High Dietary Sodium Provokes Development of Hypertension in Lean SHROB

L Conour, S Chou, R Driscoll, R Fister, C Clifford, and H Liang Charles River Laboratories, Wilmington, MA 01887, U.S.A.

charles river
accelerating drug development. exactly.

Abstract

We compared the impact of high dietary sodium on the lean Spontaneously Hypertensive Obese rats (lean SHROB +/?, or *Lepr*$^{+/?}$) with the Spontaneously Hypertensive rats (SHR) and the Wistar Kyoto rats (WKY). Compared to SHR and WKY, the lean SHROB had higher systolic blood pressure and greater urine protein excretion as a result of the treatment protocol. Histopathology in the brain, heart, and kidneys were also noted, with more severe lesions in the lean SHROB. The phenotype of this lean SHROB model closely resembles that of malignant hypertension in humans. Reduction of dietary salt intake from current treatment protocol may prolong survival time of this model. If obesity is an undesirable co-morbidity factor, the lean SHROB may serve as a alternative rat hypertension model for compound efficacy studies.

Introduction

The SHROB rats are genetically obese rats with homozygous recessive point mutation in their leptin receptor. In contrast, the heterozygous rats do not develop obesity. Although the SHROB rats and their lean controls have been used intensively in various types of metabolic disease studies, their response to excess dietary salt remains to be studied. The purpose of this study is to characterize the lean SHROB model and assess its usefulness as an animal model for human hypertension.

Materials and Methods

Animals

Eight males of each strain: genotyped lean SHROB (SHR/OBKolCrl-*Lepr*$^{+/?}$), SHR (SHR/NCrl) and WKY (WKY/NCrl)

Special Feeding Protocol

All rats were placed on Japanese diet containing 4% NaCl from Zeigler Brothers, Inc. (Gardners, PA) and 1% NaCl drinking water starting at 7.5 weeks of age for 13 weeks.

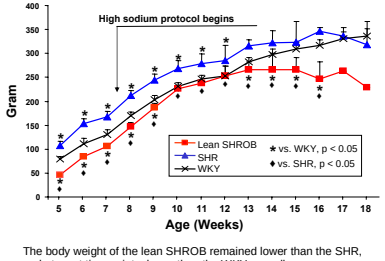
Parameters Measured

1. Weekly body weight collection starting at 5 weeks of age.
2. Pulse rate and systolic blood pressure measurement using the Visitech BP-2000 Blood Pressure Analysis System (Apex, NC).
3. Plasma sample collection at various time points for biomarker profiles analysis by Rules-Based Medicine, Inc. (Austin, TX).
4. Quantification of urine protein excretion using the sulfosalicylic acid turbidity method.
5. Histopathology assessment of the heart, lungs, brain, kidneys, liver, and any other gross abnormalities at 18 weeks of age.
6. Monitoring for morbidity and mortality.

Results

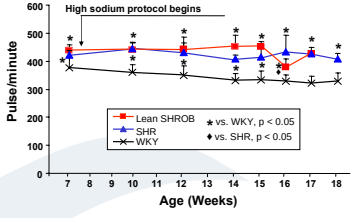
(Data presented as mean ± standard deviation)

Body Weight



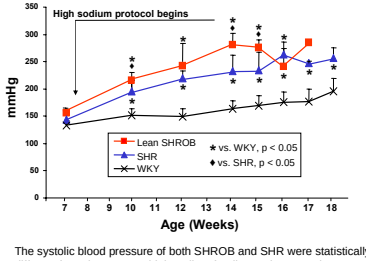
The body weight of the lean SHROB remained lower than the SHR, and at most time points, lower than the WKY as well.

Pulse Rate



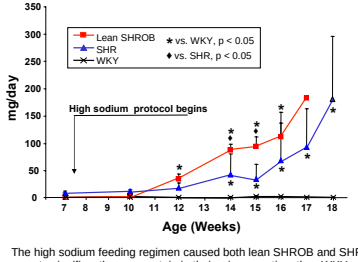
The pulse rate of both lean SHROB and SHR were higher than that of the WKY. Only at one time point (16 weeks of age) was there a statistically significant difference between lean SHROB and SHR.

Systolic Blood Pressure



The systolic blood pressure of both SHROB and SHR were statistically different from the WKY on high sodium feeding regimen. Only at 3 time points did data show a statistically significant difference between lean SHROB and SHR.

Urine Protein Excretion



The high sodium feeding regimen caused both lean SHROB and SHR to excrete significantly more protein in their urine over time than WKY.

Plasma Biomarker Profiles

revealed altered levels corresponding with disease progression. Prominent biomarkers, such as myoglobin (indicator of myocardial infarction); VEGF[1] (indicator of angiogenesis); and MCP-1[2], MCP-3[3] and MIP-2[4] (indicators of inflammation), were statistically significant in lean SHROB, but not in SHR, when compared to WKY. Select data from rats at 16 weeks of age shown below.

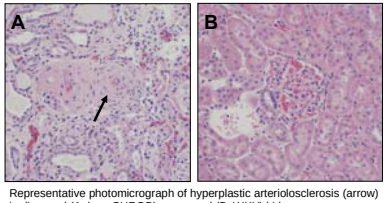
Group	Myoglobin (ng/mL)	VEGF[1] (pg/mL)	Insulin (uIU/mL)
Lean SHROB	911.6 ± 1692.3	830.8 ± 277.6*	2.4 ± 0.5*
SHR	542.0 ± N/A	251.6 ± 59.7	6.3 ± 0.4
WKY	432.0 ± 261.2	250.5 ± 35.6	4.9 ± 1.4

Group	MCP-1[2] (pg/mL)	MCP-3[3] (pg/mL)	MIP-2[4] (pg/mL)
Lean SHROB	5252.0 ± 1756.5*	2000.7 ±1000.7*	24.6 ± 6.1*
SHR	781.3 ± 428.0	397.3 ± 218.5	4.9 ± 2.5
WKY	678.1 ± 193.4	332.4 ± 100.0	2.6 ± 0.6

* : p < 0.05, vs. WKY
[1] : Vascular endothelial cell growth factor
[2] : Monocyte chemoattractant protein-1
[3] : Monocyte chemoattractant protein-3
[4] : Macrophage inflammatory protein-2

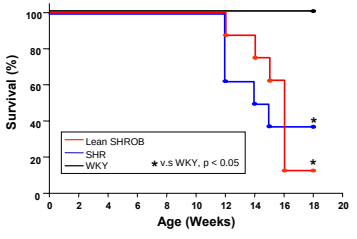
Histopathology

showed moderate to severe hyperplastic arteriolosclerosis in the kidneys of all lean SHROB. Besides arteriolosclerosis in the heart, myofiber degeneration and associated fibrosis as well as cerebral infarction were also noted. In contrast, the SHR kidneys showed mild hyaline arteriolosclerosis with infrequent hyperplastic changes. Other renal and cardiac changes in the SHR and WKY were consistent with age-related changes, likely exacerbated by hypertension. Two SHR had lesions consistent with stroke. No changes in the brain were observed in WKY.



Representative photomicrograph of hyperplastic arteriolosclerosis (arrow) in diseased (A, lean SHROB) vs. normal (B, WKY) kidney. Magnification, 100x (10x objective, 10x phototube).

Survival Analysis



There was no statistically significant difference in the average survival time between lean SHROB and SHR on high sodium feeding protocol.

Conclusions

Thirteen weeks of high dietary sodium induced the lean SHROB to develop high systolic blood pressure, severe nephropathy, as well as vascular pathologies that closely resemble malignant hypertension in human patients. Biomarker profiles revealed disease-related changes in the lean SHROB and SHR rats, compared to those of age-related changes in the WKY rats (data not shown). Future studies should include modification of dietary salt concentration in order to prolong the survival time of this model and to further characterize this lean SHROB hypertension model for compound efficacy studies.

Acknowledgement

The authors wish to acknowledge Rules-Based Medicine for providing the biomarker analysis data. We also want to thank Keli Perron, Daisy Mendonca, and Linda Gianni for their assistance with this study.