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Atorvastatin improves sodium handling and decreases blood pressure in salt-loaded rats with chronic renal insufficiency

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ABSTRACT

Objective: Oxidative stress and inflammation seem to mediate the cardiovascular risks associated with salt sensitivity. Because hydroxymethyl glutaryl coenzyme A reductase inhibitors decrease oxidation and increase nitric oxide (NO) synthesis, we examined the effects of atorvastatin (ator) on tissue injury in rats with a reduced renal mass produced by 5/6 nephrectomy. This salt-sensitive hypertension model causes kidney and cardiovascular injuries.

Methods: After undergoing 5/6 nephrectomy or sham surgery, male Sprague–Dawley rats were randomized into five groups: sham, reduced renal mass and a normal salt diet (NNaD), NNaD+ator (50 mg · kg^{-1} · d^{-1}), reduced renal mass and a high salt diet (HNaD), and HNaD+ator. After assessing the sodium balance for 7 d, we measured blood pressure (BP), creatinemia, proteinuria, nitrites, and 12(S)-hydroxy 5,8,10-heptadecatrienoic acid, the renal cortical expression of endothelial NO synthase, and the ratio of left ventricular weight to body weight.

Results: In NNaD rats, creatinine, proteinuria, and 12(S)-hydroxy 5,8,10-heptadecatrienoic acid increased, renal NO indices decreased, but the Na^+ balance, BP, and the left ventricular weight/body weight ratio remained unchanged. In the NNaD group, atorvastatin normalized the NO indices and decreased BP and proteinuria, although the remaining parameters continued unchanged. In contrast, HNaD increased creatinemia, proteinuria, and 12(S)-hydroxy 5,8,10-heptadecatrienoic acid excretion rates and decreased renal endothelial NO synthase. Salt retention was accompanied by increased BP and ventricular weight. In this HNaD group, atorvastatin prevented a BP increase, partly decreased sodium retention, but failed to improve NO indices, proteinuria, oxidant stress, and the left ventricular weight/body weight ratio.

Conclusion: Atorvastatin exerts beneficial effects on renal function, injury, and salt sensitivity in rats with a reduced renal mass on an NNaD. The HNaD hampers these beneficial effects.

Introduction

A high salt intake, a prevalent dietary habit in modern society, is an independent risk factor for cardiovascular and kidney diseases [1,2]. Indeed, clinical and experimental studies have shown an association between increased salt intake and left ventricular hypertrophy, vascular remodeling, stroke, renal fibrosis, and disease progression [2,3]. These associations seem to have a greater impact on salt sensitivity, a condition defined by an increase in blood pressure (BP) during salt loading and a decrease during salt restriction. Indeed, salt-sensitive patients have a major incidence of fatal and non-fatal cardiovascular and renal events compared with hypertensive patients who are not salt sensitive. As with hypertension, proteinuria is an important predictor and instigator of renal disease progression [4]. In fact, proteinuria intensifies tubulointerstitial injury, the single

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strongest determinant of the long-term loss of the glomerular filtration rate. In this respect, the current premise is based on the ability of albumin to stimulate proinflammatory cytokines [5]. Indeed, increased reactive oxygen species (ROS) may underlie the development and progression of renal inflammation and fibrosis [6]. There is growing evidence that ROS and inflammation are intimately implicated in the pathogenesis of peripheral vascular disease [7], salt-sensitive hypertension, and hypertensive renal disease [8]. For instance, salt-loaded Dahl salt-sensitive rats exhibit increased ROS, endothelial dysfunction, hypertension, and renal damage, which are ameliorated by antioxidant therapy [9]. Based on these observations, it seems therapies that can improve ROS and inflammation are likely to be effective in the treatment of chronic renal failure (CRF).

Hydroxymethyl glutaryl coenzyme A reductase inhibitors (statins) are known to decrease cardiovascular events in patients with coronary heart disease [10,11]. In addition, recent studies have shown the renoprotective effects of statins in several hypertension models [12]. These beneficial effects are not limited to their lipid-lowering properties. Statins seem to decrease inflammation by increasing nitric oxide (NO) synthesis (upregulating endothelial NOS synthase [eNOS] expression) and decreasing ROS generation [13].

Moreover, statins inhibit sodium reabsorption in isolated thick ascending limbs [14] and have been reported to improve BP and endothelial dysfunction, preventing glomerular sclerosis in spontaneously hypertensive rats [8]. These findings suggest that the antioxidants effects of statins could decrease salt sensitivity and the progression to chronic renal disease. Thus, we tested the hypothesis that statins decrease oxidative stress early in animals with a reduced renal mass (RRM) and thus the development of salt-sensitive hypertension, left ventricular hypertrophy, and renal injury. In addition, we tested whether atorvastatin could curb the oxidative response to salt loading by evaluating its effects on salt balance and BP, proteinuria, left ventricular weight, and renal NO and ROS in rats with CRF owing to an RRM.

Materials and methods

Experimental design

All experiments were performed in accordance with the National Institutes of Health Guide for Care and Use of Laboratory Animals guidelines and were approved by the institutional animal care and use committee of the J. Robert Cade Foundation. Male Wistar rats (150–200 g) were maintained on standard rat chow and randomized into five groups. Group 1 (sham, $n = 6$) was anesthetized with sodium pentobarbital (30 mg/kg intraperitoneally) and subjected to a ventral laparotomy and manipulation (without removal) of the kidneys and renal pedicle. The rats in the remaining four groups were anesthetized in the same manner, and then the right kidney and the two poles of the left kidney were removed. Two weeks after 5/6 nephrectomy (Nx) or sham 5/6 Nx, the rats were lodged in metabolic cages and allowed to acclimate for 1 wk. At the end of this period, we obtained the basal values for systolic BP (SBP; by tail cuff and by direct intra-arterial measurement), serum creatinine, and 24-h urinary protein excretion. The rats with an RRM were then randomized into four additional groups to receive a normal 0.4% NaCl diet (group 2, NNaD, $n = 12$), a normal NaCl diet mixed with atorvastatin (50 mg $\cdot$ kg^{-1} $\cdot$ d^{-1}, group 3, NNaD+ator, $n = 12$), a high 4% NaCl diet (group 4, HNaD, $n = 11$), or an HNaD mixed with atorvastatin (group 5, HNaD+ator, $n = 11$). Group 1 received a normal diet (0.4% NaCl). The rats were maintained for 7 days on these diets and housed in their metabolic cages. Their food intake was monitored, and their urine and fecal excretions were collected for the determination of sodium balance. On the seventh day, we repeated the BP, serum creatinine, and urinary protein measurements. At this time we also measured urinary nitrites and 12(S)-hydroxy 5,8,10-heptadecatrienoic acid (HHT), a marker of oxidative stress [15]. At the end of this collection periods, we measured BP by the direct intra-arterial method and then the animals were sacrificed. The remnant kidney and the heart were removed to determine cortical renal expression of eNOS [16] and left ventricular weight, respectively.

Data acquisition and measurements

Daily sodium balances were calculated as the difference between the Na^+ ingested and the Na^+ excreted in feces and urine. The SBP was measured in trained, conscious, restrained rats using tail cuff plethysmography, as previously described [17,18]. Because of the inherent variability in the tail cuff method, these measurements were confirmed by direct intra-arterial determinations. This was performed through percutaneous catheters placed in a carotid artery at the time of Nx. These catheters were secured to the skin in the back and kept permeable by intermittent heparin flushes. Serum creatinine and urinary protein levels were determined by the Jaffe and sulfosalicylic acid methods, respectively, and as indices of NO production, we measured urinary nitrites using the Griess reaction and the expression of renal cortical eNOS by western blot. We measured the urinary excretion of HHT as an index of oxidant stress using high-pressure liquid chromatography. We chose to use HHT as the measurement of oxidant stress because it is a physiologic metabolite of arachidonic acid and an equimolar coproduct of thromboxane biosynthesis [15], which reacts with proteins and phospholipids [19]. Because it is synthesized with malondialdehyde from the endoperoxide prostaglandin H2(PGH2) [20], it is a marker of malondialdehyde synthesis [21] and, hence, of oxidative stress. Its concentration increases in chronic renal diseases [22]. The ratios of left ventricular weight to body weight were determined as an estimate of left ventricular hypertrophy [23].

Statistical analysis

Data are presented as mean $\pm$ standard error of the mean. Unpaired and paired two-tailed t tests and two-way analysis of variance were used when indicated. $P \leq 0.05$ was considered statistically significant.

Results

Balance studies

Sodium balance, urinary excretion, and intake are depicted in Figure 1. The sodium balance was essentially neutral throughout the experimental period in the sham and NNaD groups (Fig. 1, left panels). In rats fed an HNaD, the sodium balance became positive from the first day on. As expected, neither group reached a steady state within the time frame of the present study.

However, the HNaD+ator group showed a significantly less positive sodium balance (Fig. 1, top right panel). This lower sodium accumulation was due to an increase in urinary sodium excretion (Fig. 1, middle right panel). There was no difference in sodium intake or fecal sodium excretion between the groups.

Blood pressure

Blood pressures in all groups are listed in Table 1. At baseline, BPs were not different between groups. In sham controls and untreated rats on the NNaD, the BP remained unchanged. In rats with an RRM and on the NNaD+ator, the intra-arterial measurements showed a mild but significant decrease in BP from 116 $\pm$ 1.8 to 110 $\pm$ 1.7 mmHg ($P < 0.05$). In contrast, the HNaD increased the SBP in the rats with an RRM, and this effect was blunted by atorvastatin (Table 1).

Left ventricular hypertrophy index

The mean left ventricular indices in rats with an RRM on the NNaD (2.05 $\pm$ 0.04 mg/g) and in those with an RRM on NNaD+ator (1.86 $\pm$ 0.06 mg/g) were unchanged compared with sham rats (1.67 $\pm$ 0.09 mg/g). Rats with an RRM on the HNaD showed an increased left ventricular weight that could not be reversed by atorvastatin (sham 1.67 $\pm$ 0.09 mg/g, HNaD 2.19 $\pm$ 0.10 mg/g, HNaD+ator 2.21 $\pm$ 0.11 mg/g, $P < 0.05$, analysis of variance).

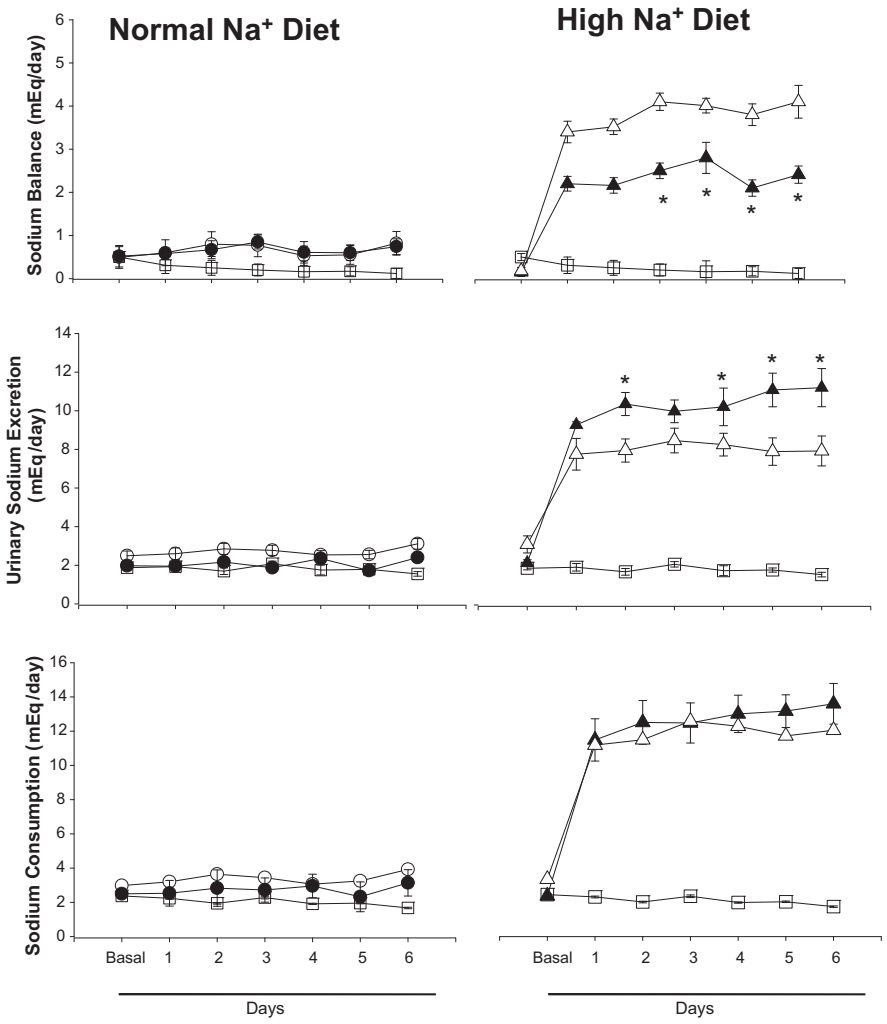

Fig. 1. Effects of atorvastatin on early sodium balance (upper graph), sodium intake (middle graph), and urinary sodium excretion (lower graph) in rats with a reduced renal mass. Black circles, normal 0.4% NaCl diet plus atorvastatin; black triangles, 4% NaCl diet plus atorvastatin; squares, sham; white circles, normal 0.4% NaCl diet; white triangles, 4% NaCl diet.

Renal parameters

The serum creatinine and urinary protein excretion in the sham rats were 0.43 ± 0.04 mg/dL and 2.7 ± 0.43 mg/d, respectively, during the basal period and did not change during the 7-d period. Serum creatinine increased in all the groups with an RRM; levels were 0.83 ± 0.07 mg/dL in the NNaD group, 0.99 ± 0.13 mg/dL in the NNaD+ator group, 0.92 ± 0.07 mg/dL in the HNaD group, and 0.92 ± 0.08 mg/dL in the HNaD+ator group at day 7 ($P < 0.05$ for all comparisons). Likewise, the subtotal Nx also increased the urinary protein excretion rate in the NNaD group (by 62 ± 10%) and the HNaD (by 63 ± 13%) group (Fig. 2). Atorvastatin decreased the urinary protein excretion from 38.0 ± 16.8 to 28.0 ± 8.2 mg/d in the NNaD+ator groups, representing a 38 ± 17% decrease ($P < 0.003$ versus NNaD). In contrast, atorvastatin in the HNaD group did not decrease proteinuria (38.1 ± 12.2 versus 49.9 ± 9.2 mg/d).

Table 1
Mean systolic blood pressure measured by tail cuff and direct carotid measurements

Groups	Systolic blood pressure (mmHg)			
	Tail cuff		Direct carotid catheter	
	Basal	1 wk	Basal	1 wk
Sham	120 ± 1.2	115 ± 2.7	116 ± 1.1	115 ± 0.1
NNaD	125 ± 2.6	125 ± 3.3	115 ± 0.5	116 ± 1.5
NNaD + atorvastatin	116 ± 1.4	116 ± 1.8	116 ± 1.8	110 ± 1.7*
HNaD	125 ± 3.0	153 ± 5.0*	126 ± 3.9	137 ± 2.2*
HNaD + atorvastatin	117 ± 2.0	119 ± 5.0	119 ± 3.5	122 ± 3.3

HNaD, 4% NaCl diet; NNaD, normal 0.4% NaCl diet
* $P < 0.05$

Renal nitric oxide

We next evaluated whether the beneficial effects of atorvastatin on BP or proteinuria were accompanied by parallel changes in NO. We assessed NO by two indirect methods: measuring nitrites in the 24-h urine sample collected during day 6 and measuring eNOS expression in the renal cortex to substantiate the urinary nitrite findings. The urinary nitrite excretion rate in the sham group was 1460 ± 239 mmol · L^{-1} · d^{-1} (Fig. 3, left panel). These values were significantly lower in nephrectomized rats (1015 ± 185 mmol · L^{-1} · d^{-1} in the NNaD group and 959 ± 75 mmol · L^{-1} · d^{-1} in the HNaD group, $P < 0.05$ for the two comparisosn). As with proteinuria, atorvastatin

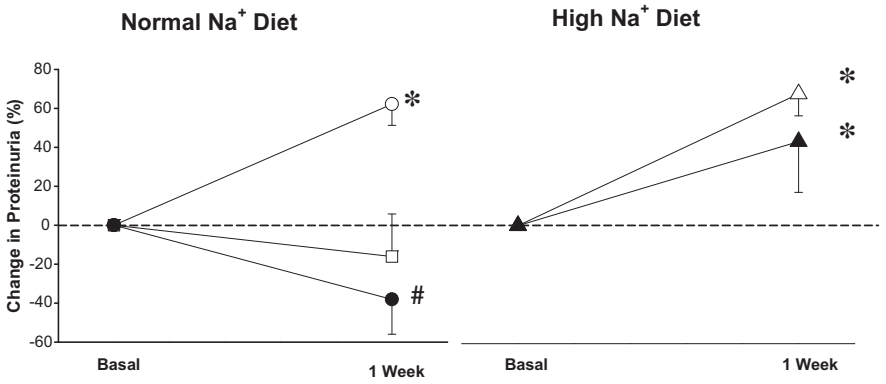

Fig. 2. Effects of atorvastatin on urinary protein excretion rate. (Left) Sham (squares), normal 0.4% NaCl diet (white circles), and normal 0.4% NaCl diet plus atorvastatin (black circles). (Right) The 4% NaCl diet (white triangles) and 4% NaCl diet plus atorvastatin (black triangles). * $P < 0.05$ versus basal, # $P < 0.003$ versus normal 0.4% NaCl diet at 1 wk.

increased urinary nitrite excretion in the NNaD group, but not in rats fed a high salt diet. A very similar pattern was found with renal eNOS expression. Renal eNOS expression increased in the rats subjected to subtotal Nx and atorvastatin increased the eNOS expression toward baseline in the NNaD group but not in the HNaD group (Fig. 3, right panel).

Oxidant stress

Subtotal Nx caused a marked increase in the urinary excretion of HHT (Fig. 4), suggesting that the oxidant stress was increased. Surprisingly, HHT excretion was not different between the NNaD and HNaD groups, despite the difference in BP. Atorvastatin caused a significant decrease in HHT excretion in the NNaD groups ($P < 0.04$) and tended to decrease HHT excretion in the HNaD group.

Discussion

The main findings of our study are that atorvastatin has beneficial effects on renal salt handling, proteinuria, and the NO/ROS balance and thus on BP and the left ventricular weight/body weight ratio in rats with 5/6 Nx. However, the beneficial effects of atorvastatin on the kidney were markedly tempered by the HNaD, although atorvastatin completely prevented the hypertensive response to the high salt intake. Modern-day salt intake greatly exceeds human needs and this may cause undesirable cardiovascular and renal outcomes; indeed, available evidence has shown that salt induces cardiovascular and renal injuries. Although some of the deleterious effects of salt may be independent of any changes in BP, its injurious effects are caused largely by the development of hypertension in susceptible individuals, a condition referred to as *salt sensitivity* [24]. Because of the considerable increase in morbidity and mortality that accompanies salt sensitivity, much effort is being channeled into elucidating the mechanisms that promote salt sensitivity. One condition that has been associated with salt sensitivity and increased cardiovascular mortality is CRF. Salt sensitivity is a major manifestation in human and experimental CRF. Moreover, it is progressive. That is, as the glomerular filtration rate decreases, renal sodium excretion becomes progressively impaired and BP becomes increasingly salt sensitive. Among the several experimental models developed to study the pathogenesis of salt-sensitive hypertension, the most commonly used is the 5/6 or subtotal Nx in the rat. The significant loss of renal mass induced by the subtotal Nx leads to the development of hypertension and progressive renal injury of the remaining kidney [25,26]. Indeed, the increase BP is transmitted to the glomerulus, causing injury, proteinuria, inflammation, and glomerulosclerosis [27]. The progressive decrease of functioning nephrons in turn further predisposes to salt-sensitive hypertension, and thus a vicious cycle ensues that ultimately leads to advanced renal failure in a similar manner to that of human CRF. Therefore, we used this model in the present study. The rats treated with 5/6 Nx had significant renal alterations by the end of the 28th day. They exhibited increased proteinuria, decreased renal indices of NO, and increased renal oxidant stress, as reported by other investigators [28]. This was associated with salt sensitivity; indeed, the HNaD groups had a positive sodium balance. This positive sodium balance was associated with a substantial increase in BP, suggesting that the sodium retention was responsible at least in part for their hypertension. Atorvastatin

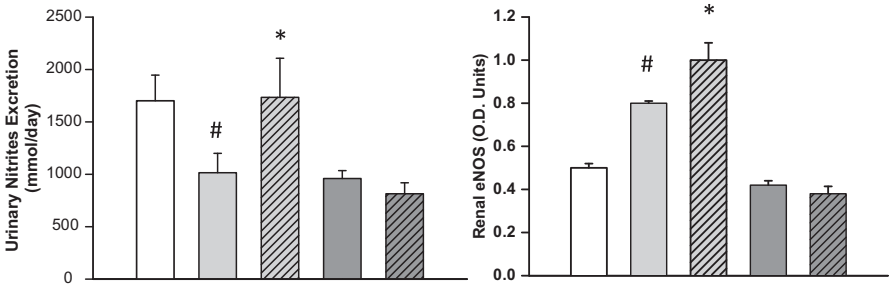

Fig. 3. Effects of atorvastatin on urinary nitrite excretion (left) and eNOS expression (right). The bars indicate results in the sham-treated rats (white bars), rats on the 0.4% NaCl diet (light gray bars), rats on the 0.4% NaCl diet plus atorvastatin (light gray striped bars), rats on the 4% NaCl diet (dark gray bars), and rats on the 4% NaCl diet plus atorvastatin (dark gray striped bars). * $P \leq 0.05$ versus 0.4% NaCl diet group, # $P \leq 0.05$ versus sham group. eNOS, endothelial nitric oxide synthase; O.D., optical density.

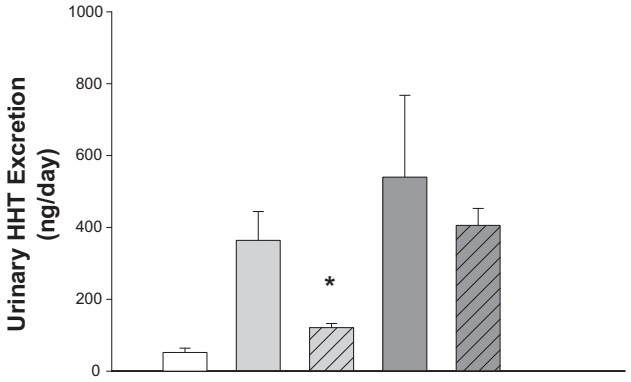

Fig. 4. Effects of atorvastatin on urinary HHT excretion. The bars indicate results in sham-treated rats (white bars), rats on the 0.4% NaCl diet (light gray bars), rats on the 0.4% NaCl diet plus atorvastatin (light gray striped bars), rats on the 4% NaCl diet (dark gray bars), and rats on the 4% NaCl diet plus atorvastatin (dark gray striped bars). * $P \leq 0.04$ versus 0.4% NaCl diet. HHT, 12(S)-hydroxy 5,8,10-heptadecatrienoic acid.

had a striking preventive effect on the increase in BP in this group: SBP in the HNaD+ator group averaged 20 mmHg less than those seen in untreated animals. These findings suggested a renal antihypertensive effect likely related to a decrease in tubular reabsorption. Indeed, studies have reported an inhibitory effect of statins on renal NaCl transport [14] and atorvastatin-attenuated sodium retention. However, the net effect of atorvastatin on sodium balance in the rats with an RRM on the HNaD was partial; these animals retained a positive sodium balance and yet their BP failed to increase. This suggests that although some of the beneficial effects of atorvastatin on BP may be due to increased sodium excretion, it is likely that its main effect is by separate mechanisms that decrease peripheral resistance. In support of this notion, atorvastatin had a mild although significant BP-lowering effect in the rats on a normal salt intake that had a neutral sodium balance.

In this respect, it is tempting to postulate that atorvastatin may have prevented the development of endothelial dysfunction, as has been described in other conditions. This notion is consistent with prior studies in which statins have been found to improve endothelial function and/or decrease BP in non–salt-sensitive hypertensive models [29]. Although the natriuretic effect of atorvastatin was not potent, it was consistently present for the duration of the experiments and thus may have contributed to the overall antihypertensive effect of atorvastatin. This natriuretic effect was predictable because statins have been shown to decrease Na and/or Cl reabsorption in various nephron segments during diverse conditions. In fact, statins have been found to decrease chloride reabsorption and oxygen consumption in isolated perfused thick ascending limbs and increase the pressure–natriuretic curve in spontaneously hypertensive rats [30]. These effects have been postulated to be caused by decreased oxidant stress and/or increased NO, either of which may act by directly inhibiting tubular sodium excretion or by increasing renal medullary blood flow with the consequent increases in renal interstitial pressure and passive back-diffusion of sodium through the paracellular pathway [31]. The present experiments did not permit us to dissect out the mechanism by which atorvastatin increases sodium excretion and lowers BP. However, it is likely that oxidant stress and NO separately influence each other's interactions. In effect, atorvastatin normalized the NO indices in the NNaD group and decreased oxidation in the HNaD group.

The second main goal of this study was to determine whether atorvastatin improves the renal indices of proteinuria together with NO and oxidant stress. The rationale for testing atorvastatin in this setting was its beneficial effects on the NO/ROS balance and its anti-inflammatory properties [8,32]. In hypertensive salt-sensitive patients, BP changes after salt loading are inversely correlated with NO activity [33]. We found that the proteinuria in all the untreated rats after Nx increased by ~60%, and this worsening in proteinuria was accompanied by parallel increases in oxidant stress and decreases in NO.

Thus, although the NO/ROS balance did not appear to be entirely implicated in the salt-sensitive hypertension induced by Nx, it closely paralleled the renal proteinuria, suggesting that it may be a culprit in renal injury. Indeed, the beneficial effect of atorvastatin on proteinuria in the NNaD group was accompanied by a normalization in renal NO indices, whereas the lack of effect of atorvastatin on proteinuria in the HNaD group was similarly associated with a lack of improvement in the renal NO indices in these rats. These findings suggest that atorvastatin has beneficial effects on renal injury even in the absence of hyperlipidemia and independently of its ability to lower BP and increase sodium excretion. Indeed, Park et al. [34] reported a protective renal effect from cerivastatin independent of BP- or cholesterol-lowering effects. In keeping with this notion, our results also suggested that atorvastatin may exert its beneficial effect on renal injury (as evidenced by decreased proteinuria) by normalizing the NO/ROS balance. Be that as it may, we recognize that an improvement in the NO/ROS balance may be a secondary phenomenon to the decreased renal injury.

In a previous study in normal rats, we found that SBP, body weight, and cholesterolemia were unchanged in rats on a high salt intake compared with animals on a low salt intake. However, the high salt diet increased the urinary protein excretion rate and glomerular volume and impaired acetylcholine-induced renal vasodilatation and decreased cortical and glomerular eNOS levels. The high salt intake also caused glomerular sclerosis and interstitial mononuclear cell infiltration and increased the cortical expression of transforming growth factor-β1. All these salt-induced changes were reversed by atorvastatin [35]. These beneficial effects agree with our present observations. However, in the present study, the beneficial actions of atorvastatin on renal NO and on protein excretion rate were completely abrogated by the HNaD, although, seemingly surprisingly, it is not a unique finding because a high salt intake can blunt the beneficial effects of other agents such as angiotensin-converting enzyme inhibitors [36].

Furthermore, a high salt intake causes severe hemodynamic renal dysfunction and proteinuria in spontaneously hypertensive rats in the absence of changes in BP [37]. A high salt diet may not only influence urinary albumin excretion independently from its effects on BP but also independently predict the risk for coronary artery disease [38]. Nonetheless, considering the efficacy of atorvastatin in preventing chronic renal insufficiency (CRI)-induced salt-sensitive hypertension [8] and the role of hypertension in promoting renal injury and proteinuria, we would have expected a significant improvement in proteinuria. Because the lack of benefit in the proteinuria was accompanied by an unimproved renal NO, it seems likely that at this early stage of Nx, the major stimulus for renal injury is due to the NO/ROS imbalance rather than the hypertension, although we cannot rule out that glomerular capillary pressure might have been somewhat increased in the HNaD groups. The mechanism by which salt prevented the atorvastatin-induced improvements in the renal parameters may have been due to the direct pro-oxidant effect that NaCl intake

possesses [8]. However, longer-term studies are needed to elucidate the contribution of these pressure-independent factors in determining the progression of chronic renal injury.

In summary, although it remains certain that the salt-sensitive hypertension in this model is a key instigator in the unrelenting progression of renal and cardiac injuries, optimal BP control remains the primary objective when treating patients with CRF. The present data underscore the presences of various mechanisms that can cause continuing renal and cardiovascular injuries, even when BP is well controlled. In this respect, sodium intake itself could be responsible for such a progression. Indeed, our findings suggest that the remarkable protective action of hydroxymethyl glutaryl coenzyme A reductase inhibition on renal indices can be negated by a high salt intake in a manner that is independent from hypertension. Although factors other than salt intake are also likely to be present, these observations raise the possibility that many of the conflicting results that have been reported with regard to the antihypertensive effects of statins may be due to differences in various confounding factors such as inconsistencies in salt intake. Care must be taken when interpreting these studies, and we believe that future trials will likely be of benefit if we target various factors in conjunction with salt intake.

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