Vascular dysfunction precedes hypertension associated with a blood pressure locus on rat chromosome 12

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1Human and Molecular Genetics Center, Medical College of Wisconsin, Milwaukee, Wisconsin; 2Biotechnology and Bioengineering Center, Medical College of Wisconsin, Milwaukee, Wisconsin; 3Department of Physiology, Medical College of Wisconsin, Milwaukee, Wisconsin; 4Department of Pediatrics, Medical College of Wisconsin, Milwaukee, Wisconsin; and 5Department of Dermatology, Medical College of Wisconsin, Milwaukee, Wisconsin

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Prisco SZ, Priestley JR, Weinberg BD, Prisco AR, Hoffman MJ, Jacob HJ, Flister MJ, Lombard JH, Lazar J. Vascular dysfunction precedes hypertension associated with a blood pressure locus on rat chromosome 12. Am J Physiol Heart Circ Physiol 307: H1103–H1110, 2014. First published August 22, 2014; doi:10.1152/ajpheart.00464.2014.—We previously isolated a 6.1-Mb region of SS/Mcwi (Dahl salt-sensitive) rat chromosome 12 (13.4–19.5 Mb) that significantly elevated blood pressure (BP) (Δ +34 mmHg, P < 0.001) compared with the SS-12BN congenic control. In the present study, we examined the role of vascular dysfunction and remodeling in hypertension risk associated with the 6.1-Mb region on rat chromosome 12 by reducing dietary salt, which lowered BP levels so that there were no substantial differences in BP between strains. Consequently, any observed differences in the vasculature were considered BP-independent. We also reduced the candidate region from 6.1 Mb with 133 genes to 2 Mb by congenic mapping. Both the 2 Mb and 6.1 Mb congenic intervals were associated with hypercontractility and decreased elasticity of resistance vasculature prior to elevations of BP, suggesting that the vascular remodeling and dysfunction likely contribute to the pathogenesis of hypertension in these congenic models. Of the 23 genes within the narrowed congenic interval, 12 were differentially expressed between the resistance vasculature of the 2 Mb congenic and SS-12BN congenic strains. Among these, *Griffin was consistently upregulated 2.7 ± 0.6-fold (P < 0.05) and 2.0 ± 0.3-fold (P < 0.01), and *Chst12 was consistently downregulated −2.8 ± 0.3-fold (P < 0.01) and −4.4 ± 0.4-fold (P < 0.0001) in the 2 Mb congenic compared with SS-12BN congenic under normotensive and hypertensive conditions, respectively. A syntenic region on human chromosome 7 has also been associated with BP regulation, suggesting that identification of the genetic mechanism(s) underlying cardiovascular phenotypes in this congenic strain will likely be translated to a better understanding of human hypertension.

Dahl salt-sensitive; Brown Norway; genetic; vessel

VASCULAR HEALTH is a strong predictor of hypertension (5, 21, 27, 36) and is highly heritable (24–26, 30), but the mechanisms contributing to alterations in vascular reactivity and elasticity that cause hypertension remain largely undefined (19, 29). One method of localizing hypertension risk genes is by consomic and congenic mapping (i.e., introgression of chromosomal regions from one genetic background onto another). Although our group typically focuses on mapping blood pressure (BP) and renal phenotypes, it is increasingly apparent that a single hypertension locus can impact multiple organ systems (14). As such, we have now taken to systematically examining additional organ systems (e.g., the vasculature) that might also impact the overall hypertension risk at a particular locus. We recently generated several rat chromosome 12 congenic strains where segments of the SS chromosome 12 were transferred back onto the SS-12BN congenic background (13). In one such locus, we identified a 6.1 Mb region of SS/Mcwi (Dahl salt-sensitive) rat chromosome 12 (13.4–19.5 Mb) that severely elevated BP (Δ +34 mmHg, P < 0.001) compared with the MAP of the SS-12BN control congenic strain (144 ± 6 mmHg) on 8% NaCl diet (13). Here, our primary goal was to determine whether changes to the vasculature contribute to the hypertension risk associated with the 6.1-Mb (13.4–19.5 Mb) locus on chromosome 12. We specifically examined mesenteric small resistance arteries because small artery elasticity has been shown to be a stronger independent predictor of hypertension than large artery elasticity (36). Second, we narrowed the candidate region from 6.1 Mb (chr12:13.4–19.5 Mb) and 133 genes to 2 Mb (chr12:13.4–15.4 Mb) and 23 genes by congenic mapping. Collectively, we identified 12 differentially expressed genes and 2 (Griffin and Chst12) that were differentially expressed on both low- and high-salt diets that could potentially be associated with decreased elasticity and enhanced sensitivity to vasoconstrictors prior to significant elevations in BP.

MATERIALS AND METHODS

Generation of SS-12BN congenic rats. Rats were provided food and water ad libitum and were housed at the Medical College of Wisconsin (MCW) Biomedical Resource Center. Protocols were approved by the MCW Institutional Animal Care and Use Committee (IACUC). Line Ca [SS.BN-(D12Hmgc3-AU047911)/Mcwi; Rat Genome Database (RGD) ID 7248453] was generated by 1) crossing the line C [SS.BN-(D12Hmgc3-D12Hmgc6)/Mcwi; RGD ID 5683890] (13) and SS-12BN/Mcwi strains; 2) intercrossing the F1 generation; 3) screening the F2 generation for recombinations by marker-assisted selection as described previously (31); 4) backcrossing any animals with recombinations in the candidate region to SS-12BN/Mcwi; and 5) intercrossing animals with recombinations in the candidate region. Line C contains a 6.1-Mb congenic interval of SS rat chromosome 12 (13.4–19.5 Mb) that was introgressed back into the SS-12BN congenic background. Line Ca contains a 2-Mb congenic interval of SS rat chromosome 12 (13.4–15.4 Mb) that was introgressed back into the SS-12BN congenic background.
**BP measurements.** Male rats were fed a 0.3% NaCl diet (7034 Teklad, Harlan, Indianapolis, IN). MAP was measured by implanting a telemetry transmitter with a catheter in the abdominal aorta of 9- to 10-wk-old rats, as described previously (13). MAP was recorded for 3 consecutive days and the reported MAP values were averages of the measurements in 3-h intervals (e.g., 9 AM–12 PM).

**Examination of vascular reactivity.** Third-order mesenteric arteries were isolated, cleaned of fat and connective tissue, and hung by tungsten wires on a wire myograph (Danish Myo Technology, Aarhus, Denmark), as previously described (46). Force measurements were re-
moved at each pressure. Strain values (\(D/D_{\text{ref}}\)) were calculated by
from 20 to 160 mmHg. The inner and outer diameters were deter-
mined to determine the mean elastic modulus for each animal, similar to previous reports (22).

**Histological analysis.** Superior mesenteric arteries were collected from 9- to 10-wk-old SS-12\(^{2\text{BN}}\) and Ca rats maintained on 0.3% NaCl diets, fixed in 10% buffered formalin, sectioned at 4-μm thickness, and stained with Verhoeff’s elastic and Masson’s trichrome stains (33). Slides were digitized with a Hamamatsu NanoZoomer. Images of entire mesenteric arteries were taken at 10× with NDP View software (Hamamatsu Photonics, Hamamatsu City, Japan) and analyzed with MetaMorph (Molecular Devices, Sunnyvale, CA). Percent areas of collagen and elastin in the tunica media were quantified by encircling the tunica media in MetaMorph and selecting for blue and black areas, respectively.

**RT-qPCR.** Mesenteric vessels were collected from 9- to 10-wk-old SS-12\(^{2\text{BN}}\) and Ca rats maintained on a 0.3% NaCl diet and from 14- to 15-wk-old rats that were switched to an 8% NaCl diet (AIN-76, Dyets, Bethlehem, PA) for 3 wk. RNA was extracted from the mesenteric vessels with the RNeasy Fibrous Tissue Kit (Qiagen, Germantown, MD) according to the manufacturer’s protocol. cDNA was synthe-
sized and RT-qPCR was performed as previously described (20). Data were normalized to GAPDH and relative mRNA expression was determined by the \(\Delta\Delta^{\text{CT}}\) method (40). Primers were designed and validated as previously described (20). Primer sequences are listed in Table S1, available with the online version of this article.

**Statistical analysis.** Statistical analyses for the BP, vascular reactivity, and mechanics data were performed using SigmaPlot 12.0 software. All data are presented as means ± standard error of the mean (SE). MAP and systolic BP data were analyzed by 2-way repeated-measures ANOVA followed by the Holm-Sidak multiple comparison test vs. the control (SS-12\(^{2\text{BN}}\)) group. Contractile forces in response to 10 μM PE were analyzed by 1-way ANOVA. Percent relaxation data in response to 10 μM ACh were analyzed by 1-way ANOVA on ranks. Curve analyses and calculations of EC\(_{50}\) values for the vascular reactivity data were completed with Prism computing software (GraphPad Software, LaJolla, CA). EC\(_{50}\) values of the vascular reactivity data were analyzed by 1-way ANOVA followed by the Holm-Sidak multiple comparison test vs. the SS-12\(^{2\text{BN}}\) control group. Since the mean elastic modulus values were not normally distributed, the data were log-transformed prior to analysis by 1-way ANOVA followed by the Holm-Sidak multiple comparison test vs. the SS-12\(^{2\text{BN}}\) control group. Lumen diameters and wall thickness-to-lumen ratios were analyzed by 2-way repeated-measures ANOVA on ranks followed by the Holm-Sidak multiple comparison test. Gene expression and histology data were analyzed by Student’s t-test.

**RESULTS**

**Blood pressure.** We recently identified a 6.1-Mb region of SS chromosome 12 (13.4–19.5 Mb) in the line C congenic interval that significantly increased BP on the SS-12\(^{2\text{BN}}\) rat background (13). One shortcoming of that study was that BP was higher on both diets (1% and 8% NaCl) than were tested, preventing us from identifying whether impairment of the resistance vasculature (structure/function) preceded BP elevation. As such, we tested whether a lower-salt diet (0.3% NaCl) had any effects on BP in SS-12\(^{2\text{BN}}\), line C, or line Ca, a smaller congenic (chr12:13.4–15.4 Mb; Fig. 1).

Previously, on 1% NaCl, line C (146 ± 6 mmHg; \(n = 11\), \(P < 0.001\)) had significantly increased MAP compared with SS (121 ± 3 mmHg; \(n = 12\)) and SS-12\(^{2\text{BN}}\) (127 ± 1 mmHg; \(n = 10\)) (13). Additionally, on 8% NaCl, line C (178 ± 7 mmHg; \(n = 11\), \(P < 0.001\)) had significantly elevated MAP compared with SS (137 ± 5 mmHg; \(n = 12\)) and SS-12\(^{2\text{BN}}\) (144 ± 6 mmHg; \(n = 10\)) (13). After lowering the salt intake in the present study, the MAP of line C (105 ± 2 mmHg; \(n = 9\);
arteries were significantly more sensitive to 5-HT compared with SS-12BN mesenteric arteries (logEC50 value of −7.34 ± 0.03 M) (Fig. 3B). However, there were no differences in response to the endothelium-dependent vasodilator ACh in line C (logEC50 value of −8.66 ± 1.03 M) and line Ca (logEC50 value of −7.91 ± 0.04 M) mesenteric arteries compared with SS-12BN mesenteric arteries (logEC50 value of −8.20 ± 0.04 M) (Fig. 3C). There were also no differences in the response of line C (logEC50 values of −8.52 ± 0.34 M) and line Ca (logEC50 value of −7.60 ± 0.04 M) mesenteric arteries to the endothelium-independent vasodilator sodium nitroprusside, compared with SS-12BN mesenteric arteries (logEC50 value of −7.98 ± 0.19 M) (Fig. 3D). Collectively, these data show that while line C and Ca mesenteric arteries have increased sensitivity to the vasoconstrictors PE and 5-HT compared with SS-12BN, they have no differences in response to the endothelium-dependent and endothelium-independent vasodilators, ACh and sodium nitroprusside, respectively.

Passive wall mechanics. To determine whether there were any inherent structural or passive mechanical differences between SS-12BN, line C, and line Ca mesenteric arteries, we examined passive stress-strain relationships in Ca2+-free PSS. There was a left shift in the passive stress-strain curves of line C and line Ca arteries compared with the SS-12BN curve (Fig. 4A). The mean elastic modulus values for line C (1.730 ± 0.303 kPa; P < 0.05) and Ca (1.574 ± 0.193 kPa; P < 0.05) mesenteric arteries were significantly elevated compared with SS-12BN (942 ± 109 kPa) mesenteric arteries (Fig. 4B). These results suggest that line C and Ca resistance arteries are intrinsically stiffer than SS-12BN arteries, which may play a role in the elevated BP levels observed in lines C and Ca when on high salt diets.

We also investigated whether there were any differences in wall thickness-to-lumen diameter ratios, which can lead to enhanced vasoconstriction (15). From 20 to 80 mmHg, there were no significant differences in the wall thickness-to-lumen ratios between lines C, Ca, and SS-12BN (Table 1). At 120 mmHg, lines C (0.070 ± 0.003; P < 0.01) and Ca (0.080 ± 0.003; P < 0.05) mesenteric arteries had significantly lower wall thickness-to-lumen ratios compared with those of SS-12BN rats (0.087 ± 0.004). Line C arteries also had significa-

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**Fig. 1.** Schematic representation of the two salt-sensitive (SS)-12BN congenic strains that were generated by introgressing segments of the SS chromosome 12 (black) into the genetic background of the SS-12BN consomic rat (white) by marker-assisted selection. Line Ca is a smaller congenic derived from line C. Mean arterial pressures from 9 AM to 12 PM while on 0.3% NaCl are shown. The thin black bars represent historical MAP data for SS and BN measured via telemetry on 0.3% NaCl diets were not available. The sample size for each group is shown. The black bars represent polymorphism. *P < 0.05 vs. SS-12BN. All other chromosomes are SS. SSLP, simple sequence length polymorphism.

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**Fig. 2.** Mean arterial pressures averaged over 3-h intervals for 3 consecutive days. Data are presented as means ± SE. Data were analyzed by 2-way repeated-measures ANOVA followed by the Holm-Sidak multiple comparison test vs. the control SS-12BN group. n = 11 SS-12BN, n = 9 C, and n = 8 Ca. *P < 0.05 vs. SS-12BN.
cantly lower wall thickness-to-lumen ratios at 100 (0.076 ± 0.002 vs. 0.094 ± 0.005; *P < 0.05) and 160 mmHg (0.063 ± 0.003 vs. 0.076 ± 0.004; *P < 0.05) compared with SS-12BN arteries (Table 1), suggesting that the wall thickness, which often increases in response to elevated BP (15), does not contribute to enhanced vasoconstriction and/or decreased elasticity observed in lines C and Ca. Finally, we observed no differences in the lumen diameters of maximally dilated arteries from line C, line Ca, and SS-12BN rats (data not shown), suggesting that the passive diameters of the third-order mesenteric arteries are unlikely to contribute to the elevated BP levels observed in our congenic animals when exposed to high-salt diets (13). Collectively, our data indicate that the line C and Ca mesenteric arteries are stiffer and have an enhanced sensitivity to the vasoconstrictors PE and 5-HT, independent of arterial wall hypertrophy or reduced lumen diameter.

Histology. To determine whether there was any histological evidence of structural differences, superior mesenteric arteries from SS-12BN and Ca animals were collected and costained with Verhoeff’s elastic and Masson’s trichrome stains. While there were no differences in the relative amount of collagen in the tunica media between Ca and SS-12BN (15.13 ± 1.97 vs. 14.88 ± 0.93%; *P < 0.05), superior mesenteric arteries from line Ca rats had significantly less elastin (14.10 ± 1.33 vs. 35.29 ± 3.32%; *P < 0.01), and consequently, significantly increased collagen-to-elastin ratios (1.11 ± 0.20 vs. 0.43 ± 0.05%; *P < 0.05) compared with SS-12BN (Fig. 5), suggesting that decreased elastin levels or elevated collagen to elastin ratios may contribute to the development of stiffer resistance arteries in line Ca.

Gene expression. We also examined whether any of the 23 genes within the line Ca region were differentially expressed between SS-12BN and Ca mesenteric vessels on 0.3% NaCl diets and 3 wk of 8% NaCl diets (Table 2). Only two genes (Grifin and Chst12) were differentially expressed in the same direction on both 0.3% and 8% NaCl diet comparisons. Grifin was upregulated 2.7 ± 0.6-fold (*P < 0.05) and 2.0 ± 0.3-fold (*P < 0.01) in line Ca on 0.3% and 8% NaCl diets, respectively. Chst12 was downregulated −2.8 ± 0.3-fold (*P < 0.01) and −4.4 ± 0.4-fold (*P < 0.0001) in line Ca on 0.3% and 8% NaCl diets, respectively. FisJ2 was differentially expressed on
Table 1. Mesenteric artery wall thickness-to-lumen diameter ratios at different intraluminal pressures

<table>
<thead>
<tr>
<th>Pressure, mmHg</th>
<th>SS-12BN</th>
<th>C</th>
<th>Ca</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>0.227 ± 0.004</td>
<td>0.205 ± 0.008</td>
<td>0.210 ± 0.004</td>
</tr>
<tr>
<td>40</td>
<td>0.172 ± 0.006</td>
<td>0.156 ± 0.005</td>
<td>0.157 ± 0.005</td>
</tr>
<tr>
<td>60</td>
<td>0.138 ± 0.008</td>
<td>0.121 ± 0.005</td>
<td>0.122 ± 0.005</td>
</tr>
<tr>
<td>80</td>
<td>0.108 ± 0.006</td>
<td>0.090 ± 0.002</td>
<td>0.095 ± 0.004</td>
</tr>
<tr>
<td>100</td>
<td>0.094 ± 0.005</td>
<td>0.076 ± 0.002†</td>
<td>0.086 ± 0.003</td>
</tr>
<tr>
<td>120</td>
<td>0.087 ± 0.004</td>
<td>0.070 ± 0.003*</td>
<td>0.080 ± 0.003*</td>
</tr>
<tr>
<td>140</td>
<td>0.078 ± 0.004</td>
<td>0.065 ± 0.003*</td>
<td>0.075 ± 0.003</td>
</tr>
<tr>
<td>160</td>
<td>0.076 ± 0.004</td>
<td>0.063 ± 0.003*</td>
<td>0.073 ± 0.003</td>
</tr>
</tbody>
</table>

Data are presented as mean wall thickness-to-lumen diameter ratio ± SE; n = 7 SS-12BN, n = 5 C and n = 12 Ca. Statistical significance was determined by 2-way repeated-measures ANOVA on ranks followed by the Holm-Sidak multiple comparison test. *P < 0.05, †P < 0.01 vs. SS-12BN.

both 0.3% and 8% NaCl diets, but in opposite directions (Table 2). Nine genes (Sdki1, LOC100363385, Brat1, Igce, Lfng, Elfn1, Mafk, Ints1, and Micall2) were differentially expressed on either 0.3% or 8% NaCl diets, but not both. Collectively, these data prioritize Grifin and Chst12 as positional candidate genes for vascular reactivity and elasticity but do not preclude the potential role(s) of the other differentially expressed genes.

DISCUSSION

We previously isolated a 6.1-Mb region on rat chromosome 12 (line C) with 133 genes that significantly increased BP when exposed to elevated salt diets (13). We have since reduced this candidate interval to a 2-Mb region (line Ca) with 23 genes. The goal of the present study was to determine whether there were any vascular alterations in lines C and Ca prior to elevations of BP. In this study, we lowered the salt content of the diets so that there were no substantial differences in BP between the congenic and consomic strains. Therefore, any vascular differences observed between strains would be occurring prior to any elevations in BP. Before developing hypertension, mesenteric arteries from lines C and Ca had an enhanced sensitivity to PE and 5-HT and were stiffer compared with mesenteric arteries from SS-12BN, suggesting that the resistance vasculature is a major contributor to the development of hypertension in our congenic models. Since this congenic region overlaps with a syntenic human locus that was previously implicated in human hypertension (1, 42), discovering the causative gene(s) involved in these vascular phenotypes could provide novel insights into the pathogenesis of human hypertension as well.

Vascular dysfunction in hypertension: disease driver, responder, or both? Vascular dysfunction is prevalent in essential hypertension (39), but its causal and temporal role in disease initiation and pathogenesis remains unclear. Historically, vascular dysfunction detected weeks after the establishment of hypertension has largely been considered a secondary response to elevated BP due to remodeling induced by increased hemodynamic stress (39). As a result of elevated BP, vascular remodeling and smooth muscle hyperplasia can lead
to increased vascular stiffening and hypercontractility (15, 39). Our data do not dispute the traditional view of hypertension-induced vascular remodeling, but rather also suggest that in some cases, vascular dysfunction (Fig. 3) and remodeling (Figs. 4 and 5) precede hypertension (Fig. 1) and therefore should also be considered a “disease-driver,” not just a response to high BP. This is consistent with the BP-independent vascular dysfunction that occurs in the SS rat (6–10) and in the elastin haploinsufficient mouse (12, 35), which, along with our data, collectively suggest that several vascular-dependent genetic mechanisms can lead to essential hypertension. Moreover, similar risk profiles exist in human hypertension, whereby vascular dysfunction and remodeling are strong predictors of hypertension risk (5, 32, 36, 45). As such, identifying the genetic components that contribute to vascular dysfunction and remodeling may help to better stratify hypertensive individuals and nominate additional targets for novel antihypertensive therapies.

A potential limitation of the present study is that BP was only measured for 3 days at 9–10 wk of age. Thus it is possible that BP levels or the rate of increase in BP varied between strains at a younger age, which could contribute to the vascular differences. Additionally, while there were no differences in MAP, there could have been differences in amplitude/frequency of BP spikes or any other BP parameters (e.g., variability) which were not measured in the present study.

Candidate genes. Our expression analysis nominated two genes, Grifin and Chst12 (Table 2), as the top candidate genes for the vascular differences because these genes were differentially expressed in the same direction under both normotensive and hypertensive conditions. Grifin is a galectin-related extracellular matrix protein that is highly expressed in the lens and may be structurally important for lens development (2, 34). Grifin is also expressed in vascular smooth muscle cells (4), but its role(s) in vascular remodeling and dysfunction have not been elucidated. Chst12 (carbohydrate chondroitin 4 sulfotransferase 12) regulates chondroitin and dermatan sulfate synthesis, which was implicated in vascular dysfunction and remodeling. Removal of chondroitin-dermatan sulfate-containing glycosaminoglycans from the arterial wall increases mesenteric vessel stiffness (17). Additionally, two human genome-wide association studies in individuals of European ancestry (11, 43) have suggestively associated a single-nucleotide polymorphism (rs2969070 [G]) that is intergenic of CHST12 and GRIFIN to hypertension. Interestingly, previous whole genome sequencing analysis of overlapping rat blood pressure loci within our candidate region found an ∼86-kb region (chr12: 14,541,567–14,627,442 bp) containing single nucleotide variants near Chst12 and Grifin that were unique to the hypertensive SS strain compared with the normotensive BN, Dahl salt-resistant, and Wistar-Kyoto strains, suggesting that the SS-derived variant(s) within this region may be involved in BP regulation (38). Thus our studies may provide insights into the potential role(s) of CHST12 and GRIFIN in the development of vascular-dependent human hypertension.

Several other genes were also differentially expressed in the line Ca congenic compared with the SS-12BN consomic (Table 2) and therefore cannot be disregarded as potential candidates. Ftsj2 was differentially expressed, but in different directions, on both 0.3% and 8% NaCl diets. This gene has not been directly or indirectly implicated in hypertension. LOC100363385, Iqce, Lfng, Elf11, and Mial2 were differentially expressed on 0.3% NaCl only, while Sdki, Bra1l, Mafk, and Ints1 were differentially expressed on 8% NaCl only, suggesting that these four genes may be differentially expressed in response to elevated BP levels and/or elevated salt intake. Of the genes that were differentially expressed on 0.3% NaCl only, Elf11 is the next likely candidate based on previously published evidence. Elf11 (PPPIR28) inhibits the phosphatase activity of protein phosphatase 1 (18), which has been implicated in hypertension (41). None of the remaining candidates (LOC100363385, Iqce, Lfng, Ints1, and Mial2) have been directly or indirectly implicated in hypertension. Narrowing the congenic interval and gene-targeted approaches will be required to include/exclude these candidate genes and determine which genes are causative or secondary to hypertension. In conclusion, our mapping studies strongly suggest that a 2-Mb region of rat chromosome 12 can lead to the development of hypertension through primary changes in the vasculature.

Perspectives. In the present study, we observed alterations in the resistance vasculature on a low-salt (0.3% NaCl) diet prior to the development of the hypertension that occurs when the animals are exposed to high-salt diets. High-salt diets have also been shown to alter vascular function (16, 28, 44, 46). However, the vascular differences that we observed in the present study may not be the same as the vascular dysfunction occurring in response to high-salt diets. Future studies will be needed to determine whether our congenic lines have additional vascular alterations when exposed to high-salt diet and to identify the nature of any salt-induced changes that occur in the vasculature prior to any increase in BP.

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DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

REFERENCES


