, many patients will require combinations of drugs to effectively control blood pressure,[4] and therefore examining different combinations may be very helpful.

To improve the effects of aliskiren, Tiradentes *et al.* combined this renin inhibitor with L-arginine, a substrate to increase NO bioavailability. The rationale for this approach is very consistent with a number of previous studies showing that NO deficiency contributes to hypertension and that therapeutic approaches designed to replenish NO deficiency may be very effective in lowering blood pressure.[6] In fact, it is clear that the activation of angiotensin II type 1 receptors (AT_1s) is associated with increased reactive oxygen species formation (particularly superoxide) as a result of angiotensin II-induced upregulation of nicotinamide adenine dinucleotide phosphate oxidase oxidase activity (Figure 1), particularly in the 2K1C hypertension model.[7] The activation of this mechanism in hypertension decreases NO activity and causes endothelial dysfunction.

Therefore, enhancing NO formation with L-arginine treatment may provide an additional, protective mechanism to counteract deleterious alterations found in the 2K1C hypertension model, as shown by Tiradentes *et al.*, possibly by improving a vasodilatory mediator (NO) to improve renal vasoconstriction triggered by elevated angiotensin II levels.

Interestingly, Tiradentes *et al.*[3] showed that 3 weeks of treatment with combined L-arginine or aliskiren exerted major antihypertensive effects, whereas treatment with L-arginine had only minor effects, and aliskiren alone had no effects. This observation may suggest that improving NO bioavailability may be more relevant that inhibiting renin activity in the 2K1C hypertension model. To further examine the role of NO, the authors tried to explore which isoforms of NO synthases are possibly involved in the pathophysiological alterations of renovascular hypertension. Although the authors advocate a possible protective effect of increased inducible NO synthase (iNOS) in this model, particularly to the ischemic kidney,[3] experimental findings in another animal model of severe hypertension in pregnancy contrasts with this suggestion.[8] Indeed, it is possible that abnormal amounts of NO produced by iNOS enhances peroxinitrite levels, particularly in a context of increased oxidative stress, which is associated with increased superoxide production, thus leading to nitrosative stress and cardiovascular dysfunction.[9] Clearly, this is a very complex issue, which would be better explored with by carrying out experiments with knockout mice or by using selective NO synthase inhibitors.

The lack of significant effects after therapy with aliskiren alone, as reported by Tiradentes *et al.*, is not surprising. A previous study by our group compared the effects of monotherapy with the AT_1 receptor antagonist losartan with those found after monoterapy with aliskiren, or the combination of both the drugs in 2K1C hypertensive rats.[10] In agreement with the findings reported by Tiradentes *et al.*,[3] aliskiren alone did not prevent the vascular remodeling and profibrotic alterations found in 2K1C hypertension,[10] even though this drug significantly reduced the plasma renin activity. In contrast, losartan or the combination of drugs prevented most biochemical and structural vascular alterations associated with 2K1C hypertension.[10] Together, these results suggest that critical mechanisms not significantly affected by renin inhibition may exert major effects. For example, it is possible that the binding of prorenin and renin to their receptors triggers a series of intracellular signaling pathways including mitogen-activated protein kinases that contribute to the alterations of hypertension[10] (Figure 1). From the clinical standpoint, a recently published meta-analysis carried out to compare the antihypertensive effects and tolerability of aliskiren with other antihypertensives showed overall similar effects of aliskiren as compared with other drugs, particularly when aliskiren was compared with angiontensin receptor blockers.[11]

Given the complexity of pathophysiological mechanisms interacting to increase blood pressure and to remodel the cardiovascular system in hypertension, it is highly probable that combinations of drugs will always be required to manage hypertensive patients. Future studies assessing the antihypertensive effects of various combinations of drugs in different animal models may help to define improved therapies.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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