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The Antihypertensive Actions of Statins: Modulation by Salt Intake

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Hydroxy methyl glutaryl CoA inhibitors (statins) are the agents most frequently used to reduce elevated serum cholesterol. In addition to their cholesterol lowering effects, statins also have nonlipid lowering pleiotropic properties. These include reducing oxidative stress, renin–angiotensin and endothelin synthesis and activity, and improving nitric oxide (NO) synthesis and availability. Thus, one would predict that statins might be able to exert an antihypertensive effect. Experimental models bear out the blood pressure lowering effects but the data from clinical trials have been inconsistent perhaps due to inappropriate experimental designs, sample size, blood pressure measurement techniques etc. Moreover, although experimental models strongly suggest a role for salt intake in the potential antihypertensive responses to statins, available clinical trials fail to report salt intake in the studied populations. The statins' antihypertensive effects remain an unsettled hypothesis and calls for a large clinical trial at a wide range of doses and a controlled salt intake. Statins meanwhile remain as a excellent option to control high cholesterol and in tissue injury prevention.

Keywords: *blood pressure; chronic renal failure; high cholesterol; hypertension; salt sensitive hypertension*

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Statins are the most commonly prescribed agents for the treatment of hypercholesterolemia. They inhibit hydroxy methyl glutaryl CoA reductase, thus decreasing low-density lipoprotein and triglyceride levels, resulting in a reduction of cardiovascular morbidity and mortality.[1–4] Although most of these beneficial effects are attributed to their ability to lower serum cholesterol,[5–7] statins have other biological effects that may promote cardiovascular health. These include increases in the synthesis and bioactivity of nitric oxide (NO), and decreases in the expression of angiotensin II AT1 receptor, endothelin, transforming growth factor (TGF)-β1, fibronectin, and reducing sympathetic activity, oxidative stress, and angiotensin II- and phenylephrine-induced vasoconstriction.[8–20] Because imbalances in the above parameters lead to vascular abnormalities such as endothelial dysfunction, decreased arterial compliance, and activation of inflammatory and fibrotic pathways (important pathophysiological determinants of essential hypertension), the ability of statins to reverse these abnormalities raise the possibility that they may also lower blood pressure (**Figure 1**) and thus be useful for simultaneously treating dyslipidemias and hypertension. This is a particularly attractive prospect because high blood pressure and hyperlipidemia frequently coexist in patients and independently promote cardiovascular and renal disease progression.[21–26] In fact, published guidelines encourage the simultaneous aggressive treatment of these conditions.[27,28] However, despite the potential effects of statins on blood pressure, clinical trials have not conclusively proven the effectiveness of statins on lowering blood pressure. The aim of this review is to examine experimental findings that may help explain the conflicting findings of these clinical trials.

THE EFFECTS OF STATINS ON BLOOD PRESSURE IN EXPERIMENTAL HYPERTENSION

Statins have been found to lower blood pressure in various models of experimental hypertension[29–37] Indeed, over a decade ago, Jiang and Roman found that lovastatin decreased blood pressure in the spontaneously hypertensive rat (SHR).[30] These findings were confirmed shortly later by Regrigny *et al.*[34] and then by Wassmann *et al.* while assessing the effects of atorvastatin in the same model.[31] These investigators found that statins not only lowered systolic blood pressure, but they also improved endothelial-dependent vasodilation, and reduced expression of vascular AT1 receptor mRNA. These blood pressure lowering actions in the SHR seem to be a class effect as simvastatin and pravastatin also have shown similar results in the SHR.[35] These antihypertensive effects of statins are not limited to the SHR. For instance, statins have also been found to lower the blood pressure in Dahl salt-sensitive rat,[14,29,36,37] deoxycorticosterone acetate (DOCA)-salt mice,[37] and in angiotensin II-induced hypertension.[32,38–40] Statins have also been found to decrease blood pressure in fructose-induced metabolic syndrome in the rat,[41] in the insulin-resistant obese Zucker rat[42] and in the obese dyslipidemic mice,[33] including the ApoE$^{-/-}$ mice.[43]

The effects of statins on L-NAME–induced hypertension are particularly interesting because one of the main effects

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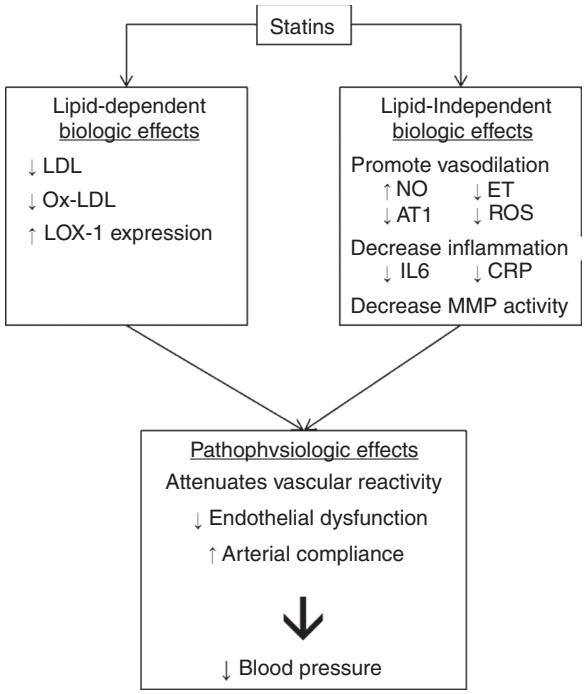

Figure 1 | A simplified schematic of some potential mechanisms by which statins may decrease blood pressure. CRP, C-reactive protein; LDL, low-density lipoprotein; NO, nitric oxide; ROS, reactive oxygen species.

of statins is presumed to be by protecting endogenous NO from being degraded. Because endogenous synthesis of NO is already inhibited in this model, statins would not be expected to as effective at lowering blood pressure as in other models. However, two separate studies in this model found that cerivastatin and atorvastatin both lowered blood pressure.[44,45] Likewise, statins also have antihypertensive effects in endothelial nitric oxide synthase (eNOS) knockout mice. Indeed, mevastatin blunted saline-induced increases in blood pressure by 20–30% in $eNOS^{+/+}$ and $eNOS^{-/-}$ mice, reduced serotonin- and phenylephrine-induced vasoconstriction in aortic rings from these mice, and modulated the receptor-dependent vascular contraction in eNOS-deficient mice.[19]

Despite the effectiveness of statins in the abovementioned studies, not all studies have shown that statins lower blood pressure in experimental hypertension, particularly models in which blood pressure was increased by increasing salt intake[46–49] For instance, Zhou *et al.*[49] found that atorvastatin did not reduce blood pressure in Dahl salt-sensitive rats maintained on high salt intake. Similarly, statins did not decrease blood pressure in experimental DOCA-salt hypertension.[46,48] These studies suggest that the antihypertensive efficacy of statins may vary depending on the experimental model. An alternative explanation; however, is that differences in salt intake may account for the different antihypertensive effect of statins in the studies, therefore making it important to understand the interactions between cholesterol and salt intake in modulating blood pressure and renal function.

Interactions between cholesterol and salt intake in modulating salt sensitivity, renal function, and hypertension

High serum cholesterol causes upregulation of the AT1 receptor and causes endothelial dysfunction,[11] (M.C. Fiore, S.T. Baigorria, A. Eynard, D. Cremonezzi, L.I. Juncos, L.A. Juncos, N.H. García unpublished data); whereas lowering serum cholesterol reduces arterial stiffness in isolated systolic hypertension and improves acetylcholine-induced vasodilatation,[31,50–52] thus raising the possibility that the antihypertensive actions of statins may be a result of their lipid lowering properties. However, several lines of evidence suggest that this is not the primary mechanism by which statins lower blood pressure. First, although most experimental studies used statin doses that lower serum lipids (thus not establishing whether the antihypertensive effects of statins are lipid-dependent vs. lipid-independent)[51–54] some have shown a blood pressure lowering effect at doses that do not change serum lipid concentrations.[32] Second, experimental studies have shown that increasing serum cholesterol (via a high cholesterol diet) does not usually increase blood pressure despite inducing endothelial dysfunction (M.C. Fiore, F.L. Martin, S.T. Baigorria, N.H. García, L.I. Juncos, unpublished data). Finally, clinical studies have not found a direct pathophysiologic relationship between cholesterol and blood pressure.[55–57] Thus, taken together, these studies suggest that while high cholesterol may induce mechanisms that promote hypertension, it does not appear to cause established hypertension; an additional factor may be needed for this. Consequently, the primary antihypertensive effects of statins are likely independent of their lipid lowering effects.

The abovementioned observations that statins were not effective at lowering blood pressure in salt-sensitive hypertension models during a high-salt diet raised the possibility that cholesterol levels may alter salt sensitivity. Indeed, high cholesterol is associated with experimental and human salt-sensitive hypertension.[21,22,58–62] Thus, we evaluated whether interactions between cholesterol and salt intake may govern the antihypertensive responses to statins. For this, we tested whether high cholesterol intake in normal Wistar-Kyoto rats causes endothelial and renal dysfunction, leading to increased salt sensitivity.[63] Serum cholesterol increased in all groups on high cholesterol intake (high cholesterol and high cholesterol + high sodium). Forty-five days of a high salt caused mild endothelial and renal dysfunction/injury; represented by alterations in renal hemodynamics, and worse indexes of renal injury (**Figure 2a–e**); these salt-induced vascular and renal effects are similar to those reported by others.[64–67] High cholesterol caused marked endothelial dysfunction, but similar degrees

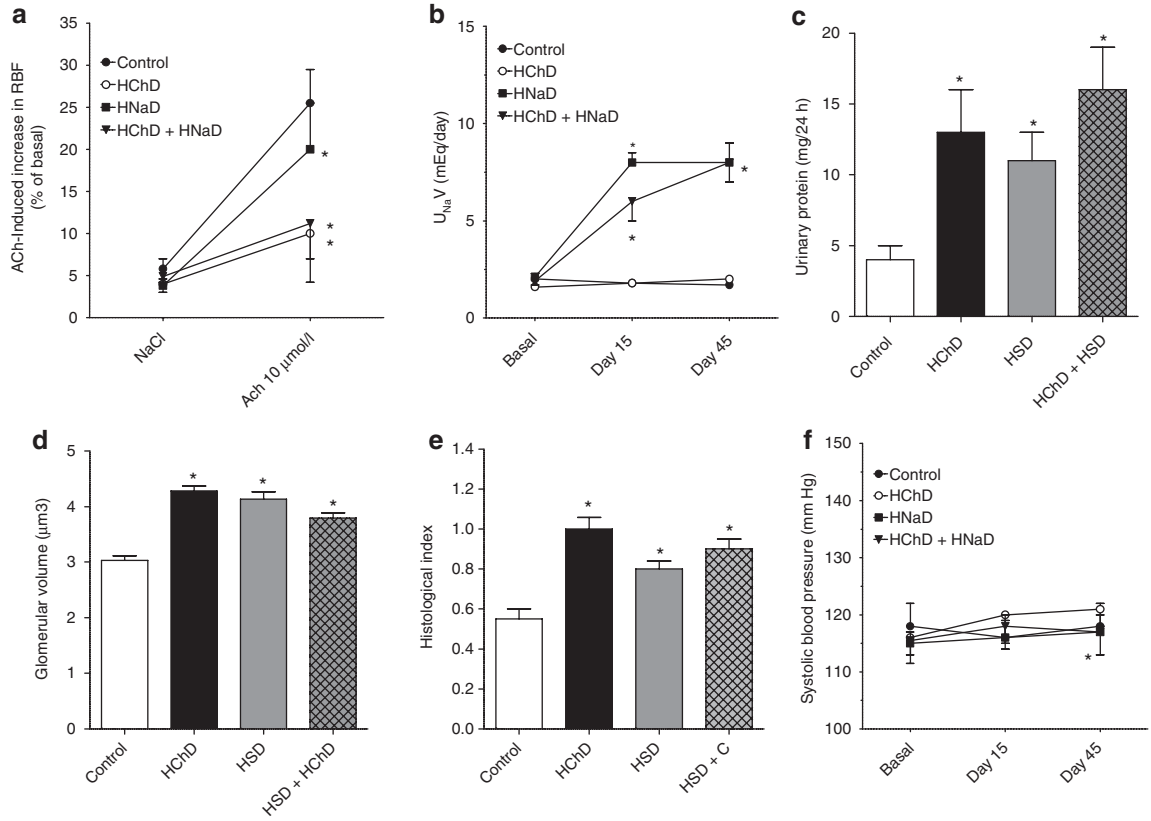

Figure 2 | The effects of high cholesterol (HChD) and/or high sodium intake (HSD) on (**a**) acetylcholine (ACh)-induced renal vasodilation, (**b**) urine sodium excretion rate ($U_{Na}V$), (**c**) proteinuria, (**d**) glomerular volume, (**e**) histologic index, and (**f**) blood pressure. *$P < 0.05$. C, control; RBF, renal blood flow.

of renal injury (Figure 2a–e). Despite these changes, renal salt handling was unaffected and blood pressure remained unchanged throughout the 45 days (Figure 2b–f). Moreover, maintaining the animals simultaneously on a high-salt and high-cholesterol diet did not exacerbate any of the alterations (Figure 2). In other words, even though the high cholesterol and the high sodium diets caused endothelial dysfunction and renal injury, the kidneys remained capable of excreting the sodium load without raising blood pressure. Interestingly, atorvastatin ameliorated all of the salt- and cholesterol-induced renal and vascular changes (Figure 3), but did not change the Na excretion rate, nor did it lower the blood pressure (albeit this would have been difficult to detect because the untreated rats failed to develop hypertension).

Although we failed to see an additive effect between high cholesterol and high salt on either blood pressure, renal dysfunction, or salt sensitivity (at least within the time frame of our study), we found marked beneficial effects of atorvastatin on the renal and vascular parameters (Figure 3) in all the groups. This led us to consider that the beneficial effects of statins on salt sensitivity and blood pressure may be more evident in animals that have more advanced renal disease, or a greater susceptibility to salt sensitivity. This notion is supported by statin-induced improvement in NO release, oxidative stress, renal hemodynamics, kidney injury, and blood pressure in the Dahl salt-sensitive rat.[29,49] Thus, we tested the effects of statins on rats subjected to 5/6 nephrectomy.[68] In this model, the primary injury is the surgical reduction of the renal mass, after which, a second injury progressively sets in, mainly due to glomerular hyperfiltration and eventually to arterial hypertension.[69] Hence, this model provides a window that allows the assessment of the interactions between salt and statins effects before hypertension sets in. The subtotal nephrectomy, regardless of the sodium intake, increased urinary protein excretion and 12S-12-hydroxy-5-8,10-heptadecatrienoic acid (HHT; a marker of oxidative stress) (Figure 4a,b), whereas decreasing urinary nitrites and renal cortical eNOS expression (Figure 4c,d). Despite these harmful changes, the blood pressure remained unchanged in rats on normal sodium diet, but increased in rats on a high sodium diet (Figure 5a). Atorvastatin had a marked protective effect against the 5/6 nephrectomy-induced changes in proteinuria, oxidative stress, nitrites and eNOS; however, only when the rats were maintained on a normal sodium (Figure 4). In marked contrast,

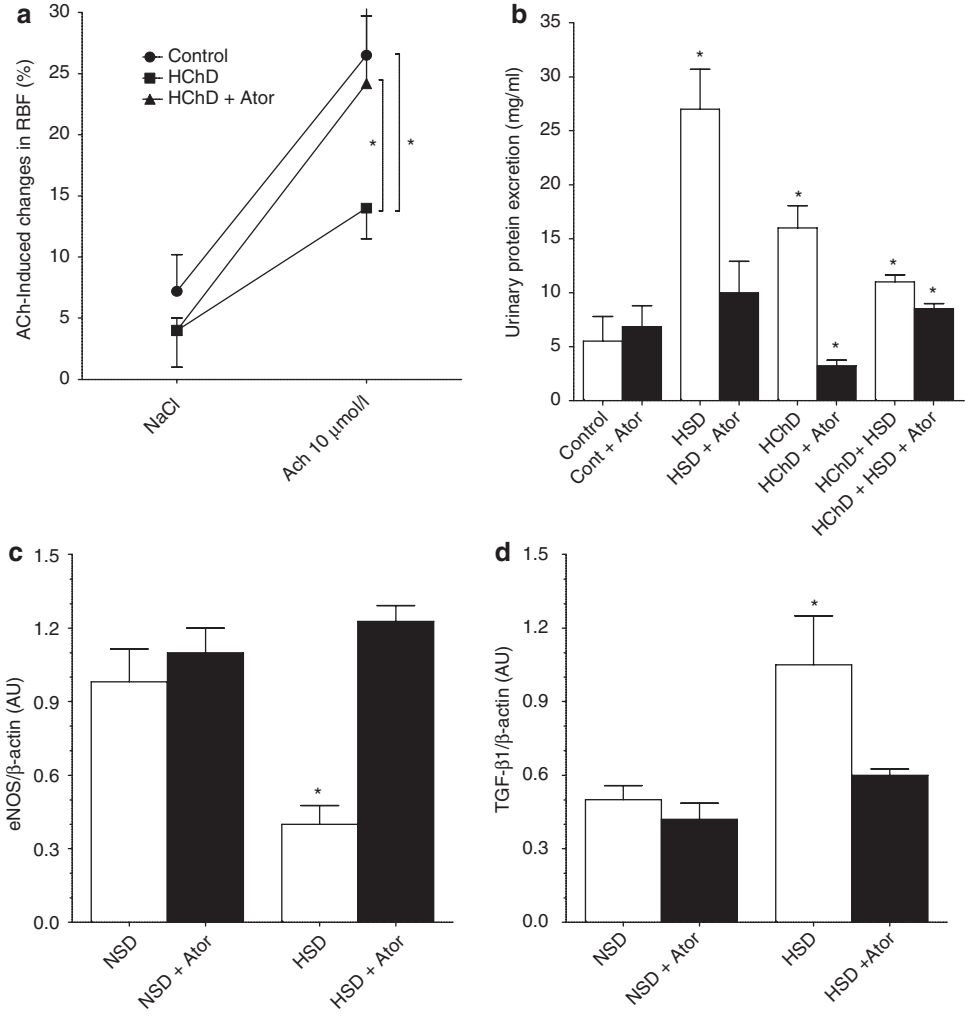

Figure 3 | The effects of HMG CoA inhibition (atorvastatin) on salt-induced alterations in (**a**) acetylcholine (ACh)-induced vasodilation, (**b**) proteinuria, and renal expression of (**c**) eNOS and (**d**) TGF-β1. Ator, atorvastatin; AU, arbitrary unit; eNOS, endothelial nitric oxide synthase; HChD, high cholesterol diet; HSD, high sodium diet; NSD, normal sodium diet; RBF, renal blood flow; TGF, transforming growth factor. *$P < 0.05$.

atorvastatin did not improve the manifestations of renal injury in the rats on a high sodium diet, and although it enhanced urinary sodium excretion, it only delayed the development of hypertension (**Figure 5b**). This is consistent with a previous study in SHR by Jiang and Roman who found that although lovastatin improved pressure natriuresis;[30] higher blood pressures were still needed to increase salt excretion.

The mechanism by which statins increased sodium excretion was not defined in our study but does not appear to be due to NO because eNOS expression and urinary nitrites remained low. This is consistent with previous studies that also found that the protective effects of statins are present in models where eNOS is either inhibited or absent.[44,45] Nevertheless, it is important to underscore that while atorvastatin delayed the onset of salt-induced hypertension, it did not prevent it. Blood pressure was increased by the end of the study, although it had not reached levels as in the untreated group (**Figure 5**). Thus looking at it from another angle, one could speculate that although atorvastatin could ameliorate salt sensitivity, high-salt intake eventually leads to resistance to the antihypertensive effects of the statins and likely to renal injury progression. Indeed, there are several studies in other models of salt-sensitive hypertension in which statins were not effective at lowering blood pressure during liberal salt intake. For instance, Zhou *et al.*[49] found that atorvastatin did not reduce blood pressure in Dahl salt-sensitive rats when they were maintained on high-salt intake. However, the blood pressure normalized when the rats were switched from high- to normal-salt diet. This reduction in blood pressure did not occur in rats not treated with statins, raising the possibility that the reduction in dietary

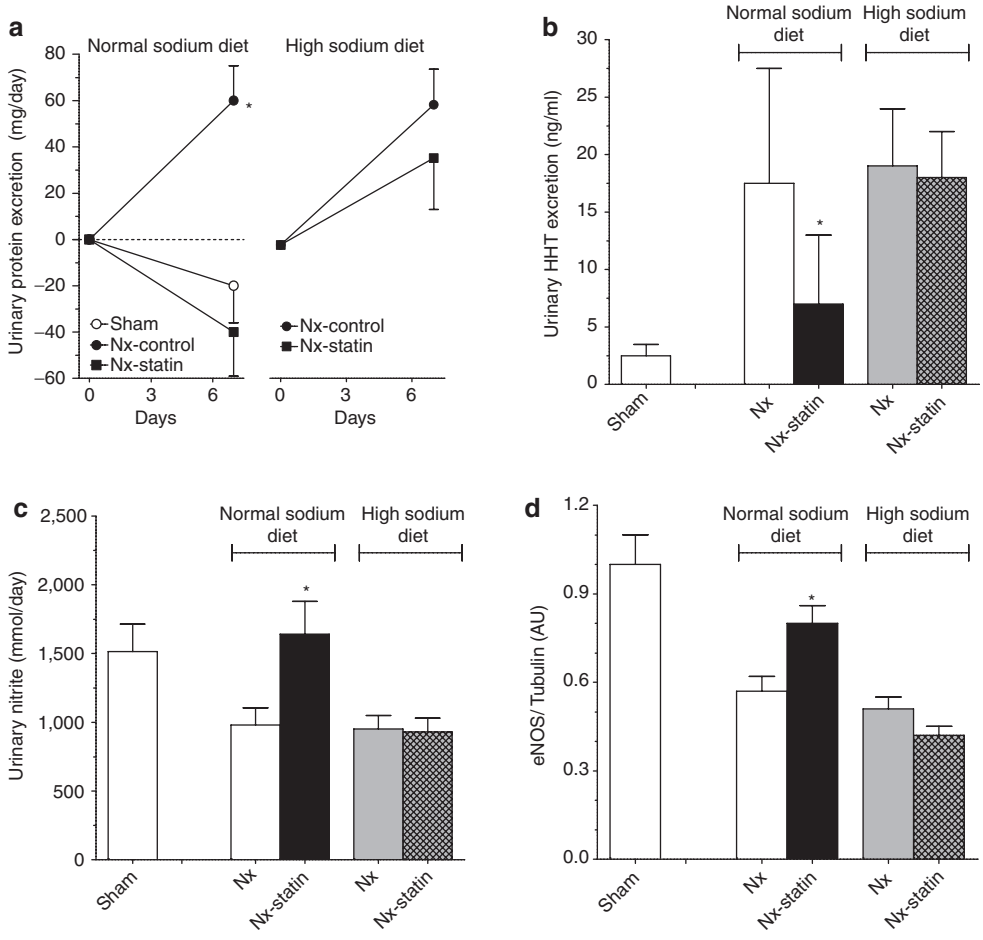

Figure 4 | The effect of atorvastatin on salt-induced alterations in urinary excretion of (**a**) protein, (**b**) 12S-12-hydroxy-5-8,10-heptadecatrienoic acid (HHT), (**c**) urinary nitrites, and on renal expression of (**d**) eNOS in rats subjected to 5/6 nephrectomy. AU, arbitrary unit; eNOS, endothelial nitric oxide synthase; Nx, nephrectomy. *$P < 0.05$.

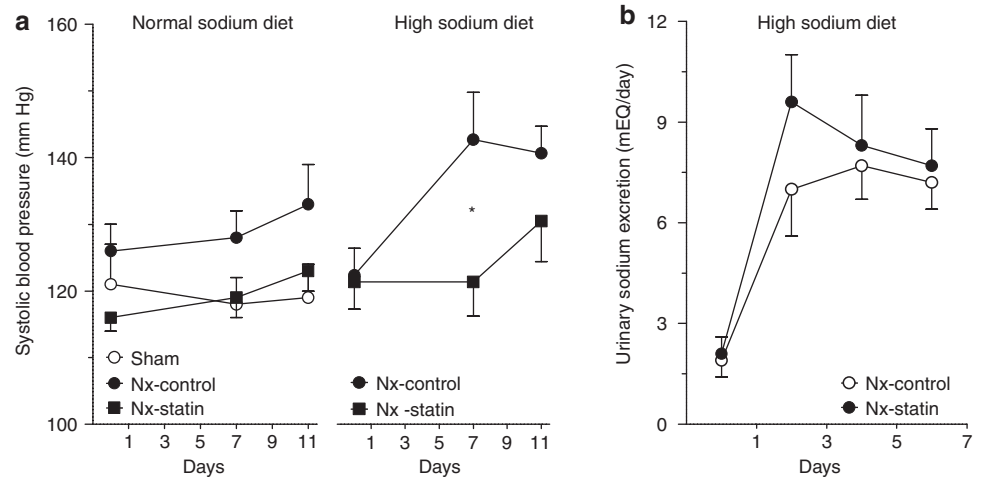

Figure 5 | The effects of atorvastatin (statin) on salt-induced alterations in (**a**) blood pressure and (**b**) urine sodium excretion rate in rats subjected to 5/6 nephrectomy. Nx, nephrectomy. *$P < 0.05$.

salt unmasked the antihypertensive effect of statins. Similarly, increasing salt intake prevents statin-induced decreases in blood pressure in experimental DOCA-salt hypertension[46,48] Thus taken together, these studies suggest that statins may improve salt sensitivity, protein excretion rate, renal NO markers, and oxidative stress and perhaps delay the development of salt-sensitive hypertension; however, all of these beneficial effects of statins may be negated by high-salt intake and thus eventually lead to increased blood pressure and progressive renal injury. Because excessive salt intake may also preclude the potential beneficial actions of antihypertensive therapy in human salt-sensitive hypertension,[70,71] it raises the possibility that salt sensitivity and salt intake may also determine the effectiveness of statins as antihypertensive agents.[49,70,72]

THE ANTIHYPERTENSIVE EFFECTS OF STATINS IN HUMAN HYPERTENSION

Unfortunately, most of the information regarding statins blood pressure lowering effects comes from relatively small studies, many of which were uncontrolled, unblinded, nonrandomized, and not specifically designed to assess the antihypertensive effects of statins,[57,73–75] Despite these shortcomings, several patterns emerge. Most published reports suggest that statins do not lower blood pressure significantly in normotensive hypercholesterolemic patients, or in well-controlled hypertensives.[76,77] However, this is not surprising for several reasons. Many medications only lower blood pressure when hypertension is present, and it may be more difficult to detect minor changes in blood pressure in the absence of hypertension. In addition, many of the antihypertensives used in the studies may already target the same pathway as statins (e.g., angiotensin-converting enzyme inhibitors and angiotensin receptor blockers decrease responses to angiotensin II, improve endothelial dysfunction, and decrease endothelin levels and inflammation).

On the other hand, the antihypertensive effect of statins in patients with untreated or uncontrolled hypertension is much more ambivalent. Several studies suggest that statins have a modest antihypertensive effect[55,56,58,72–80] but most of these are small studies of limited duration, or post hoc analyses of trials. A few larger studies have also evaluated this question.[57,80–82] For instance, the UCSD Statin Study,[80] a large randomized, double blind, placebo-controlled trial, found that 20 mg simvastatin or 40 mg pravastatin lowered systolic and diastolic blood pressure (these results extended to normotensive patients). In contrast, the Conduit Artery Function Evaluation–Lipid-Lowering Arm (CAFELLA) Study, an ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial) substudy, showed no differences in brachial and central aortic pressures between atorvastatin-treated and placebo-treated patients at the end of the study.[81] The Brisighella Heart Study,[57] a prospective, longitudinal cohort, found that simvastatin or pravastatin significantly decreased blood pressure in hypertensive patients (particularly those who were poorly controlled), but not in patients with normal blood pressures. Finally, a meta-analysis of 20 randomized, controlled trials of statins therapy showed a mean systolic of 4 mm Hg that was particularly evident in hypertensive patients.[82] This seemingly small blood pressure reduction was statistically significant and certainly could be clinically meaningful.

Thus, despite physiologic rationale suggesting that statins should reduce blood pressure, the available clinical evidence fails to establish a definite antihypertensive effect. A potential explanation for these inconsistent results may be derived from the experimental studies done under controlled salt intake; that is, as with antihypertensive drugs, high-salt intake could interfere with the antihypertensive effect of statins.[70,82] Thus, it is important to consider the sodium content in the diet when investigating the effects of statins on blood pressure.

Salt intake in clinical trials

Despite the importance of salt intake when evaluating blood pressure responses to drugs, most studies examining the antihypertensive effects of statins lack information on sodium intake. This is an important consideration as most large intervention trials in hypertension begin with lifestyle adjustments. For instance, Strazullo P *et al.*, published a large meta-analysis attempting to unravel the doubts regarding the blood pressure lowering effects of statins.[82] A number of strict criteria were used to select 18 studies from a very abundant list of publications (175 original reports and 63 reviews). Using these criteria, this meta-analysis reported that statins have a statistically significant effect on blood pressure that is unrelated to age, changes in serum cholesterol, or length of the trial. Unfortunately, reporting salt intake was not a selection condition, and the studies selected for this meta-analysis did not provide details on the prescribed sodium intake. In contrast to the above meta-analysis, the PHYLLIS Study (Plaque Hypertension Lipid-Lowering Italian Study)[83] a prospective randomized double-blind trial, found that statins did not affect blood pressure. Again, salt intake was not reported and the effectiveness of the statin may have been concealed by the active antihypertensive treatment or negated by increased salt ingestion as is common in most occidental diets. Similarly, neither the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm (ASCOT-LLA),[81] and the Cholesterol and Recurrent Events (CARE) trial[84] mention the prescribed or measured sodium intake.

Consequently, the available studies do not provide sufficient information on salt intake to allow a proper assessment of whether differences in salt intake may affect the antihypertensive actions of statins in humans, and whether this could have contributed to the inconsistent results from the clinical trials.

SUMMARY

Statins possess various beneficial pleiotropic effects including improvement in endothelial function, reduction in inflammation and oxidative stress, and downregulation of angiotensin II receptors and endothelin, which would suggest that statins may reduce blood pressure in patients with hypertension. Indeed, there is good evidence from various experimental models suggesting an antihypertensive action. However, the evidence from clinical studies has been inconclusive. This may be due to a variety of methodological limitations of the studies including inadequate sample size, limitations in study design, differences in blood pressure measurement techniques and patient populations, as well the confounding effects of antihypertensive drugs used in many of the trials. However, salt intake may be an important, under-recognized component. Experimental studies suggest that salt intake is a decisive factor in determining the effects of statins on blood pressure. Indeed, their antihypertensive and renal-protective effects may be canceled by an unrestricted salt intake. Because high-salt intake is the norm in the western society, we suspect that excessive salt may also be implicated in the diminished responses to statins, as described for many antihypertensive drugs used in clinical practice. Thus future studies should account for sodium intake and investigate whether adherence to proper sodium restriction may uncover/enhance the beneficial effects of statins on organ injury, salt sensitivity, and hypertension.

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