Renal Effects of Omapatrilat and Captopril in Salt-Loaded, Nitric Oxide–Deficient Rats

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Abstract—Inhibition of nitric oxide synthases causes systemic hypertension and renal injury in rats. Our objective was to examine whether omapatrilat, a vasopeptidase inhibitor that inhibits both angiotensin-converting enzyme (ACE) and neutral endopeptidase, could induce better regression of renal injury than ACE inhibitor alone. Ten groups of rats were studied. They were fed either a normal (0.8% NaCl) or a high (4% NaCl) sodium diet. Eight of these groups received N\textsuperscript{\textalpha}-nitro-l-arginine methyl ester (l-NNAME, 20 mg · kg\textsuperscript{-1} · d\textsuperscript{-1}) in their drinking water. After 4 weeks, 1 group on each diet was killed and considered the l-NNAME group, whereas the others received l-NNAME alone, captopril (200 mg · kg\textsuperscript{-1} · d\textsuperscript{-1}) plus l-NNAME, or omapatrilat (80 mg · kg\textsuperscript{-1} · d\textsuperscript{-1}) plus l-NNAME for 4 additional weeks. In rats receiving l-NNAME alone for 8 weeks, the mortality rate was \textapprox 90%, irrespective of the diet. In contrast, all rats survived in the captopril and the omapatrilat groups. In rats fed a normal-sodium diet, captopril and omapatrilat normalized systolic blood pressure and induced a complete regression of renal injury. Creatinine clearance and proteinuria were also normalized. In the high-sodium-diet groups, both treatments were less efficient: blood pressure remained elevated, and the regression of renal fibrosis was only partial. Although proteinuria decreased significantly with captopril or omapatrilat, creatinine clearance remained lower than in the controls. These results demonstrate that, in nitric oxide–deficient rats fed a normal-sodium diet, ACE and vasopeptidase inhibitors exhibit a marked renoprotective effect, whereas these treatments are less efficient in rats fed a high-sodium diet. (Hypertension. 2003;42:937-944.)

Key Words: hypertension, renal \(\bullet\) kidney failure \(\bullet\) angiotensin-converting enzyme \(\bullet\) peptides \(\bullet\) nitric oxide \(\bullet\) sodium, dietary

Vasopeptidase inhibitors are novel molecules that inhibit both angiotensin-converting enzyme (ACE) and neutral endopeptidase 24.11 (NEP).\textsuperscript{1} The emergence of this new class of drugs followed the demonstration that ACE and NEP are 2 key enzymes that play a major role in regulating cardiovascular and renal functions. The simultaneous inhibition of these 2 enzymes can reduce the vasoconstrictive, hypertrophic, and antinatriuretic activities of the renin-angiotensin system and potentiate the vasodilatory, natriuretic, and anti-proliferative effects of bradykinin and natriuretic peptides.\textsuperscript{2} As a component of the circulating and local renin-angiotensin system, ACE catalyzes the conversion of angiotensin I (Ang I) to Ang II, a vasoconstrictor agent playing a central role in the pathogenesis of hypertension. In addition to its direct actions, Ang II increases the production of endothelin-1 (ET-1), and plasminogen activator inhibitor-1, both of which promote vasoconstriction, thrombosis, and fibrosis.\textsuperscript{3,4} ACE inhibition is a well-established and effective treatment for hypertension. Nevertheless, it has been recently proposed that, in addition to ACE inhibition, inhibition of NEP, which augments the effects of natriuretic peptides, including atrial, B-type, and C-type natriuretic peptides, could also have a therapeutic benefit.

In this regard, the purpose of this study was to determine whether omapatrilat, 1 of these novel vasopeptidase inhibitors, might produce enhanced hemodynamic effects in a rat model of hypertension and nephroangiosclerosis. Inhibition of long-term nitric oxide (NO) synthesis by a nonselective inhibitor of NO synthases (NOSs), such as N\textsuperscript{\textalpha}-nitro-l-arginine methyl ester (l-NNAME), in rats and mice promotes severe and progressive arterial hypertension and renal injury, with a decrease in glomerular filtration rate and appearance of glomerular ischemia, glomerulosclerosis, interstitial expansion, and proteinuria.\textsuperscript{5-8} Several investigators have shown that during NOS inhibition, continuous Ang II blockade by ACE inhibitors or by Ang II receptor type 1 antagonists prevented\textsuperscript{6,9} these effects. Even more, there was a regression of renal fibrosis and hypertension when the treatment was applied in a second stage,\textsuperscript{10} suggesting an essential role for Ang II in the pathogenesis of renal injury in a model of NO deficiency. It has been shown that in rats with long-term NOS inhibition, excessive sodium intake aggravates hypertension...
and renal parenchymal injury. In this model, the natriuretic peptide system is activated, and involvement of the renin-angiotensin system might not be so marked. This salt-dependent hypertensive effect was a function of the inhibitor dose, and renal injury varied directly with the level of salt intake.13 This prompted us to compare the effects of omapatrilat and captopril in this model of salt-loaded, NO-deficient rats. In accordance with previous studies from our laboratory,10 rats were given 20 mg · kg·d⁻¹ · d⁻¹ L-NAME in the drinking water. They received a rat chow containing standard sodium (0.8% NaCl) or a high sodium (4% NaCl) content. This dietary salt excess has been shown to induce a proteinuria that reaches nephrotic levels.12 After 1 month of L-NAME administration, NaCl content. This dietary salt excess has been shown to induce a proteinuria that reaches nephrotic levels.12 After 1 month of L-NAME administration, omapatrilat or captopril was added to the diet for 4 additional weeks. Therefore, in the present study, we associated long-term NO blockade and NaCl overload to examine the hypothesis that inhibition of both ACE and NEP with omapatrilat will produce a better regression of hypertension and renal fibrosis than captopril at a similar intensity of ACE inhibition and thus, result in a greater therapeutic benefit.

Methods

Experimental Protocol

All experiments were conducted according to European Community guidelines. Male Sprague-Dawley rats, weighing 200 g at the beginning of the protocol, were given free access to regular (0.8% NaCl) or high-sodium (4% NaCl) rat chow, which corresponds to an intake of 17 mEq Na⁺/d, along with tap water ad libitum. As expected, Na⁺ excretion, reported as urinary Na⁺/urinary creatinine, was markedly increased in the high-sodium group (19.7 ± 1.46 vs 6.25 ± 0.50 mEq/mmol, P = 0.001). NO synthesis was inhibited by administering L-NAME (20 mg · kg⁻¹ · d⁻¹) in drinking water for 4 or 8 weeks. After 4 weeks of L-NAME treatment, each group of rats (normal and high-sodium diet) was divided into 4 subgroups: 1 was humanely killed, another 1 continued to receive L-NAME, and the remaining 2 received L-NAME, in combination with either captopril or omapatrilat for 4 additional weeks. Adequate concentrations of these 2 drugs were determined in preliminary studies according to Trippodo et al.13 Their potency in inhibiting the pressor response to Ang II was studied in conscious rats treated for 1 week before the test with increasing doses of each of these molecules, so that we could choose for each drug the dose that gave the same inhibition of ACE activity. Captopril was given at a dose of 200 mg · kg⁻¹ · d⁻¹ in drinking water and omapatrilat, at a dose of 80 mg · kg⁻¹ · d⁻¹, in food. This dose has been shown to inhibit NEP activity in several studies.14,15 The results of all L-NAME-treated rats were compared with those of age-matched control rats given a normal or a high-sodium chow. Eighteen to 22 rats were used in each experimental subgroup.

Before being euthanized, the rats were housed in metabolic cages for 24 hours for collection of urinary samples. At the end of the experiment, animals were anesthetized; the trunk blood was collected into heparinized tubes, centrifuged at 1600g, and stored at −80°C until analysis; and the kidneys were removed.

Blood Pressure Recording

Systolic blood pressure (SBP) was estimated in conscious animals by the tail-cuff method, as previously described.8

Kidney Histopathology

Kidneys from at least 5 rats from each group were immersed in Duboscq solution. After fixation, 4 to 6 cortical slices of each kidney were embedded in paraffin after conventional processing (alcohol dehydration), and 3-μm-thick sections were stained with Masson’s trichrome solution for extracellular matrix protein staining or with Sirius red for collagen staining. Assessment of glomerulosclerosis was performed as previously described.7 Sections of kidneys were examined on a blinded basis, using the 0 to 4 injury scale.

Measurement of Urinary Protein and Creatinine and Plasma Creatinine

Urinary protein concentration was measured by protein assay (Bio-Rad). Values are expressed as milligrams of protein excreted per 24 hours. Creatinine was measured by the automated Jaffe method. Creatinine clearance was expressed as milliliters per minute.

Measurement of Plasma CGMP and Urinary, Plasma, and Renal ET-1

Plasma CGMP was measured with a radioimmunooassay kit (Amersham International) after ethanol extraction. Plasma, urinary, and renal ET-1 values were estimated with a radioimmunooassay kit (Amersham International) after extraction on C18 cartridges (Sep-Pak). For measurement of tissue ET-1, kidneys were removed from the rats and quickly frozen, and then ET-1 was extracted by using the protocol described by Sasser et al.16 Results were expressed as femtomoles of ET per milligram of total protein. Plasma was acidified and centrifuged before extraction. Concentrations of plasma and urinary sodium were determined by flame photometry.

Statistical Analysis

Data, presented as mean ± SEM, were compared by a 2-way ANOVA analysis (diet and treatment). When there was no significant difference according to Na⁺ intake, comparisons between drug treatments were performed with a 1-way ANOVA. ANOVA was followed by the Fisher protected least significance difference test. A value of P < 0.05 was considered statistically significant (Stat-View software package).

Results

Effect of Captopril and Omapatrilat on Survival Rates of L-NAME–Treated Rats

After 4 weeks of L-NAME treatment, the survival rate averaged 87% for rats given a normal sodium diet and 91% for rats given a high-sodium diet. After 8 weeks of treatment, the survival rate in these 2 groups was 10% and 5%, respectively. When rats received captopril or omapatrilat from the fourth to the eighth week of L-NAME treatment, all of them survived, regardless of dietary assignment (Figures 1A and 1B).

Effect of Captopril and Omapatrilat on the Renal Vascular Structure of L-NAME–Treated Rats

In agreement with our previous results,8 renal vascular and glomerular sclerosis was evident after 4 weeks of L-NAME treatment, as demonstrated by Masson’s staining (Figures 2A and 2B, a and b). Semiquantitative evaluation of extracellular matrix formation after 4 weeks of L-NAME treatment confirmed renal injury in L-NAME–treated rats versus control rats. Glomerulosclerosis indices (Figures 3A and 3B) were 2.58 ± 0.26 and 2.28 ± 0.21 in L-NAME–treated rats given a normal or a high-sodium diet, respectively, versus 0.31 ± 0.064 and 0.45 ± 0.083 in the matched control groups (P < 0.05).

When L-NAME–treated rats received captopril or omapatrilat from the fourth to the eighth week, renal vascular histology was improved (Figures 2A and 2B, c and d). Glomerulosclerosis indices were 0.93 ± 0.27 with captopril and 0.88 ± 0.13 with omapatrilat in the groups of rats given a
normal-sodium diet, whereas they were 1.26/0.22 with captopril and 1.75/0.13 with omapatrilat in the group of rats given a high-sodium diet. Both drugs blunted significantly the degree of glomerulosclerosis, compared with L-NAME matched groups, regardless of sodium intake (P<0.05), but the effect of omapatrilat was significantly smaller than that of captopril in the group of L-NAME rats given a high-sodium diet (P<0.05).

Staining of renal sections by Sirius red showed collagen accumulation in glomeruli and arterial walls after 4 weeks of L-NAME treatment. This accumulation was reduced by captopril or omapatrilat treatment regardless of diet, but to a lesser extent in the group of L-NAME rats given a high-sodium diet (Figures 4A and 4B).

Effect of Captopril and Omapatrilat on SBP of L-NAME–Treated Rats

In the first group of rats given a normal-sodium diet, SBP rose after 4 weeks of L-NAME treatment (191±4 mm Hg vs 114±2 mm Hg, P<0.05). When captopril or omapatrilat was coadministered with L-NAME from the fourth to the eighth week. SBP was identically improved and returned to basal values (116±2 mm Hg with captopril and 112±2 mm Hg with omapatrilat; Figure 5A).

In the second group of rats given a high-sodium diet (Figure 5B), basal SBP was not modified (110±3 mm Hg). After 4 weeks of L-NAME treatment, SBP rose to 195±3 mm Hg (P<0.05 vs matched controls). Coadministration of captopril or omapatrilat from the fourth to the eighth week of L-NAME treatment induced the same significant decrease of SBP (172±3 mm Hg with captopril and 162±3 mm Hg with omapatrilat; P<0.05 vs L-NAME treated rats), but these SBP values remained significantly higher than basal values (P<0.05).

Effect of Captopril and Omapatrilat on Renal Functional Parameters in L-NAME–Treated Rats

Structural L-NAME–induced changes were associated with deterioration of renal function, as indicated by a decrease in creatinine clearance and an increase in urinary protein excretion. In the normal-salt-diet group of rats, the decrease in creatinine clearance after 4 weeks of L-NAME treatment (0.80±0.08 vs 1.85±0.16 mL/min, P<0.05 for control rats) was totally reversed by coadministration of captopril or omapatrilat from the fourth to the eighth week of L-NAME treatment.
treatment (1.77±0.13 mL/min for captopril and 1.88±0.13 mL/min for omapatrilat; \( P<0.05 \) vs l-NAME–treated rats; Figure 6A). When rats were fed a high-salt diet (Figure 6B), creatinine clearance was not modified in controls (1.67±0.11 mL/min) and decreased to 0.67±0.07 mL/min after 4 weeks of l-NAME treatment. Creatinine clearance was significantly increased by coadministration of captopril or omapatrilat with l-NAME (1.25±0.11 and 1.09±0.07 mL/min, respectively; \( P<0.05 \) vs l-NAME–treated rats) from the fourth to the eighth week of the experiment. However, it remained significantly lower than controls after administration of both drugs. Proteinuria was elevated after 4 weeks of l-NAME treatment in the groups fed a normal- or a high-sodium diet (58.1±13.5 and 162±16.2 mg/24 h, respectively, vs 20.4±1.4 and 22.5±1.5 mg/24 h for controls; \( P<0.05 \)). It was significantly reduced (\( P<0.05 \)) by coadministration of captopril (26.4±2.11 and 79.15±9.06 mg/24 h) or omapatrilat (33.1±5.18 and 87.6±12 mg/24 h; Figures 7A and 7B). As was the case for creatinine clearance, omapatrilat or captopril treatment had a similar effect on proteinuria, with complete normalization in the normal-diet group but only partial decrease in the high-salt-diet group (\( P<0.05 \)).

Effect of Captopril and Omapatrilat on Plasma cGMP and Plasma, Urinary, and Renal ET-1 Concentrations of l-NAME–Treated Rats

In the group of rats fed a normal-salt diet, plasma cGMP was not modified by l-NAME treatment. Coadministration of captopril with l-NAME from the fourth to the eighth week did not significantly modify this value, whereas coadministration of omapatrilat with l-NAME induced a significant increase in cGMP production, confirming omapatrilat’s efficiency in NEP inhibition. In the high-salt-diet group, l-NAME treatment induced a significant increase in plasma cGMP. This increase was reversed by cotreatment with captopril but not with omapatrilat (Table 1).

Because ET-1 participates in the mechanism of renal vascular fibrosis, we measured plasma, renal, and urinary
ET-1 levels in the different groups of rats. Plasma ET-1 levels were not significantly modified by the diet and the treatment, as shown by the 2-way ANOVA (Table 2). Renal ET-1 tissue levels were not significantly altered by the increase in Na\(^+\) intake (\(P=0.15\)). However in L-NAME–treated rats, these levels were significantly increased (\(P<0.05\)), especially in the high-salt-diet group. In rats treated with captopril or omapatrilat, renal ET-1 tissue levels returned to basal values (Table 2). Changes in ET-1 urinary excretion during captopril or omapatrilat treatment were not parallel to those in ET-1 renal content. Urinary ET-1 concentration did not vary according to the Na\(^+\) intake (\(P=0.46\)), and after 4 weeks, L-NAME did not significantly increase this parameter (\(P=0.19\)). In rats receiving L-NAME and captopril, urinary ET-1 concentration was slightly elevated compared with L-NAME alone (\(P=0.048\)). This increase was much more marked in rats treated with omapatrilat (\(P<0.01\)).

**Discussion**

Vasopeptidase inhibitors open new perspectives in the treatment of hypertension and its consequences on target organs.\(^{17,18}\) Several experimental studies have demonstrated their efficiency in lowering high blood pressure.\(^{19,20}\) However, few studies have evaluated their effects on end-stage renal disease during the course of hypertension. Here, we compared the effects of the selective ACE inhibitor captopril and of the vasopeptidase inhibitor omapatrilat on renal injury induced by NO deficiency in rats fed a normal- or a high-sodium diet. The experimental procedure reproduced a usual clinical situation in which antihypertensive therapy is initiated after the onset of hypertensive disease. Both antihypertensive treatments dramatically improved the survival rate, independent of the sodium diet. Data in rats receiving only L-NAME for 8 weeks could not be collected because of the high rate of mortality (>90%) in these groups. This led us to
Ang II and ET-1 are involved in the process leading to hypertension, renal failure, and mortality in rats receiving an inhibitor of NO synthases while being fed a normal-sodium diet.\textsuperscript{5,6,8,10} In recent studies, we observed that losartan, an Ang II type 1 receptor antagonist, or bosentan,\textsuperscript{10} a mixed ET-1 receptor antagonist, not only prevented but also reversed renal fibrosis induced by NO deficiency. Our present results are in agreement with these data. We found that blockade of the renin-angiotensin system by captopril normalized SBP and improved histology and function of the kidneys in rats that had received L-NAME for 4 weeks. In this model, the efficiency of captopril can be explained by the inhibition of several Ang II–dependent mechanisms, including the decrease in glomerular pressure with its beneficial consequences on proteinuria,\textsuperscript{21} the inhibition of collagen synthesis,\textsuperscript{22} the blockade of plasminogen activator inhibitor-1 synthesis,\textsuperscript{3,23} and the decrease of renal ET-1 synthesis.\textsuperscript{4} Regarding this major parameter of renal injury in the L-NAME model of hypertension,\textsuperscript{7,8} we demonstrated here that ACE inhibitors, AT-1 blockades, or renin inhibitors – which inhibit Ang II and ET-1 generation – might have induced deleterious effects on renal hemodynam-
ics by inhibiting Ang-(1-7) formation from Ang I accumulated during ACE inhibition.\textsuperscript{24} In fact, in previous studies performed in renin-dependent hypertensive models, dual inhibition of NEP and ACE was as efficient as selective ACE inhibition on blood pressure\textsuperscript{1,2,17} and end-organ protection.\textsuperscript{19,25–27} Moreover, in recent studies, Ferrario et al\textsuperscript{28,29} observed that omapatrilat did not decrease but increased the renal levels of Ang-(1-7) by blocking its catabolism. Confirming these data, our study shows that SBP, as well as plasma creatinine, proteinuria, and glomerulosclerosis index, were equally reduced with both drugs. Both groups differed regarding plasma cGMP concentration, which was more elevated with omapatrilat. cGMP is the second messenger of natriuretic peptides in their target cells.\textsuperscript{30} As previously demonstrated, the rise of plasma or urinary levels of cGMP is a very sensitive index of NEP inhibitor activity.\textsuperscript{31,32} especially when the NO-dependent production of cGMP is blocked, as was the case with \textsuperscript{L}-NAME in our study.\textsuperscript{5,7} Of note, cGMP was increased in both treated groups compared with controls, although the improvement in glomerular filtration rate should have favored a decrease of its plasma levels.\textsuperscript{31} This observation suggests that prolonged NO deprivation associated with ACE inhibition induced sodium retention, which was counterbalanced by an increased production of natriuretic peptides.

In the second part of this study, \textsuperscript{L}-NAME was administered in rats fed a high-sodium diet. Ribeiro et al\textsuperscript{6} have reported that a sodium load aggravates renal injury during NO deprivation and that in this model, hypertensive disease and its renal consequences are explained concomitantly by the sodium excess and an inappropriate release of renin. Natriuretic peptide activity is known to significantly counteract hypertension in salt-dependent models.\textsuperscript{33} Consequently, we hypothesized that the increase in atrial and B-type natriuretic peptide levels in the presence of an NEP inhibitor would accentuate the beneficial effects of ACE inhibition and that omapatrilat would confer a better protection against renal damage than captopril. Our hypotheses were only partially confirmed. In this group of rats, we observed a more marked proteinuria after 4 weeks of \textsuperscript{L}-NAME administration. Captopril still prevented mortality and induced a moderate regression of high blood pressure and renal damage. These results confirm those of Fujihara et al,\textsuperscript{44} who blocked the renin-angiotensin system with losartan, an Ang II type 1 receptor antagonist. In rats treated with omapatrilat, the biologic activity of natriuretic peptides was elevated, as reflected by the high plasma levels of cGMP. Interestingly, the rise of cGMP induced by omapatrilat was more marked in the group receiving a high-sodium diet than in those fed a normal-sodium diet. This was likely due to the highest degree of renal failure\textsuperscript{45} and to increased stimulation of natriuretic peptide production in relation to sodium excess. However, the blood pressure decrease was only partial with omapatrilat and equivalent to that observed in the group treated with captopril. Moreover, although partially efficient on renal indexes, omapatrilat was less protective against histologic damage than captopril. These data suggest that chronic blockade of NEP decreased not only the catabolism of the vasodilatory peptides, atrial and B-type natriuretic peptides, and kinins but also that of pathogenic vasoconstrictive peptides capable of counterbalancing the beneficial effects of the former.

It has been reported that ET-1 activity was increased in some sodium-dependent models of hypertension\textsuperscript{36,37} and that NEP inhibition can decrease its catabolism.\textsuperscript{38,39} Therefore, we tested the hypothesis that omapatrilat could enhance the pathogenic action of this peptide. We did not find any effect of a salt diet on urine ET-1 excretion of the difference noted by Sasser and al,\textsuperscript{16} but this result might have been due to the difference in salt concentration (our 4% vs 10%). ET-1 was more elevated in urine with omapatrilat than with captopril. However, neither its plasma levels nor its renal content was increased in rats fed a high-sodium diet treated or not with omapatrilat. Such a discrepancy between renal content and urinary concentration of ET-1 has already been described\textsuperscript{16} and can be explained by the NEP renal predominant localization in the brush border of proximal tubular cells. However, ET-1 is a paracrine factor, and its concentration (as well as that of NEP\textsuperscript{40}) varies within the different renal compartments.\textsuperscript{16} For this reason, it is possible that ET-1 concentrations were elevated in renal vessels and glomeruli with omapatrilat treatment. This hypothesis can explain why rats receiving a high-sodium diet treated with omapatrilat displayed a lesser degree of histologic regression compared with the captopril group.

Several long-term studies comparing the renoprotective effects of ACE inhibitors and vasopeptidase inhibitors have been performed in the model of 5/6 nephrectomy.\textsuperscript{19,41–44} These studies concluded that vasopeptidase inhibitors conferred greater renal protection than did ACE inhibitors. The major quantitative effect of omapatrilat overwhelming that of enalapril affected proteinuria, as reported by Taal et al\textsuperscript{41} in a protocol characterized by delayed treatment with both drugs until 4 weeks after the onset of hypertension. Moreover, in that study, omapatrilat seemed to reduce more efficiently than captopril the long-term progression of glomerulosclerosis. In contrast, in the Dahl salt-sensitive model, captopril afforded greater glomerular protection than did omapatrilat, despite a similar degree of blood pressure reduction. In this study, the renal effects of NEP inhibition seemed to be detrimental, although the vascular ones were beneficial. To explain this dissociation, the authors suggested that the consequences of NEP inhibition on ET-1 levels differed according to the tissue studied.\textsuperscript{15}

**Perspectives**

It appears from the aforementioned studies that the superiority of vasopeptidase inhibitors over ACE inhibitors against the progression of glomerulosclerosis depends on the hypertensive model, the level of blood pressure reduction, and the duration of treatment. In our case, both treatments exhibited a similar efficiency in preventing the premature death of \textsuperscript{L}-NAME-treated rats and in reducing blood pressure, although incompletely in the salt-dependent model. Further studies will be necessary to better understand the consequences of endothelial dysfunction on the renal action of vasopeptidase inhibitors. Furthermore, the demonstration that blockade of the renin-angiotensin system was only partially efficient on renal failure in the high-salt diet, \textsuperscript{L}-NAME-treated rats, which mimics what occurs in human vascular nephropathies, suggests that this experimental model could be useful to test new therapeutic approaches.
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