Beneficial Renal and Cardiac Effects of Vasopeptidase Inhibition With S21402 in Heart Failure

Louise M. Burrell, Nicole K. Farina, Leanne C. Balding, Colin I. Johnston

Abstract—S21402 is a vasopeptidase inhibitor that simultaneously inhibits neutral endopeptidase (NEP) and angiotensin-converting enzyme (ACE). This study determined whether chronic treatment with S21402 produced different effects on sodium and water excretion, hormonal parameters, and cardiovascular structure compared with selective inhibition of ACE and NEP in a rat model of myocardial infarction–induced congestive heart failure (CHF). CHF rats received the vasopeptidase inhibitor (S21402, 100 mg·kg⁻¹·d⁻¹), an ACE inhibitor (captopril, 50 mg·kg⁻¹·d⁻¹), a NEP inhibitor (SCH42495, 60 mg·kg⁻¹·d⁻¹), or vehicle for 4 weeks. S21402 alone caused a diuresis and natriuresis (P<0.01) in CHF. After 4 weeks, blood pressure was lowered by captopril but not other treatments (P<0.01). Both S21402 and captopril increased plasma renin activity (P<0.01), all treatment lowered plasma aldosterone (P<0.05) and plasma natriuretic peptide levels were unchanged. In the kidney, S21402 inhibited NEP and ACE (P<0.01), SCH42495 inhibited NEP (P<0.01), and captopril inhibited ACE (P<0.01). Heart mass was reduced by all active treatments; captopril reduced left ventricular mass (P<0.01), SCH42495 reduced right ventricular mass (P<0.01), and S21402 decreased left (P<0.05) and right ventricular mass (P<0.01), atrial mass (P<0.05), and lung mass (P<0.01). In CHF, vasopeptidase inhibition with S21402 produces effects that differ from those of selective NEP or ACE inhibition. S21402 improved sodium and water excretion, reduced pulmonary congestion, and attenuated both right and left ventricular remodeling. These effects, which occurred in the absence of any hypotensive action, suggest that S21402 may offer several advantages over ACE inhibition alone in the treatment of heart failure. (Hypertension. 2000;36:1105-1111.)

Key Words: vasopeptidase inhibitors ■ neutral endopeptidase ■ heart failure ■ natriuretic peptides ■ cardiac remodeling

Congestive heart failure (CHF) is a progressive disease characterized by neurohormonal activation, salt and water retention, and cardiac remodeling. Inhibitors of angiotensin converting-enzyme (ACE), which prevent the formation of the constrictor, antinatriuretic, and trophic hormone angiotensin (Ang) II, attenuate ventricular remodeling, improve cardiac function and survival, and are standard treatment for CHF. Atrial natriuretic peptide (ANP) is elevated in proportion to the degree of left ventricular dysfunction and acts as an endogenous antagonist of the renin-angiotensin system (RAS) to cause natriuresis and diuresis, and vasodilation and suppression of the sympathetic nervous system. An increase in endogenous levels of ANP by inhibition of its enzymatic degradation by neutral endopeptidase 24.11 (NEP) is a potential therapeutic strategy in heart failure. Selective NEP inhibition has met with limited success as hyporesponsiveness to the biological actions of ANP occurs with increasing severity of heart failure, whereas the addition of an ACE inhibitor restores some benefits of NEP inhibition, including natriuresis. Several compounds that simultaneously inhibit NEP and ACE, or vasopeptidase inhibitors, have been developed including S21402 and omapatrilat. Although the renal actions of ANP suggest that vasopeptidase inhibitors may be a useful alternative to diuretics, their long-term effects on sodium and water excretion have not yet been assessed in experimental CHF. Because the natriuretic peptides also cause vasodilation, treatment with a vasopeptidase inhibitor has the potential to reduce ventricular preload and afterload and thus ventricular remodeling. Whether such effects will be over and above those seen with selective enzyme inhibition is not clear. In a 4-week study in the infarct rat model, the vasopeptidase inhibitor fasidotril regressed ventricular remodeling in rats to the same extent as an ACE inhibitor, and to date, the effect of vasopeptidase inhibition versus NEP inhibition alone in CHF has not been assessed.

The aims of this study were to investigate whether the vasopeptidase inhibitor S21402 offers any advantage over selective ACE or NEP inhibition in terms of sodium and water excretion, blood pressure, and hormonal and cardiovascular structural responses in a rat model of myocardial infarction–induced CHF. S21402, which simultaneously inhibits NEP and ACE, was compared with the NEP inhibitor, SCH42495, and the ACE inhibitor, captopril, at a dose...
that caused similar NEP and ACE inhibition to that seen with selective enzyme inhibition.

Methods

Experimental procedures were performed according to the National Health and Medical Research Council of Australia guidelines for animal experimentation. S21402 an inhibitor of NEP and ACE\(^1\) (K\(_{i}\) values of 1.7±0.3 nmol/L and 4.2±0.5 nmol/L, respectively) and the selective NEP inhibitor, SCH42495, were gifts from IRIS Pty Ltd (Courbevoie, France) and Schering-Plough Corporation (Kenilworth, New Jersey), respectively. Captopril was purchased from Sigma Chemical Co (St. Louis, Missouri). Female Sprague-Dawley rats from the Austin and Repatriation Medical Center were housed at 23°C to 25°C in a 12-hour light/dark cycle with access to a standard rat chow (0.4% to 0.6% NaCl) and normal water ad libitum.

Experimental Design

The first objective of the study was to select an appropriate dosing regimen for the selective ACE inhibitor captopril, the selective NEP inhibitor SCH42495, and S21402. Previously, we used in vitro autoradiography to show SCH42495 (60 mg \(\cdot\) kg\(^{-1}\) \(\cdot\) d\(^{-1}\)) and S21402 (100 mg \(\cdot\) kg\(^{-1}\) \(\cdot\) d\(^{-1}\)) had similar effects to inhibit renal NEP\(^9\)\(^,\)\(^10\) and that captopril (60 mg \(\cdot\) kg\(^{-1}\) \(\cdot\) d\(^{-1}\)) and S21402 (100 mg \(\cdot\) kg\(^{-1}\) \(\cdot\) d\(^{-1}\)) inhibited renal ACE\(^2\)\(^,\)\(^9\) to the same degree. Assessment of plasma and tissue ACE is complicated because S21402 and captopril contain a sulphydryl group that oxidizes easily, and the results may underestimate the degree of ACE inhibition.\(^9\)\(^,\)\(^10\) Therefore, in this study, inhibition of the pressor responses to Ang I was also used to provide information on the degree of inhibition of circulating ACE.

The second aim was to assess in a rat model of myocardial infarction–induced CHF whether the vasopeptidase inhibitor S21402 offered any advantage over selective ACE or NEP inhibition in terms of sodium and water excretion, blood pressure, and hormonal and cardiovascular structural responses. S21402 was compared with SCH42495 and captopril at a dose that caused similar NEP and ACE inhibition to that seen with selective enzyme inhibition.

In Vivo ACE Inhibition

The potency and duration of action of S21402 and captopril to inhibit the pressor response to Ang I was determined in conscious Sprague-Dawley rats. Rats were anesthetized with an intraperitoneal injection of methohexitone sodium (0.4 mg/kg) and a polyethylene cannula (PE-50) inserted into the right carotid artery and left jugular vein for measurement of mean arterial blood pressure (MAP) and administration of Ang I, respectively. Cannulae were exteriorized to the back of the neck, and rats were allowed to recover for 24 hours with free access to food and water. On the study day, rats were weighed and a blood pressure transducer (model DPT 3003-S, Peter von Berg) was calibrated and connected to the intra-arterial catheter. After a 30-minute baseline period, MAP was recorded and an intravenous bolus of Ang I (300 ng/kg) given. Once MAP had returned to baseline values, rats (n=4 per group) were gavaged with vehicle (5% arabic gum), captopril (25 mg/kg), SCH42495 (30 mg/kg), or S21402 (50 mg/kg). Rats were then rechallenged with Ang I (300 ng/kg) every 10 minutes for 1 hour after gavage. Data were recorded and stored on a MacLab (8TM, Analog Digital Instruments Pty, Ltd). Results are expressed as change in MAP from baseline values.

Heart Failure Study

Left ventricular free-wall myocardial infarction was induced in rats (150 to 200 g) by ligation of the proximal left anterior descending artery.\(^13\)\(^,\)\(^14\) Sham-operated (Control) rats underwent an identical operation but the suture was not tied. Twenty-four hours after surgery, the surviving rats were randomized to 1 of 5 treatment groups: vehicle (5% arabic gum), captopril (50 mg \(\cdot\) kg\(^{-1}\) \(\cdot\) d\(^{-1}\)), SCH42495 (60 mg \(\cdot\) kg\(^{-1}\) \(\cdot\) d\(^{-1}\)), or S21402 (100 mg \(\cdot\) kg\(^{-1}\) \(\cdot\) d\(^{-1}\)). Drugs were given by oral gavage in 2 divided doses daily for 4 weeks. Control rats received vehicle. Body weight was measured weekly. Systolic blood pressure (SBP) was measured weekly by tail-cuff plethysmography (38L flatbed recorder, model 229 Amplifier, IITC Life Science). SBP was measured in a subset of rats (n=30) preoperatively and in all rats postoperatively.

After 1 week of treatment, Control (n=14) and CHF (n=8 to 12 per group) rats were placed in metabolic cages, and the following day (ie, on Day 9 of treatment), a 24-hour urine collection was made to assess urinary sodium and volume. After 4 weeks of treatment, rats were killed by decapitation and trunk blood was collected into prechilled tubes that contained EDTA/aprotinin for measurement of ANP and plasma renin activity (PRA) and into lithium heparin tubes for measurement of aldosterone. Kidneys were snap-frozen in isopentane at –40°C for in vitro NEP and ACE autoradiography. The heart was weighed and dissected into left ventricle and interventricular septum (LV), right ventricle (RV), and atria and weighed. The LV was fixed in 10% formalin and sectioned at 4 levels from the base to the apex, and the paraffin was fixed and its sections were cut and stained with Masson’s trichrome. The mean epicardial and endocardial scar circumference was compared with total left ventricular circumference to calculate infarct size.\(^13\)

In Vitro Autoradiography

Quantitative in vitro autoradiography was performed on renal sections (20 \(\mu\)m) from CHF rats (n=4 per group) with the radioligand \(^125\)I-RR104 for NEP and \(^125\)I-MK351A for ACE as previously described.\(^15\)\(^,\)\(^17\) Quantification of binding density was determined by computerized densitometry with radioactive standards, which were corrected for decay and fitted to calibration curves to convert the optical density of the autoradiographs to dpm per mm\(^2\).

Biochemical Assays

PRA and ANP were measured by radioimunoassay.\(^18\)\(^,\)\(^19\) Urine sodium was measured with an ion-selective electrode (ILyte, Instrumentation Laboratory). Plasma aldosterone was measured by radioimunoassay with a commercially available kit (Diagnostic Products Corporation).

Statistical Analysis

Results are presented as mean±SEM. Data were analyzed using ANOVA followed by post-hoc analysis with the Fisher test when appropriate. Significant differences were obtained when P<0.05.

Results

In Vivo ACE Inhibition

Baseline MAP in conscious rats was similar in all groups (vehicle, 94±6; captopril, 98±5; SCH42495: 111±6; and
Infarct Size, Body Weight, Blood Pressure, Hormonal Changes and Organ Weights After 4 Weeks of Treatment in Control and CHF Rats

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Vehicle</th>
<th>Captopril</th>
<th>SCH42945</th>
<th>S21402</th>
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<tr>
<td>Infarct size, %</td>
<td></td>
<td>40±3†</td>
<td>44±2</td>
<td>42±2</td>
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<tr>
<td>Body weight, g</td>
<td>238±5</td>
<td>241±3</td>
<td>218±7**</td>
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<td>SBP, mm Hg</td>
<td>117±2</td>
<td>115±5</td>
<td>94±4**</td>
<td>104±6</td>
<td>120±2</td>
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<td>Hormonal parameters</td>
<td></td>
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<tr>
<td>PRA, nmol Ang l/L/h</td>
<td>4.4±0.4</td>
<td>5.1±1</td>
<td>37.4±3.7**</td>
<td>9.9±0.9</td>
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<tr>
<td>Plasma ANP, pmol/L</td>
<td>27±3.4</td>
<td>77±17†</td>
<td>50±10</td>
<td>66±8</td>
<td>56±13</td>
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<tr>
<td>Plasma aldosterone, pmol/L</td>
<td>928±92</td>
<td>756±122</td>
<td>469±75*</td>
<td>481±57*</td>
<td>464±47**</td>
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<td>Organ data</td>
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<td>Heart weight, g/kg</td>
<td>3.61±0.1</td>
<td>4.72±0.3†</td>
<td>4.05±0.2**</td>
<td>4.13±0.2*</td>
<td>3.78±0.1**</td>
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<td>LV weight, g/kg</td>
<td>2.27±0.04</td>
<td>2.53±0.1†</td>
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<td>2.36±0.06</td>
<td>2.33±0.04*</td>
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<td>RV weight, g/kg</td>
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<td>1.37±0.14†</td>
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<td>1.03±0.09**</td>
<td>0.84±0.05**</td>
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<td>Atrial weight, g/kg</td>
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<td>0.73±0.11†</td>
<td>0.59±0.07</td>
<td>0.6±0.07</td>
<td>0.51±0.05*</td>
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<td>Lung weight, g/kg</td>
<td>6.26±0.38</td>
<td>8.98±0.96†</td>
<td>8.55±1.4</td>
<td>6.89±0.49</td>
<td>5.84±0.45**</td>
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<td>Tissue enzymes</td>
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<tr>
<td>Renal NEP, % of vehicle</td>
<td>100±11</td>
<td>83±5</td>
<td>31±3**</td>
<td>26±1**</td>
<td></td>
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<tr>
<td>Renal ACE, % of vehicle</td>
<td>100±5</td>
<td>64±9**</td>
<td>79±3</td>
<td>52±8**</td>
<td></td>
</tr>
</tbody>
</table>

Values are given as mean±SEM; n=17 for Control rats. In CHF rats, n=7 to 14/group except for enzymes where n=4/group.
†P<0.01 Control vs. CHF vehicle; *P<0.05; **P<0.01 CHF vehicle vs. CHF treatment.

S21402, 88±9 mm Hg) (n=4 per group). The average pressor response to Ang I was 48±4 mm Hg (time 0, Figure 1). Vehicle and SCH42495 had no effect on Ang I–induced increases in MAP. Both S21402 (50 mg/kg) and captopril (25 mg/kg) inhibited the pressor responses to Ang I for up to 60 minutes (P<0.05), which indicated significant and equipotent inhibition of circulating ACE.

Infarct Size, Body Weight, and Blood Pressure
All control rats were alive at the end of the treatment period and none had histological evidence of cardiac damage (n=17). The operative mortality for CHF rats was ~20%. Rats with small infarcts (<20%) or subendocardial infarcts were excluded from the data analysis. Thus, results are reported on 46 CHF rats (vehicle, n=11; captopril, n=10; SCH42495, n=11; and S21402, n=14). The average infarct size was 40±3% and was similar in all CHF rats irrespective of treatment (Table 1). Baseline body weight was similar in all groups (182±2 g), and all rats gained weight during the study period (P<0.001). At week 4, rats treated with captopril or S21402 had reduced body weight compared with vehicle-treated CHF rats (P<0.01) (Table 1).

Baseline SBP measured preoperatively in a subset of rats was 116±2 mm Hg (n=30). One week after infarction, blood pressure was reduced in all infarct rats (n=8 to 14 per group) compared with the Control (n=14) rats (P<0.01) (Figure 2). After 4 weeks of treatment, captopril alone significantly reduced blood pressure compared with vehicle-treated CHF rats (P<0.01) (Figure 2, Table 1).

Renal Effects
CHF rats had sodium retention as indicated by reduced sodium excretion compared with Control rats (P<0.05) (Figure 3). S21402 markedly increased urine volume and urine sodium excretion compared with vehicle (P<0.01) (Figure 3). Neither captopril nor SCH42495 had diuretic nor natriuretic actions in CHF rats.

Hormonal and Tissue Enzyme Inhibitory Effects
CHF rats had increased plasma ANP (P<0.01) and unchanged PRA and aldosterone compared with Control rats (Table 1). In rats with CHF who received treatment with captopril, SCH42495, or S21402, plasma ANP was unchanged compared with vehicle alone. PRA increased with captopril and S21402 (P<0.01), with no difference between the 2 drugs. Plasma aldosterone was significantly reduced by all active treatment compared with levels in vehicle-treated CHF (captopril, SCH42495, P<0.05; S21402, P<0.01).
This page contains a single paragraph of text discussing the results of a study on the effects of vasopeptidase inhibition with S21402 in experimental heart failure. The text describes the inhibition of renal NEP and ACE with SCH42495 and S21402, and the reduction in LV, RV, atrial, and lung masses with S21402 compared to control rats.

Cardiovascular Structural Effects

Rats with CHF were characterized by increased relative heart, LV, RV, and lung mass compared to control rats. S21402 reduced whole heart mass through a reduction in all heart chambers (ie, LV, RV, and atria). Captopril reduced LV mass, and SCH42495 reduced RV mass.

Discussion

The objective of this study was to investigate whether vasopeptidase inhibition with S21402 would offer any advantage over selective ACE or NEP inhibition in experimental heart failure, such as enhanced renal sodium and water excretion, or improved blood pressure, hormonal, and cardiovascular structural responses. The results of this study suggest that treatment with S21402 does offer specific advantages in CHF in that inhibition of both ACE and NEP was associated with major benefits to increase sodium and water excretion and to relieve pulmonary congestion compared with ACE inhibition alone. Furthermore, although inhibition of ACE with S21402 was accompanied by improved cardiac remod-
ling, treatment with S21402 did not have the adverse effect of causing hypotension in CHF.

To date, no studies in experimental heart failure have compared a vasopeptidase inhibitor with selective NEP and ACE inhibitors used at doses that cause a similar level of NEP or ACE inhibition as the vasopeptidase inhibitor itself. In this study, we confirmed previous work that showed SCH42495 (60 mg·kg\(^{-1}\)·d\(^{-1}\)) and S21402 (100 mg·kg\(^{-1}\)·d\(^{-1}\)) had similar effects to inhibit renal NEP and that captopril (60 mg·kg\(^{-1}\)·d\(^{-1}\)) and S21402 (100 mg·kg\(^{-1}\)·d\(^{-1}\)) inhibit renal ACE to the same degree.\(^9,10\) Because results from in vitro autoradiographic studies with sulfhydryl group–containing drugs such as S21402 and captopril may underestimate the degree of ACE inhibition,\(^6\) inhibition of the pressor responses to Ang I after treatment was also assessed. The results of this study clearly show that captopril and S21402 cause potent inhibition of circulating ACE and result in similar renal tissue ACE inhibition after 4 weeks’ use in heart failure.

This model of myocardial infarction–induced heart failure results in hemodynamic alterations and neurohumoral activation seen in patients with myocardial infarction and results from such studies have clinical implications.\(^1,13\) All infarcted rats had histological verification of infarct sizes, and all showed signs of pulmonary congestion. In addition, there was evidence of sodium retention, which suggested reduced effectiveness of an elevated ANP to maintain a natriuresis in this model of CHF.

A major finding of this study was that S21402, but not selective NEP or ACE inhibition, caused natriuresis and diuresis in CHF. Urinary measurements of sodium and volume from an ongoing study (Leanne Balding, unpublished data, 2000) in the same model of CHF show that on day 28 of treatment with S21402, there is a significant natriuresis (vehicle, 0.46±0.1 versus S21402, 0.65±0.1 μmol/min/100 g, \(P<0.05\)), and diuresis (vehicle: 7±1 versus S21402, 10±1 mL/100 g/24h, \(P<0.05\)). The renal responses to long-term vasopeptidase inhibition in experimental CHF have not previously been investigated, and the data from short-term studies has been variable. This study confirms the finding that acute administration of S21402 in a rat model of CHF\(^8\) produced a natriuresis, although acute studies that combine a NEP inhibitor with an ACE inhibitor in experimental CHF may\(^6\) or may not\(^20,21\) increase sodium excretion.

Resistance to the renal effects of ANP in CHF\(^22\) is well known. Several mechanisms are likely to be involved in the restoration of these responses with S21402, including the maintenance of blood pressure with S21402, which may result in improved renal perfusion. It is also likely that sustained inhibition of both renal ACE and NEP with S21402 resulted in reduced intrarenal Ang II and increased tissue ANP levels, respectively, with the consequent effects to oppose the antinatriuretic actions of an activated renal RAS and renal sympathetic activity.\(^23\) An advantage of the technique of in vitro autoradiography is the ability to demonstrate in the kidney that NEP and ACE are inhibited by S21402; inhibition of renal NEP prevents the degradation of ANP filtered by the glomerulus and enables ANP to reach receptors in the distal segment of the nephron to cause a natriuresis and diuresis.

Changes in ANP may not be the sole mediator of the renal response because inhibition of NEP may also increase endogenous levels of other natriuretic peptides, such as brain natriuretic peptide.\(^24\) In addition, because both NEP and ACE inactivate kinins, combined NEP/ACE inhibition with S21402 may result in enhanced kinin levels. Kinins were not measured in this long-term study, but acute studies in heart failure have reported natriuresis and increased renal excretion of bradykinin with S21402.\(^8\)

Hypotension with ACE inhibition is a well-recognized adverse effect of treatment in CHF,\(^25\) and the lack of hypotensive effect of S21402 differentiates it from captopril. The mechanism underlying the blood pressure response to S21402 is not clear but because both S21402 and captopril produced equivalent inhibition of systemic and tissue ACE, the difference in blood pressure response with S21402 may relate to improved cardiac function. Certainly in the same model of CHF, 40 weeks of treatment with the NEP/ACE inhibitor fasidotril was associated with improved cardiac hypertrophy and survival\(^26\) in the absence of blood pressure reduction. These data suggest that vasopeptidase inhibitors such as S21402 may confer some benefit in heart failure in which excess hypotension can be deleterious.\(^27\)

Experimental and clinical trials have shown ACE inhibitors slow the deterioration of the failing heart and improve long-term survival partly through reversal of the neurohumoral activation and also through inhibition of cardiac ACE\(^28\) and attenuation of remodeling.\(^1,13\) In real terms, the modest effect of ACE inhibitors on mortality and the continued remodeling even in the face of ACE inhibition\(^29\) highlights the need for additional therapy. In this study, the beneficial effects of S21402 on cardiac remodeling were equal to the sum of the effects of selective ACE or NEP inhibition. Thus, captopril regressed left ventricular mass, SCH42495 reduced RV mass, and S21402 reduced the mass of both ventricles. Although myocardial function was not directly assessed, the Pfeffer group has reported that improvements in cardiac remodeling were associated with improved function.\(^13\) S21402 led to a reduction in LV mass in the absence of a reduction in blood pressure consistent with the suggestion that inhibition of an activated cardiac RAS and reduction in cardiac Ang II levels\(^30\) are important in regression of remodeling.

The finding that both S21402 and the selective NEP inhibitor SCH42495 caused regression of right ventricular hypertrophy, a marker of overload hypertrophy, suggests the natriuretic peptides may be involved in the structural remodeling of the failing heart in an autocrine or paracrine manner, particularly as neither drug caused any change in circulating ANP. Certainly, NEP is expressed in the heart,\(^31\) and natriuretic peptide receptor genes have been localized in myocardial cells.\(^32\) In the spontaneously hypertensive rat, NEP inhibition with SCH42495 reduced left ventricular hypertrophy and fibrosis with minimal effects on blood pressure.\(^10\) Furthermore, cell culture work indicates that ANP is a specific effector of cardiac myocyte apoptosis via receptor-mediated elevation of cGMP\(^33\) and inhibits noradrenaline-
induced hypertrophy in ventricular myocytes and fibroblasts. Thus, NEP inhibition may not only promote the natriuretic peptides’ growth inhibitory effects in the heart but also protect the heart from the effects of progressive adrenergic activation, which occurs in CHF even in the presence of ACE inhibition.

Other factors may also play a role in the regression of cardiac remodeling. Plasma aldosterone concentrations were reduced in response to all active treatment, and the decrease in plasma and possibly tissue aldosterone may contribute to the ability of captopril, SCH42495, and S21402 to attenuate cardiac hypertrophy. The role that NEP and ACE play in the inactivation of kinins in the heart also requires assessment; the combination of NEP and ACE inhibition with ecadotril and perindopril in the rat infarct model showed an interaction between remodeling and increased cardiac bradykinin levels.

In practice, ACE inhibitors are often combined with diuretics to relieve congestive symptoms. The renal actions of S21402 and its effects to reduce pulmonary congestion suggest it may be a useful alternative to a diuretic, especially as diuretics cause further stimulation of the RAS and sympathetic nervous system, which may limit their long-term efficacy. Although the influence of the diuretics on survival in CHF is unknown, recent studies in experimental CHF have shown promising effects of vasopeptidase inhibitors on survival.

Further studies are needed to determine the precise mechanism of action of the vasopeptidase inhibitors. This is made complex because NEP is a ubiquitous ecto-enzyme present not only in the kidney but also in the lung, brain, intestine, spleen, endothelial cells, and neutrophils, and has multiple substrates. As well as its involvement in the degradation of the natriuretic peptides and bradykinin, NEP also degrades Ang I and II and endothelin, whereas NEP inhibition can modulate endothelin-converting enzyme. A word of caution is needed in interpreting data from studies of NEP and vasopeptidase inhibitors because increasing evidence suggests that data obtained with one NEP inhibitor cannot be extrapolated to another. For example, in this study in heart failure, NEP inhibition did not change plasma ANP, yet in both experimental hypertension and essential hypertension, SCH42495 increased plasma ANP. NEP also degrades Ang I and II and endothelin, whereas NEP inhibition can modulate endothelin-converting enzyme.

The relative degree of ACE versus NEP inhibition also varies between vasopeptidase inhibitors; in the rat, omapatrilat has similar potency to inhibit renal NEP and ACE, whereas S21402 has greater efficacy to inhibit renal NEP compared with ACE. The long-term benefits of ACE inhibitors in preventing or reversing target organ damage depends on their ability to inhibit tissue ACE and whether differences in the degree or the site of NEP inhibition are of importance remains to be determined.

To summarize, vasopeptidase inhibition with S21402 in a rat model of CHF improved sodium and water excretion, attenuated right and left ventricular remodeling, and reduced pulmonary congestion. These improvements occurred in the absence of any hypotensive effects and suggest S21402 may offer several advantages over ACE inhibition alone in the management of heart failure. Studies are ongoing in our laboratory to assess whether the differential effects of S21402 compared with ACE inhibition are associated with any difference in survival in experimental CHF.

Acknowledgments

This work was supported by the National Heart Foundation of Australia and by IRIS Pty Ltd (Courbevoie, France). Nicole Farina was supported by a scholarship from the Wenkhart Foundation, and Leanne Balding was supported by a scholarship from the Cardiac Society of Australia and New Zealand.

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Hypertension. 2000;36:1105-1111
doi: 10.1161/01.HYP.36.6.1105

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