Oxidative Stress in Dahl Salt-Sensitive Hypertension

Shumei Meng, Garrick W. Cason, Anthony W. Gannon, Lorraine C. Racusen, R. Davis Manning, Jr

Abstract—The role of oxidative stress in the long-term regulation of arterial pressure, renal hemodynamics, and renal damage was studied in Dahl salt-sensitive rats. Twenty-eight Dahl S/Rapp strain rats, equipped with indwelling arterial and venous catheters, were subjected to a 3-week intravenous infusion of either low Na (0.9 mmol/d) or high Na (20.6 mmol/d) or the superoxide dismutase mimetic, 4-hydroxyl-2,2,6,6-tetramethylpiperdine-1-oxyl (Tempol), at 125 μmol·kg⁻¹·h⁻¹ plus low Na or high Na. After 21 days, mean arterial pressure was 140±3 mm Hg in the high-Na group, 118±1 mm Hg (P<0.05) in the high-Na/Tempol group, and unchanged in the low-Na/Tempol and low-Na groups. Tempol did not change renal blood flow, glomerular filtration rate, or glomerular cross-sectional area in rats subjected to the high-Na intake but did decrease urinary protein excretion, the percentage of sclerotic glomeruli, and the kidney weight to body weight ratio. In 15 additional Dahl S rats subjected to high or low Na intake for 3 weeks, renal cortical and medullary O₂⁻ release increased significantly in the high-Na group when compared with the low-Na group. Tempol decreased both renal cortical and medullary O₂⁻ release in the high- and low-Na rats, but the decrease in O₂⁻ release was greater in high-Na rats. The data suggest that oxidative stress contributes to Dahl salt-sensitive hypertension and the accompanying renal damage. (Hypertension. 2003;41:1346-1352.)

Key Words: arterial pressure ■ renal disease ■ urine ■ glomerulosclerosis ■ oxidative stress

Reactive oxygen species, including superoxide anions (O₂⁻), hydroxyl radicals, and hydrogen peroxide (H₂O₂), have been found in pathological conditions such as atherosclerosis, diabetes, renal disease, and hypertension. O₂⁻ and H₂O₂ production by polymorphonuclear leukocytes and the plasma level of lipid peroxides were higher in uncontrolled hypertensive patients than in controls. After blood pressure was reduced in these patients, free-radical generation and lipid peroxide levels returned to normal values. Hypertensive subjects have been shown to have lower levels of the endogenous antioxidants serum ascorbic acid and serum thiols, which might reflect greater consumption of antioxidants.

Oxidative stress has also been shown to be involved in hypertensive animal models. The spontaneous hypertensive rat (SHR) is characterized by increased oxidative stress, as demonstrated by the increased O₂⁻ production in mesenteric arterioles of the SHR. In the stroke-prone SHR, O₂⁻ generation in abdominal aortic tissue was increased compared with their Wistar-Kyoto counterparts. Swei et al found enhanced production of superoxide radicals in the microvessels of the mesentery, and plasma H₂O₂ concentration was increased in hypertensive Dahl salt-sensitive (S) rats compared with Dahl salt-resistant (R) rats. Yet whether increased O₂⁻ generation contributes to the salt-induced hypertension in the Dahl S rat is not known.

Hypertension induces important functional and structural alterations in the kidney, resulting in proteinuria, glomerular sclerosis, and other morphological changes, eventually leading to end-stage renal disease. Reducing blood pressure in hypertensive patients retards the progression of renal failure and reduces the morbidity and mortality rates, but the mechanisms by which hypertension causes renal damage are not clear. Recent experimental data have shown that renal damage in Dahl S rats occurs concomitantly with the long-term increases in arterial pressure, but the kidney damage might be partly related to an increase in oxidative stress. Administration of the antioxidant vitamin E did not suppress blood pressure in Dahl S rats but ameliorated their renal damage. However, the role of O₂⁻ in Dahl S hypertension and its accompanying renal damage are still not clear.

Our goal was to test the hypothesis that release of O₂⁻ in the Dahl S rat during high salt intake (high Na) exacerbates the hypertension and renal damage that occurs in these animals. Studies were conducted in Dahl S rats on a low-salt (low-Na) or high-Na intake that also received the superoxide dismutase (SOD) mimetic 4-hydroxyl-2,2,6,6-tetramethylperidine-1-oxyl (Tempol) for a 3-week period and also in low-Na or high-Na timed-control S rats. Measurements of mean arterial pressure (MAP), renal O₂⁻ release, renal hemodynamics, urine sodium and water excretion, urine protein excretion, and percentage of glomerulosclerosis and glomerular area were made during the experiment.

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Methods

Animal Preparation, Experimental Measurements, and Instrumentation

Experiments were conducted in group 1, which consisted of 28 conscious 7- to 8-week-old male Dahl S rats, Rapp strain (Harlan, Indianapolis, Ind) as described before.9 The project had the approval of the local institutional Animal Committee. When the rats reached a weight of 200 g, femoral arterial and venous catheters were implanted under isoflurane anesthesia, and experiments began 1 week later. Each day, 15 mL of either low NaCl (0.9 mmol/d NaCl) or high NaCl (20.6 mmol/d NaCl), with or without Tempol (125 μmol·kg⁻¹·h⁻¹), was infused intravenously and contained the antibiotics mezlocillin sodium (30 mg/d) and penicillin G (5000 U/d). Rats were placed in a temperature-controlled room with a 12-hour light/dark cycle and maintained in metabolic cages 24 h/d for the entire length of the study.

Solutions were infused with a syringe pump (Harvard Apparatus) through a 0.22-μm filter (Cathivex, Millipore Corp). The arterial catheter was filled with 1000 U/mL heparin and connected to a pressure transducer (Cobe), which in turn was connected to a pressure amplifier. Pulsatile arterial pressure and heart rate from the amplifier were sent to a digital computer through an analog-to-digital converter and were sampled throughout the entire 24-hour period. Heart rate and arterial pressure were determined from these data samples. Water intake and urinary volume output were measured daily. Twenty-four-hour urine samples were collected daily, and urine sodium concentration was determined by flame photometry. Urine protein concentration was measured twice a week by the Bradford method. Glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) were determined as before10 by measuring the radioactivity and aminohippurate concentration of a 4-hour fasted plasma sample after a 24-hour period of intravenous infusion of 125I-iothalamate and aminohippurate sodium. A sample of the infusate was analyzed for 125I and aminohippurate concentration, and infusion rates of iothalamate and aminohippurate were calculated and substituted for the urinary excretion rates of these substances. This constant-infusion method for determining GFR and ERPF gives the same values as urinary clearance techniques.11,12

Experimental Protocols

The following 4 groups of rats were studied in group 1: Dahl S/low-Na/Tempol (n=8); Dahl S/low-Na alone (n=6); Dahl S/high-Na/Tempol (n=7); and Dahl S/high-Na alone (n=7). During a 7-day surgical recovery period and throughout the experiment, rats were fed a low-sodium food (Teklab Test Diets). Data were collected during a 1-day control period followed by a 3-week period of vehicle infusion or oxidative stress inhibition with intravenous infusion of Tempol.

Tissue Preparation and Histology Study

On day 21 kidneys were collected, and coronal slices of kidney were fixed in buffered formalin and embedded in paraffin for the low-Na/Tempol, low-Na alone, high-Na/Tempol, and high-Na alone groups. Tissue sections were cut at 3 μm and stained with methenamine silver with periodic acid-Schiff counterstain by using standard methods. The percentage of glomerulosclerosis was calculated by counting all glomeruli and those with focal and global glomerulosclerosis and expressing the result as the percentage of total glomeruli. Maximal glomerular planar area was measured in 14 or 15 glomeruli sectioned perpendicular to the vascular pole and/or tubular take-off. Area was determined by using a point-counting method, with image capture, as previously described.13

Tissue Preparation and Chemiluminescence Measurement of O2⁻ Release in Renal Tissues

Group 2, which consisted of 15 additional S rats, was subjected to 3 weeks on the specific diets, the rats were anesthetized, and the renal cortex (n=7) of high- and low-Na-fed rats and the medulla of high-Na rats (n=8) and low-Na rats (n=7) were dissected out. Chemiluminescence of renal cortical and medullary tissue from rats with or without Tempol (8 mmol/L) in 5 μmol/L lucigenin (bis-N-methylacridinium nitrate) was detected with a scintillation counter (Beckman LS 6500) in the out-of-coincidence mode with a single, active photomultiplier tube,14 as we have done before.15 The validity of 5 μmol/L lucigenin for measuring O2⁻ production has been confirmed with electron spin resonance methods.16,17 The amounts of protein in the renal tissues were quantified with the Lowry assay. The final readings were expressed as counts per minute per milligram protein.

Data Analysis

Statistics were performed by first using a 2-way ANOVA for repeated measures, followed by a 1-way analysis of repeated measures for each group and a Newman-Keuls test for post hoc analysis at each experimental time point. Data were considered to be statistically different from control when P<0.05. All data are expressed as mean±SE.

Results

MAP and Heart Rate Responses to Tempol Infusion

Figure 1 illustrates that on day 0, the low-Na control period, MAP was ∼90 mm Hg in all 4 groups. MAP progressively increased in the high-Na-alone group, and its value on day 21 was 140±3 mm Hg, which was significantly increased compared with all other groups. In the high-Na/Tempol group,
there were no significant changes in MAP for the first 12 days of high-Na intake, and MAP was 118±1 mm Hg on day 21 (P<0.05 compared with the high-Na group). Therefore, the increase in MAP was significantly delayed and blunted by Tempol. Tempol did not significantly affect MAP in S rats on the low-Na intake during the experimental period, except on day 15. Heart rate changed little in the low-Na, low-Na/Tempol, and high-Na groups. There was a small decrease in heart rate in the high-Na/Tempol group on days 19 to 21.

**Urine Protein Excretion Responses to Tempol Infusion**

Figure 2 indicates that urine protein excretion, an index of renal damage, was significantly decreased beginning at day 14 in the high-Na/Tempol group compared with the high-Na-alone group (P<0.05). On day 21, urine protein excretion reached 157±20 mg/d in the high-Na/Tempol group and increased to 252±15 mg/d in the high-Na-alone group (P<0.05). In the low-Na/Tempol and low-Na groups, urine protein excretion remained at very low levels throughout the experiment, and these values were not significantly different from one another.

**Urine Volume and Urine Na Excretion Responses to Tempol Infusion**

Figure 3 shows that there were no significant differences in urine volume or urine Na excretion between the high-Na/Tempol group and the high-Na-alone group except on day 4 for both and day 17 for urine Na excretion. There were no significant changes in either urine volume or urinary Na excretion in the low-Na/Tempol group compared with the low-Na group.

**Renal Hemodynamic Responses to Tempol Infusion**

The Table shows that GFR per body weight was affected little by Tempol treatment in both the low- and high-Na groups. GFR per kidney weight was also not significantly different in any of the groups. The ratio of kidney weight to body weight, an index of renal hypertrophy, were higher in the high-Na/Tempol group and the high-Na-alone group compared with the low-Na/Tempol group (P<0.05). Tempol significantly decreased the kidney weight–to–body weight ratio in the high-Na/Tempol group compared with the high-Na-alone group (P<0.05). There were no differences in GFR per body weight, renal blood flow per body weight, renal blood flow per kidney weight, renal resistance, and filtration fraction between the high-Na/Tempol group and the high-Na-alone group. Renal blood flow per body weight, renal resistance, and filtration fraction in the low-Na/Tempol group were significantly different from the low-Na group, particularly in the early part of the experiment. However, GFR per body weight was not significantly different in the low-Na/Tempol group compared with the low-Na group.

**Changes in Percentage of Glomerular Sclerosis and Glomerular Area in Response to Tempol Infusion**

Figure 4 shows that Tempol significantly decreased the percentage of sclerotic glomeruli in the high-Na/Tempol group compared with the high-Na group. There were no significant differences in the percentage of sclerotic glomeruli in the high-Na group, high-Na/Tempol, low-Na, or low-Na/Tempol groups. The high-Na group had a larger glomerular cross-
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Renal Hemodynamic Responses to Tempol and Sodium Intake

<table>
<thead>
<tr>
<th>Time</th>
<th>Hi</th>
<th>Hi + Tempol</th>
<th>Low</th>
<th>Low + Tempol</th>
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<td>1 Wk</td>
<td>2 Wk</td>
<td>3 Wk</td>
<td>1 Wk</td>
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<tr>
<td>GFR/BW, mL/min/100 g</td>
<td>1.41 ± 0.06*</td>
<td>1.39 ± 0.06</td>
<td>1.23 ± 0.07</td>
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<td>RBF/BW, mL/min/100 g</td>
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<td>7.62 ± 0.39</td>
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<tr>
<td>RR, mm Hg</td>
<td>6.94</td>
<td>7.45</td>
<td>8.68</td>
<td>6.78</td>
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<tr>
<td>FF</td>
<td>0.31 ± 0.03*</td>
<td>0.29 ± 0.05*</td>
<td>0.28 ± 0.03*</td>
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<tr>
<td>GFR/KW, mL/min/g</td>
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</tr>
<tr>
<td>RBF/KW, mL/min/g</td>
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<td>11.05</td>
<td>11.16</td>
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<tr>
<td>KW/BW, g/100 g</td>
<td>1.30 ± 0.03*</td>
<td>1.30 ± 0.03*</td>
<td>1.30 ± 0.03*</td>
<td>1.30 ± 0.03*</td>
</tr>
</tbody>
</table>

GFR indicates glomerular filtration rate; BW, body weight; RBF, renal blood flow; RR, renal vascular resistance; FF, filtration fraction; KW, kidney weight; Hi, high sodium; and Low, low sodium.

*P < 0.05 compared with the Low Na Tempol group at the same time; †P < 0.05 compared with the high Na Tempol group at the same experimental time.

sectional area than did the low-Na group. However, Tempol did not significantly change the glomerular cross-sectional area in the high-Na/Tempol group when compared with the high-Na group.

Renal Cortical and Medullary O$_2^-$ Release Responses to Tempol

The upper panel of Figure 5 shows that renal cortical O$_2^-$ release significantly increased in S rats after 3 weeks of high-Na intake, and the value was 71.6 ± 8.1 cpm/mg protein in S high-Na rats and 29.0 ± 4.1 cpm/mg in the S low-Na rats (P < 0.05). The SOD mimetic Tempol significantly decreased these readings to 22.0 ± 3.2 cpm/mg and 18.2 ± 4.6 cpm/mg, respectively. The inhibitable O$_2^-$ release with Tempol in the medulla was 23.3 ± 3.4 cpm/mg in the S high-Na rats and 14.9 ± 1.5 cpm/mg in the S low-Na rats (P < 0.05).

The lower panel of Figure 5 shows that renal medullary O$_2^-$ release also significantly increased in S rats on a high-Na intake when compared with low-Na intake (35.1 ± 4.0 vs 26.0 ± 1.8 cpm/mg). Tempol also significantly decreased O$_2^-$ release in S high-Na and S low-Na rats to 11.8 ± 2.1 and 11.1 ± 1.6 cpm/mg, respectively. The inhibitable O$_2^-$ release with Tempol in the medulla was 23.3 ± 3.4 cpm/mg in the S high-Na rats and 14.9 ± 1.5 cpm/mg in the S low-Na rats (P < 0.05).

Discussion

The major new finding in this study is that a 3-week intravenous infusion of Tempol, a membrane-permeable, SOD mimetic, markedly blunted the salt-induced increase in arterial pressure in Dahl S rats and significantly decreased renal damage. These findings were confirmed by both a delay in the increase in arterial pressure in the high-Na/Tempol group and a lower final arterial pressure. Decreased renal damage in the high-Na/Tempol group was evidenced by significant decreases in urinary protein excretion, kidney weight-to-body weight ratio, and the percentage of glomeruli with glomerulosclerosis. Because Tempol prevents O$_2^-$-
induced damage during radiation, inflammation, and ischemia/reperfusion injury and decreases arterial pressure in hypertensive rats. These data suggest that the Dahl S rat has increased O$_2^-$ activity during increased Na intake, which contributes to their renal damage and hypertension.

O$_2^-$ release significantly increased in S high-Na rats compared with S low-Na rats, suggesting that a high Na intake in S rats causes increased oxidative stress. Tempol markedly decreased O$_2^-$ release in the renal cortex and medulla, which might have helped to decrease renal damage. The amount of O$_2^-$ release that was inhibitable by Tempol was significantly greater in S high-Na rats in both the cortex and medulla.

Oxidative stress might play an important role in both human and experimental hypertension. The serum levels of thiols and vitamin C were decreased in hypertensive subjects, suggesting an increased consumption of these antioxidants. Administration of vitamin C or other antioxidants significantly reduced arterial pressure in hypertensive subjects. Several investigators have shown that oxidative stress is associated with the increased blood pressure in experimental hypertension. In the Dahl S rat on a high-Na diet, O$_2^-$ in the mesentery and plasma H$_2$O$_2$ levels were increased compared with the Dahl R rat. Furthermore, an increased vitamin E diet ameliorated arterial and renal injuries in Dahl S rats. In Wistar rats, elevation of arterial pressure in isolated gracilis arterioles increased release of O$_2^-$ and prevented nitric oxide (NO)–mediated dilations in response to increased perfusate flow, and SOD and catalase restored the NO-mediated dilation. In the SHR, studies with fluorescence micrography indicated that mesenteric arterioles have an elevated O$_2^-$ production. In addition, SHR aortic rings are more sensitive to O$_2^-$ than are Wistar-Kyoto aortic rings. In that study, the aortic contractions caused by O$_2^-$ were blocked by SOD.

There are problems with some of the O$_2^-$ scavengers. Native SOD is not very permeable to the cell membrane, and Cu-Zn SOD is inactivated by intracellular divalent cations. Some O$_2^-$ scavengers, such as allopurinol, also produce O$_2^-$.

Recently, Schnackenberg et al showed that an acute bolus injection of Tempol reduces arterial pressure and renal vascular resistance in the SHR but not in the Wistar-Kyoto rat and that this response was blocked by nitro-L-arginine methyl ester administration but not by norepinephrine. This implies that Tempol might prevent the inactivation of NO by O$_2^-$, thus increasing the bioavailability of NO. A later study with oral administration of Tempol suggested that hypertension in the SHR is associated with increased release of O$_2^-$ and that Tempol can effectively reduce oxidative stress and decrease blood pressure. However, whether reduction of O$_2^-$ in Dahl S rats with Tempol will ameliorate salt-induced hypertension is not known.

We have shown in this study for the first time that administration of Tempol to the Dahl S rat significantly decreased salt-induced hypertension. However, the mechanism of the amelioration of hypertension in the high-Na/Tempol S rats in the present study is not clear. Tempol significantly reduced heart rate on days 19 to 21 in high-Na-fed rats, indicating that Tempol might have some effect on sympathetic function at this time. However, the lack of any change in heart rate before day 19 of the high-Na/Tempol group and in the other groups implies that the effect of Tempol on sympathetic function does not play a major role in the mechanism of Tempol to reduce blood pressure in the high-Na/Tempol group. Recent studies by Xu et al have shown that administration of large doses of Tempol (up to 300 μmol/kg IV bolus) significantly decreased renal sympathetic nerve activity and reduced blood pressure in anesthetized deoxycorticosterone acetate-salt rats. The actions of Tempol are believed to be due to its scavenging of O$_2^-$.

Yet large doses of Tempol have been shown to cause hypotension in the pig, which might indicate a direct vasodilatory or hypotensive effect. Our dosage was lower than that used in the study on pigs, and evidence that Tempol did not cause a direct hypotensive action was provided by the low-Na/Tempol S rats. Figure 1 shows that the control MAP in these low-Na rats on day 0 was 91 ± 1 mm Hg, and Tempol did not change MAP from this value, indicating no direct hypotensive effect of Tempol. Also, the MAP of low-Na/Tempol rats was not significantly different from low-Na rats except on day 15. The Table also shows that renal vasodilation did not occur during Tempol infusion in either the low- or high-Na groups.

A leftward shift or rotation in the renal pressure natriuresis relation could explain why Tempol lowered arterial pressure in the high-Na S rats. These rats had the same Na intake as the S rats on high-Na alone, but their arterial pressure was decreased, indicating that the salt sensitivity of arterial pressure was decreased. One possible mechanism to decrease the salt sensitivity of the S rats is to increase the bioavailability of NO. We have previously shown that the S rat has decreased NO production and that infusion of the NO substrate L-arginine increased NO production and decreased both arterial pressure and the salt sensitivity of arterial pressure.

The Table indicates that ratio of renal blood flow to body weight was significantly lower and renal vascular resistance was higher in low-Na/Tempol-treated rats compared with low-Na-treated rats. However, the Tempol effect on the renal vasculature did not occur in the high-Na groups. The reason why Tempol affected renal vascular resistance in the low-Na groups only is not clear from our data, but there is a possible mechanism that could explain it. Because Tempol is a SOD mimic, it can dismutate oxygen free radicals to H$_2$O$_2$. Thus, Tempol plus endogenous SOD could produce excess H$_2$O$_2$, which has been shown to have vasoconstrictor activity. H$_2$O$_2$ levels are elevated in humans with essential hypertension, and H$_2$O$_2$ is correlated positively with plasma renin activity in these patients. H$_2$O$_2$ might exacerbate the vasoconstrictor actions of angiotensin II, and this was shown in transgenic mice. In that study, the long-term arterial pressure response to angiotensin II infusion was markedly blunted in transgenic mice that overexpressed catalase, which will decrease H$_2$O$_2$ levels. Therefore, in the present experiment, excess levels of H$_2$O$_2$ could have increased the angiotensin II

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vasoconstriction of the renal vasculature in the low-Na/Tempol group. This synergistic effect of angiotensin II and H$_2$O$_2$ would not occur in the high-Na rats, because the angiotensin system is suppressed.$^{37}$ Figure 5 shows that Tempol decreased superoxide release from the cortex and medulla of Dahl S rats subjected to high- or low-Na intake. However, the amount of superoxide inhibitable with Tempol was much greater in high-Na rats. For example, in the cortex, the Tempol-inhibitable superoxide release was twice as great in the high-Na group as in the low-Na group. This suggests that there was some basal level of oxygen free-radical generation in the renal cortex and medulla during low Na intake, and this low level of free-radical release could play a role in normal signaling pathways but not necessarily in arterial pressure control or renal damage. This finding is consistent with a recent study that showed that there was a basal production of oxygen free radicals in venules of low-Na Sprague-Dawley rats.$^{38}$

One mechanism to increase the bioavailable NO is to decrease excess levels of O$_2^{-}$. The scavenging of O$_2^{-}$ by Tempol will increase the half-life of NO. In coronary arterial rings, O$_2^{-}$ has been shown to inactivate NO.$^{39}$ Gryglewski et al.$^{40}$ showed that O$_2^{-}$ was important in the decomposition of NO to peroxynitrite. Under normal circumstances, abundant SOD in the body reacts with O$_2^{-}$ and keeps O$_2^{-}$ at very low levels. Whenever O$_2^{-}$ is increased or there is a deficiency of the antioxidant system, the breakdown of NO by O$_2^{-}$ will increase, which might contribute to the progression of this type of hypertension. The peroxynitrite formed by the interaction of NO and O$_2^{-}$ can cause tissue damage of proteins throughout the body, including the kidney. In the present experiment, this could have been an important mechanism in causing the increases in urinary protein excretion and glomerulosclerosis in the high-Na S rats.

It is not clear from our study whether the increased oxidative stress was caused directly by the increased arterial pressure, as has been seen in human and experimental hypertension, or whether the increased Na intake caused increased oxidative stress, as was shown recently in normotensive rats on a high-Na diet.$^{41}$ They showed that the basal activities of NAD(P)H oxidase and xanthine oxidase increased in microvessels of Sprague-Dawley rats during increased Na intake.

In Dahl S high-Na rats with Tempol infusion, the percentage of glomeruli with sclerosis decreased, the urinary protein excretion fell, the kidney weight–body weight ratio was lower, and the glomerular cross-sectional area was unchanged compared with the high-Na group. However, it is not clear from our data whether the decrease in renal damage in Tempol-treated high-Na S rats was due to a primary decrease in O$_2^{-}$ or secondarily because of a decrease in MAP. Nevertheless, Tempol resulted in significant decrease in renal damage.

In conclusion, the development of salt-induced hypertension was delayed and the level of hypertension was significantly decreased in Dahl S rats on high-Na intake and continuous intravenous Tempol infusion. Renal damage in these rats was decreased compared with Dahl S rats on a high-Na intake alone. In the renal cortex and medulla, O$_2^{-}$ release increased in S high-Na rats compared with low-Na rats. Tempol decreased O$_2^{-}$ release in the cortex and medulla, with the greatest decreases occurring in the high-Na rats. Therefore, Tempol significantly decreased hypertension and renal damage in Dahl S rats on a high-Na intake. These data suggest that increased oxidative stress contributes to renal damage and the level of arterial pressure in salt-sensitive hypertension.

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References


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