

Journal of Clinical and Basic Cardiology

An Independent International Scientific Journal



Journal of Clinical and Basic Cardiology 2001; 4 (1), 47-51

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The Renin-Angiotensin System and the Sympathetic Nervous System in Hypertension and Congestive Heart Failure: Implications for Therapeutic Interventions

H. Rupp¹, B. Jäger²

The renin-angiotensin system (RAS) and the sympathetic nervous system (SNS) are both contributors to the development and maintenance of hypertension. It has recently been recognised that extensive interactions occur between the RAS and SNS. In addition to the classical interactions occurring between the SNS and RAS on an organ and cellular level, there is evidence that disordered subcellular crosstalk can occur between the effectors of the SNS and angiotensin II. This results in the promotion of structural remodelling of cardiac tissue seen in both hypertension and congestive heart failure. Therefore, optimal drug therapy for hypertension and congestive heart failure would attenuate both the RAS and SNS while also restoring the balance of disordered crosstalk between the systems. AT₁ receptor blockers are the most recent class of cardiovascular therapeutic agents. Preclinical studies to date show that the antihypertensive effects of AT₁ receptor blockers may be mediated through their effects on the SNS as well as the RAS. Eprosartan was found to be more potent in its effects on the sympathetic nervous system than other non-peptide AT₁ receptor blockers and shows the lowest ratio between the effective doses on RAS and SNS. This high sympatholytic potency may be a result of differences in chemical structure and receptor-binding characteristics of eprosartan when compared with other AT₁ receptor blockers. It remains to be seen whether these potentially significant therapeutic implications for hypertension and congestive heart failure translate into the clinical setting. *J Clin Basic Cardiol* 2001; 4: 47–51.

Key words: sympathetic nervous system, renin-angiotensin system, eprosartan

Introduction

There are two important contributors to the control of blood pressure – the sympathetic nervous system (SNS) and the renin-angiotensin system (RAS).

The autonomic nervous system is important in regulating cardiovascular homeostasis as it modifies both cardiac output and the diameter of resistance vessels. Blood vessels, however, are innervated almost exclusively by fibres of the SNS, which regulate vasomotor tone. Increased SNS activity results in increased vasomotor tone and, therefore, is causally related to the development and maintenance of high blood pressure.

The RAS has become established as an endocrine system that plays important roles in the physiological regulation of cardiovascular, renal, and endocrine functions. It contributes to the development and persistence of various forms of hypertension [1]. Activation of this system leads to the formation of renin in the kidney, which converts angiotensinogen to the inactive peptide, angiotensin I. Angiotensin I is then converted by angiotensin converting enzyme (ACE) to angiotensin II, a potent vasoconstrictor which also stimulates aldosterone secretion and fluid retention. Pharmacological interventions that inhibit the RAS have been proven to be efficient antihypertensives and, more recently, have been shown to be beneficial in congestive heart failure. The RAS is often considered to exert its effect on blood pressure in an independent manner. It is now clear, however, that extensive interactions occur between the RAS and other blood pressure control systems, in particular the SNS [2]. The SNS controls the process by which angiotensin II is produced through the release of renin from the kidneys. As the rate of renin release by the kidneys is crucial for the formation of angiotensin II, the SNS is a key determinant of circulating angiotensin II

levels. Circulating angiotensin II itself then interacts with the SNS at various sites and appears to amplify sympathetic activity. It may act on the brain to increase sympathetic outflow, on the sympathetic ganglia and adrenal medulla to increase catecholamine release, and at presynaptic sympathetic nerve endings to facilitate sympathetic neurotransmission through an enhanced norepinephrine release [2, 3].

This review concentrates on the interaction of angiotensin II at the presynaptic sympathetic nerve endings and evidence will be presented indicating that this interaction may contribute to systolic hypertension. We then explore the possibility that inhibition of this interaction by therapeutic interventions may not only have effects on tissue remodelling, but may also reduce cardiovascular morbidity and mortality.

Subcellular Crosstalk and Tissue Remodelling During Development of Hypertension

In addition to the classical interactions between the SNS and RAS occurring at the organ and cellular level (Figure 1), there is increasing evidence for a complex subcellular crosstalk between the effector systems of catecholamines and angiotensin II. For example, it has been shown that in vascular smooth muscle cells the cyclic AMP signaling system can counteract the growth-promoting effects of angiotensin II [4].

Since catecholamines and angiotensin II have marked effects on gene expression and thus the protein phenotype of a cell, any imbalance in the influences of their effectors may promote a structural remodelling of tissues. Indeed, it appears most likely that the deleterious remodelling of arterioles observed in hypertensive patients arises from disordered subcellular crosstalk between the angiotensin II and catecholamine effector systems, as well as from their independent actions [5].

Received February 5th, 2001; accepted March 15th, 2001.

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Although thickening of the vascular media is involved in establishing high blood pressure, an increased arterial stiffness can occur leading to isolated systolic hypertension. This type of hypertension has only recently been recognized as an important drug target [6]. The therapeutic advantages of treating isolated systolic hypertension (systolic blood pressure > 160 mmHg and diastolic blood pressure < 90 mmHg) have been demonstrated in large clinical trials such as the Systolic Hypertension in Europe (Syst-Eur) Trial [7], the Systolic Hypertension in the Elderly Program (SHEP) [8], and the Systolic Hypertension in China (Syst-China) trial [9]. The study populations in these three trials included elderly hypertensive patients with hypertension (systolic blood pressure ranging between 130 and 219 mmHg). When systolic blood pressure was lowered, the risks of stroke and any cardiovascular event were reduced by 34 % and 19 %, respectively, in Syst-Eur [7], 33 % and 17 %, respectively, in SHEP [8], and 38 % and 37 %, respectively in Syst-China [9]. However, it must be remembered that in addition to reducing acutely high blood pressure, it is also important to promote the reversal of adverse remodelling of the vascular wall.

Subcellular Crosstalk and Tissue Remodelling During Progression of Heart Failure

Progression of heart failure has been associated with an adverse remodelling of the extracellular matrix and is characterized by fibrosis [10]. Although an excessive collagen deposition is deleterious and contributes to deteriorating cardiac performance, there is accumulating evidence that a disordered gene expression in cardiomyocytes, leading to depressed pump function, is particularly critical during the early stages of heart failure [11, 12]. The impaired performance of cardiomyocytes is thought to activate the SNS, thereby initially favouring the expression of genes influenced by cyclic AMP signalling. As a consequence of the raised SNS activity and because of locally produced angiotensin II, the influences of angiotensin II on gene expression will also become enhanced. Angiotensin II raises intracellular free Ca^{2+} and collagen synthesis in cardiac fibroblasts [13] and reduces cardiomyocyte alpha-myosin heavy chain expression [14]. At later stages, downregulation of beta-adrenergic receptors oc-

curs [15], resulting in impaired signalling of cyclic AMP. Locally produced angiotensin II could be involved, leading to enhanced norepinephrine release from nerve terminals, which could contribute to downregulation of beta-adrenergic receptors. Since various cyclic AMP-dependent pathways counteract signalling by angiotensin II [4], an exaggerated angiotensin II response may ensue.

The question arises as to whether current drug interventions targeted at neuro-endocrine activation can counteract such an imbalance in signalling for cardiomyocyte and cardiac fibroblast gene expression. It appears particularly important not to only interfere with one system, but to restore a balanced influence of effectors arising from both catecholamines and angiotensin II. It seems that AT_1 receptor blockers, in particular eprosartan, have an influence on both effectors, and this will be discussed.

Therapeutic Approaches for Reducing Dual Influences of Catecholamines and Angiotensin II

Inhibition of the SNS is an effective means of lowering blood pressure, treating congestive heart failure and preventing recurrence of myocardial infarction. Currently, there are a number of pharmacological agents available that can interact with the SNS at a variety of points. Apart from peripheral receptor blockade, central sympatholytic agents, such as monoxidine and rilmenidine, attenuate sympathetic overactivity at its point of origin in the brainstem, while preserving normal reflex responses of the sympathoadrenal system. They have the advantage of maintaining normal physiological activation of sympathetic activity during postural adjustments, exercise, and hypercapnia [16]. Both monoxidine and rilmenidine modulate sympathetic activity through I_1 -imidazoline receptors localized in the rostral ventrolateral medulla of the lower brainstem [17, 18]. ACE inhibitors block the conversion of angiotensin I to angiotensin II and thus reduce the influence of angiotensin II on presynaptic AT_1 receptors. However, angiotensin II can also be produced by non-ACE proteases such as chymase. This local tissue production of angiotensin II by non-ACE pathways requires inhibition by additional drugs such as mast cell chymase inhibitors [19] or AT_1 receptor blockers.

AT_1 receptor blockers are the most recent class of cardiovascular therapeutic agents developed, and include candesartan, eprosartan, irbesartan, losartan, telmisartan, and valsartan. It is possible that these drugs inhibit the SNS by blocking presynaptic AT_1 receptors on sympathetic nerve terminals [20] as shown in Figure 2 [21, 22].

Actions of AT_1 Receptor Blockers on the SNS in Preclinical Studies

Data from experimental animal studies strongly indicate that the antihypertensive effects of AT_1 receptor blockers may be mediated at least in part through their effects on the SNS. Dendorfer et al. [20] showed that the AT_1 receptor antagonists candesartan, eprosartan, losartan or its metabolite EXP 3174 and irbesartan exert similar inhibitory potencies at vascular and presynaptic neuronal receptors. In the pithed rat model, an increase in stimulation frequency elicited a pressure response that was sympathetically mediated and was enhanced by angiotensin II. Experiments with losartan and the AT_2 receptor blocker PD 123177 demonstrated that the angiotensin II receptors situated on the sympathetic ganglia are of the AT_1 subtype [23–25].

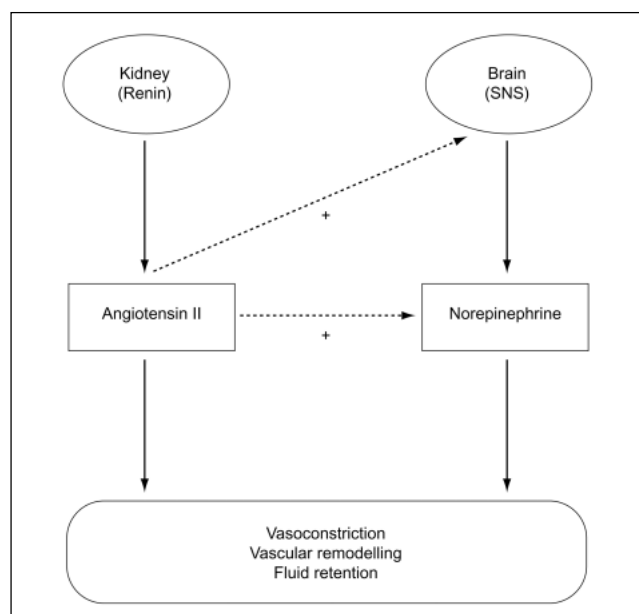


Figure 1. The relationship between the renin-angiotensin system and the sympathetic nervous system (SNS).

Ohlstein et al. [21] showed that the pressor responses to spinal cord stimulation were inhibited by the peptide angiotensin II receptor antagonist saralasin (10 µg/kg body weight/min). This confirms the existence of prejunctional angiotensin II receptors at the vascular neuroeffector junction that facilitate release of norepinephrine. Furthermore, at a dose which completely blocked angiotensin II AT₁ receptors (0.3 mg/kg, i.v.), the non-peptide AT₁ receptor blocker eprosartan significantly inhibited the pressure response mediated by spinal cord stimulation. This high potency regarding presynaptic sympathetic inhibition in the pithed rat may be unique to eprosartan because other AT₁ receptor blockers such as losartan, valsartan and irbesartan failed to inhibit the pressure responses at the same dose [21, 22, 26] and/or were active at three to 30 times higher i.v. doses (1.0–10 mg/kg i.v.) [27–30].

An inhibitory effect of eprosartan on sympathetic overactivity was recently also demonstrated in a model of hyperkinetic hypertension involving a hypercaloric diet intake [31, 32]. The diet contained 24 % fat and 32 % sucrose and resembled a typical westernized diet. Similar diets have been shown to increase norepinephrine turnover in the heart [33]. The radio telemetry data from the study showed that during hypercaloric feeding, heart rate and blood pressure were significantly increased in conscious, spontaneously hypertensive rats (Figure 3) [32]. A daily dose of 30 mg/kg body weight only transiently reduced ($P < 0.05$) systolic (Figure 3) and diastolic (not shown) blood pressure to the level before hypercaloric feeding was started. After 6 days, blood pressure increased and returned to the starting value (Figure 3). However, a higher dose (90 mg/kg, p.o.) not only prevented the blood pressure rise due to the hypercaloric diet intake but also consistently reduced the high blood pressure that is characteristic of spontaneously hypertensive rats. The increased heart rate was reduced significantly only after administration of 90 mg/kg p.o. eprosartan. This dose of eprosartan did not, however, completely blunt the rise in heart rate due to the hypercaloric diet intake. Whether a higher dose of eprosartan reduced the heart rate even further is a subject for future investigation.

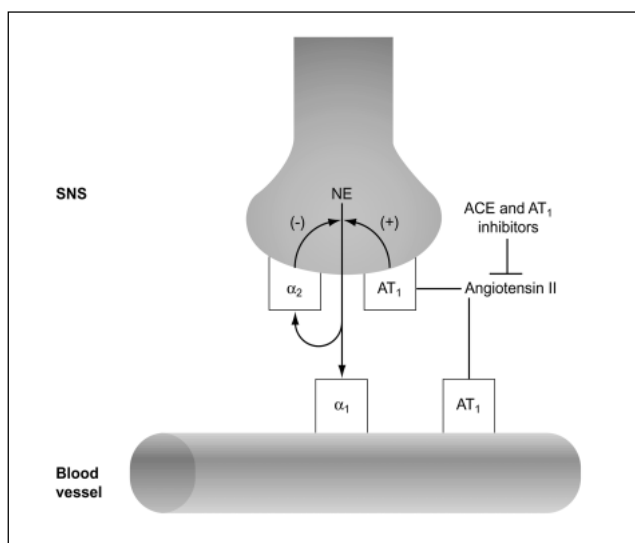


Figure 2. Sympathetic neuroeffector junction. Norepinephrine (NE) is released from the sympathetic nerve at the sympathetic neuroeffector junction, stimulating postsynaptic alpha₁-adrenoreceptors (α₁) leading to vasoconstriction. Angiotensin AT₁ receptors are present presynaptically at this junction as well as postsynaptically on blood vessels. Stimulation of the presynaptic receptors enhances SNS-induced norepinephrine release. Adapted from Ohlstein [21, 22].

Although an increased SNS activity is expected to raise the amount of circulating angiotensin II, the actual extent to which angiotensin potentiated SNS activity during the hypercaloric diet intake has not been determined. It should be pointed out that the reduction in heart rate was observed at a dose of eprosartan that consistently reduced blood pressure. This indicates that the dose of eprosartan required to lower blood pressure also has an inhibitory effect on heart rate. In the pithed rat, the dose required for inhibition of sympathetic neurotransmission was generally higher than that needed for inhibition of an angiotensin II induced blood pressure response but eprosartan showed the lowest ratio between the effective doses on RAS and SNS [34].

The potent sympathoinhibitory action of eprosartan *in vivo* has not been displayed by other non-peptide AT₁ receptor blockers to date. Although it remains to be elucidated, one possible reason for this disparity could be due to the chemical structure of eprosartan (imidazole substituted by a benzylcarboxylic and a methylene thiophene propanoic acid moiety), which is different to that of other AT₁ receptor blockers (biphenyltetrazole structure based on chemical modifications of losartan's prototypical structure; Figure 4).

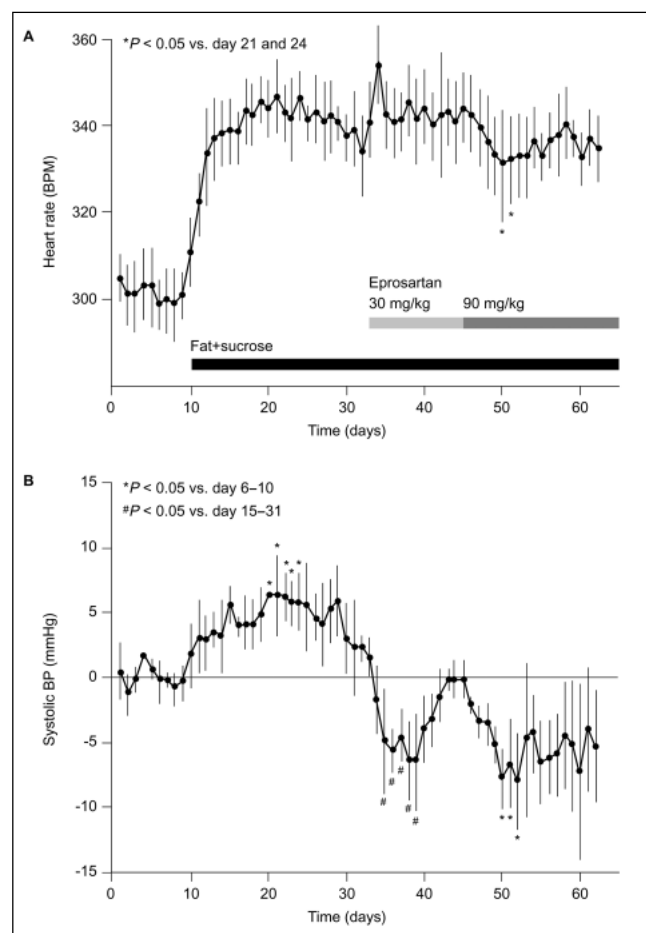


Figure 3. Radiotelemetry-monitored (top) heart rate (beats per minute [BPM]) and (bottom) systolic blood pressure (BP) averaged (288 30-sec measurements) over 24 h. Rats were fed a 24 % coconut fat/32 % sucrose (wt/wt) diet and were treated daily with 30 mg/kg body weight or 90 mg/kg eprosartan. The radiotelemetry system consisted of TA11PA-C40 pressure transmitters and RA 1010 receivers (Data Sciences, St. Paul, MN, U.S.A.). Statistical comparisons were made by ANOVA with repeated measures using 4 spontaneously hypertensive rats. Values are means ± S.D. Figure reprinted from Rupp et al; 2000 with permission from Kluwer Publishers.

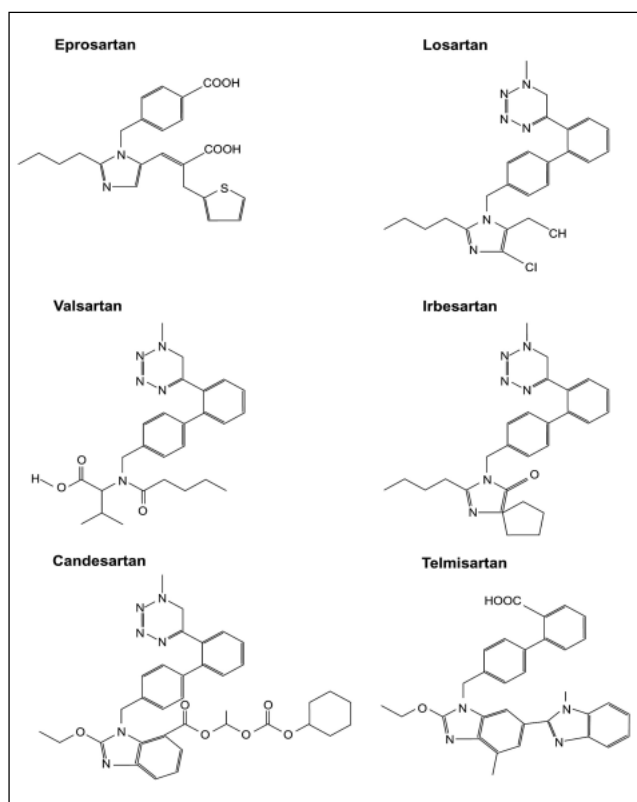


Figure 4. Chemical structures of various angiotensin II antagonists resembling the prototypic compound losartan. Eprosartan exhibits a chemically distinct structure.

Its receptor binding characteristics (competitive rather than non-competitive binding) or still unknown unique effects on presynaptic AT₁ receptors [35, 36] could also be responsible.

Contrary to *in vivo* studies, *in vitro* experiments with isolated rat left atrial preparations showed valsartan and irbesartan to be more potent inhibitors of the electrical stimulation-induced efflux of [³H]-norepinephrine from cardiac sympathetic nerves than eprosartan [37]. This *in vitro* model, however, is characterized by a low sensitivity, requiring high drug concentrations and a high stimulation frequency (3 Hz). It therefore remains unclear whether these effects can be extrapolated into the *in vivo* situation, and it appears that the pithed rat studies are more representative of the clinical setting than the reported study involving atrial preparations.

To summarize, the results of preclinical studies to date indicate that the inhibition of sympathetic outflow by the angiotensin II AT₁ receptor blockers is a class effect, with eprosartan being more potent than other agents in this class, at least in the *in vivo* pithed rat experiments. This increased potency may be due to differences in the chemical structure and receptor binding characteristics of eprosartan when compared with the other angiotensin II receptor blockers.

Clinical Evidence for SNS Inhibition by AT₁ Receptor Blockers

The prejunctional facilitating effects of angiotensin II on peripheral sympathetic neurotransmission by AT₁ receptor blockers have significant therapeutic implications, not only for hypertension where systolic blood pressure may be more effectively controlled but also for congestive heart failure where locally produced angiotensin II is increased. Clinical studies to date have shown that in severely hypertensive patients (sitting diastolic blood pressure ≥ 115 and ≤ 125 mmHg),

eprosartan significantly reduces sitting systolic blood pressure by 29.1 mmHg (versus 21.1 mmHg in the enalapril treated group; $P < 0.05$) [38]. Other AT₁ receptor blockers have not shown significant reductions in systolic blood pressure when compared with ACE inhibitors, suggesting that differences may exist between the AT₁ receptor blockers in terms of their effects on the SNS in the clinical setting.

A study by Osei et al. [39] suggests that eprosartan may modulate local SNS activity. Eprosartan increased renal plasma flow in volunteers with high sodium balance and moderate hyperglycaemia, while no change was noted in normoglycaemic subjects. These findings suggest that the increased renal plasma flow seen in hyperglycaemic conditions is caused by the activation of the intrarenal RAS, since no changes in plasma renin activity or plasma angiotensin II were noted. Osei et al. [39] concluded that this effect on the intrarenal RAS may arise as a result of reduction of renal sympathetic nerve activity.

To more clearly identify the clinical relevance of the animal studies, clinical trials on the effect of eprosartan on autonomic function in relevant cardiovascular disease states are currently being conducted. One such study is a three-way, double-blind, cross-over trial comparing effects of losartan, eprosartan, and placebo on autonomic parameters in hypertensive patients.

Conclusions

As preclinical studies have shown, there is evidence that AT₁ receptor blockers can reduce sympathetic outflow. At the doses used, eprosartan appears to be the most potent inhibitor of sympathetic outflow of all agents in this class. In a model of diet-induced hyperkinetic hypertension, eprosartan was found to reduce heart rate at a dose that was effective at consistently lowering blood pressure. It remains to be determined whether the sympatholytic action of eprosartan can be confirmed in clinical studies, and whether these potential benefits are reflected in a reduced mortality and morbidity in patients with systolic hypertension and heart failure.

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