The 25th Budapest Nephrology School

Nephrology, Hypertension, Dialysis, Transplantation, Nephropathology

Under the Auspices of
ISN, ERA-EDTA, RPS, IFKF and **ISP**

26 - 31 August, 2018

What is New in the Pathogenesis of Salt-sensitive Hypertension?

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I would like to thank ERA-EDTA for selecting me as an „ambasador" during this course

Andrzej Wiecek

Finacial disclosure

- Clinica trials:

Astellas Glaxo Smith Kline, Medice

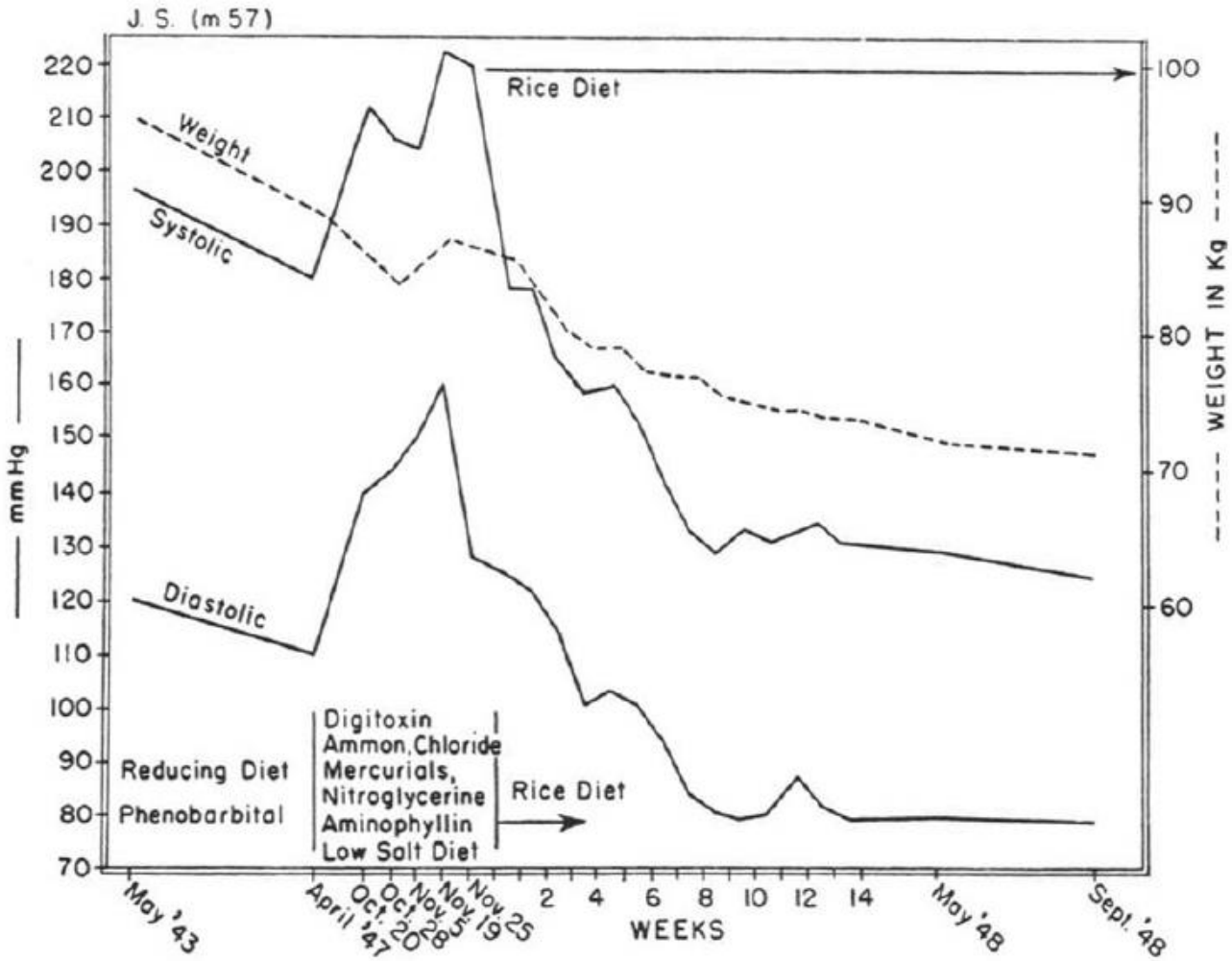
- Advisory Boards:

Fresenius, Daiichi Sankyo

- Lecturing, chairing lectures or participation in symposia/panel discussions:

Astra Zeneca, Berlin Chemie, Astellas

Kempner rice diet (low sodium diet) and blood pressure in a patient treated in 1943 -1948



Klemmer P. et al. Hypertension, 2014, 64, 684 - 688

Outline of the lecture

- Definition of the salt – sensitive hypertension
- Pathogenesis (classical) of the salt - sensitive hypertension
- New concepts of the salt - sensitive hypertension
- Salt - sensitive hypertension and the risk of CKD development
- Summary of the lecture

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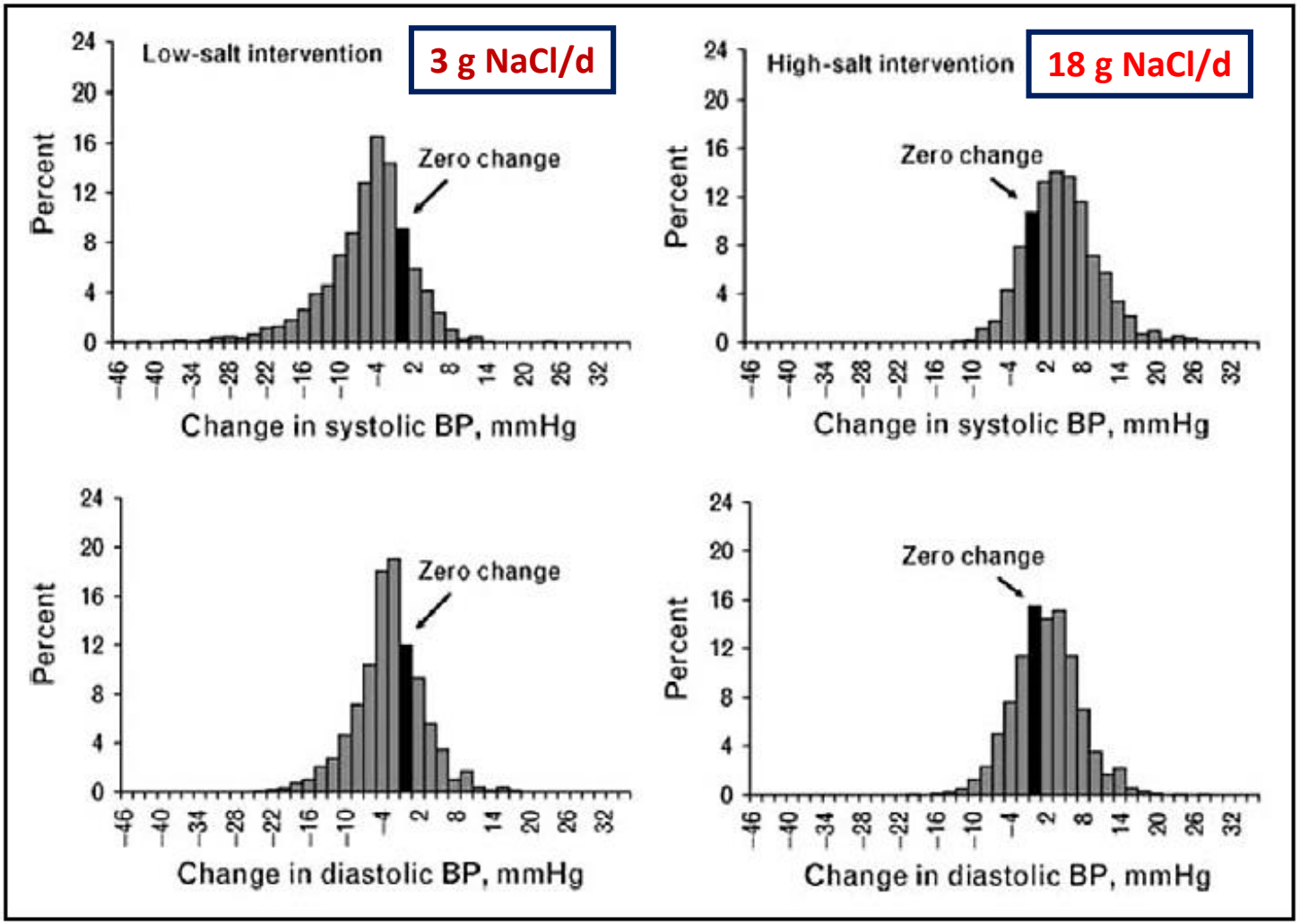
Continuous distribution of blood pressure (BP) responses to 7-day changes in dietary salt in the Genetic Epidemiology **Network of Salt Sensitivity (GenSalt)** study



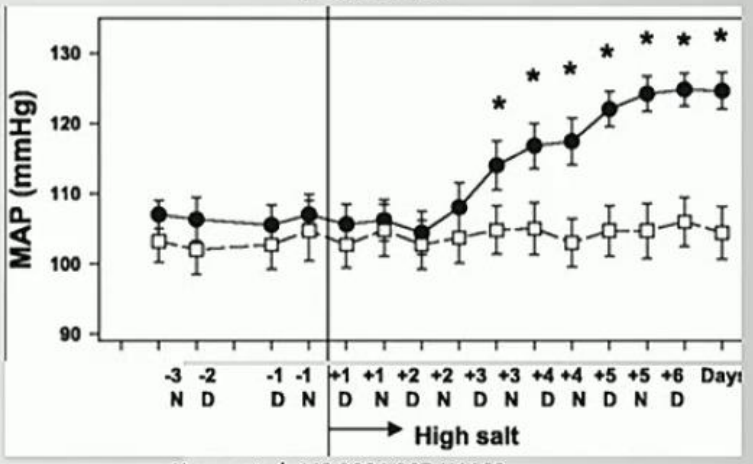
Elijovich F. et al. Hypertension, 2016, 68, e7 - e46

Salt sensitivity of blood pressure - definition

Salt Sensitivity of Blood Pressure

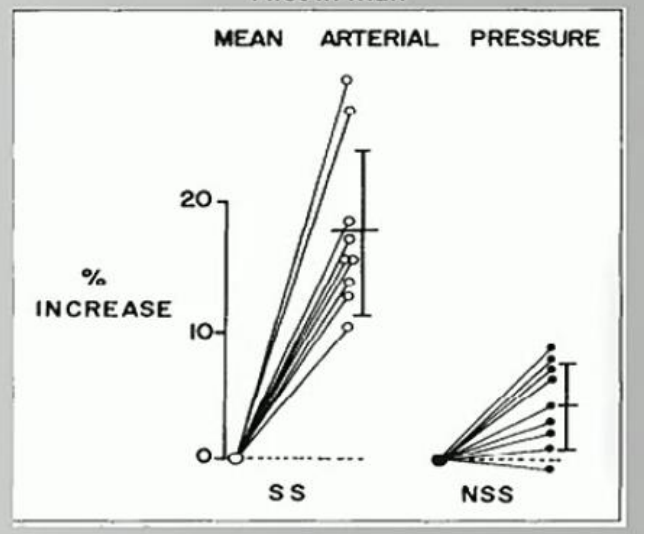
A pathophysiological trait by which a percent of members of a population (animals or humans) sustain changes in blood pressure parallel to changes in Na^+ intake or Na^+ balance

Dahl-S rats



Huang et al, AJP 2004;287:H1160

First in man



Kawasaki et al, AJM 1978;64:193

Fernando Elijovich, MD, FAHA. Vanderbilt University

Sodium sensitivity – definition, classification and frequency

Subjects (*n*)	Sodium-sensitive	Indeterminate	Sodium-resistant
Normotensive (375)	26.0%	15.7%	58.4%
Hypertensive (192)	51.0%	15.7%	33.3%

Sodium sensitivity was defined as a change of at least 10 mm Hg in mean arterial blood pressure (MABP), and sodium resistance as a change of less than 5 mm Hg; indeterminate responses were defined as values falling in between (< 10 mm Hg but ≥ 5 mm Hg).

Hypertension, 1986

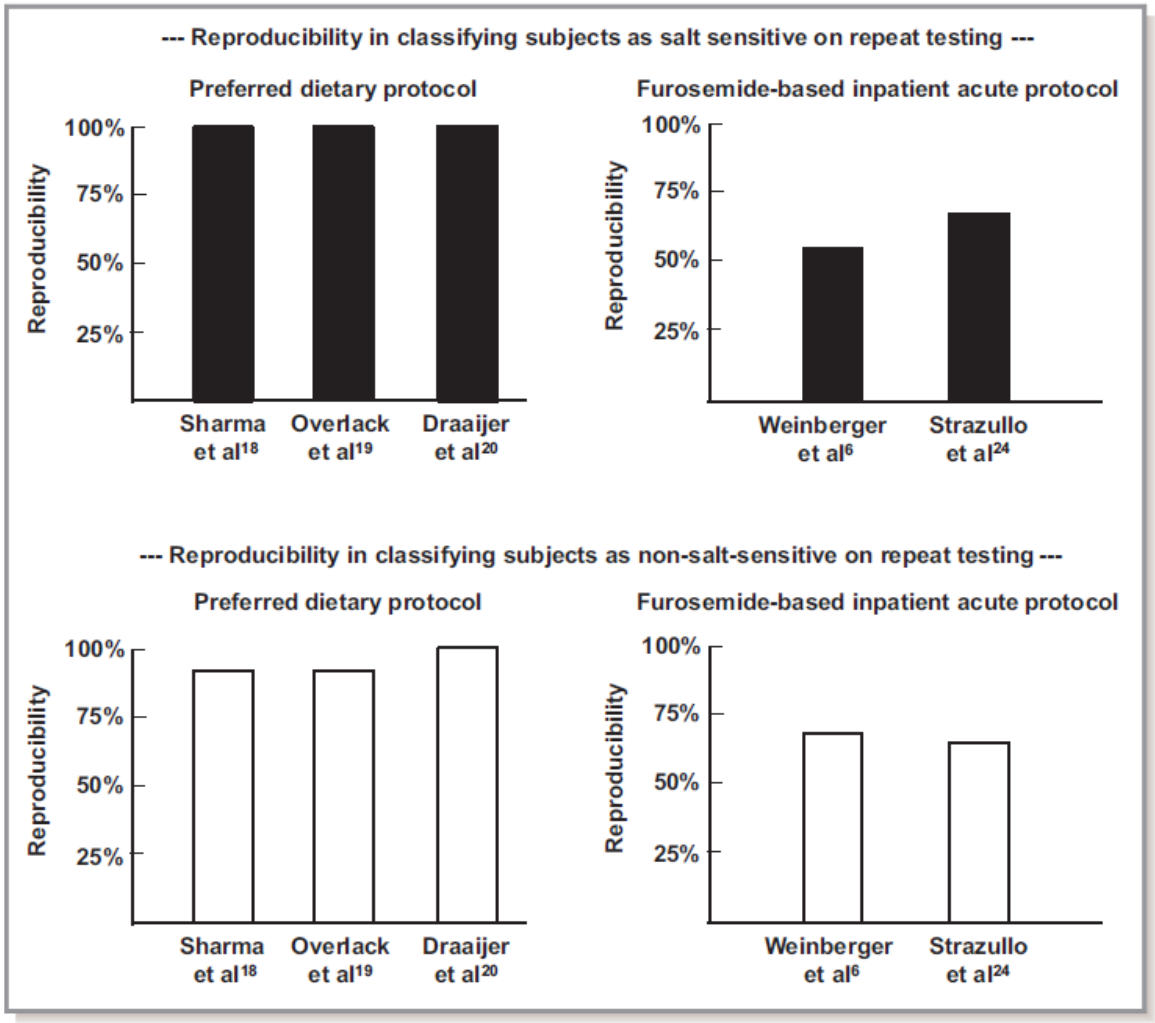
Metods of testing for salt sensitivity

Table. Candidate Reference Method of Testing for Salt Sensitivity

Dietary protocol with the following features:
1-week period of low salt intake of no more than 50 mmol NaCl/day
1-week period of high salt intake of ≈250 mmol NaCl/day*
Order of administration of different salt diets may vary per study objective
Prescription and monitoring of well-characterized diets throughout entire study†
Multiple measurements of 24-hour urine Na^+ excretion to confirm NaCl intake
BP measurements based on a highly reproducible salt sensitivity test protocol‡
Cutoff to classify normotensives as salt sensitive: MAP change ≥3 to 5 mm Hg§
Cutoff to classify hypertensives as salt sensitive: MAP change ≥8 to 10 mm Hg§

Kurtz T. W. et al., J. Am. Heart Assoc., 2017, 6: e005653

Reproducibility in classifying subjects as salt-sensitive or non-salt sensitive on repeat testing



Kurtz T. W. et al., J. Am. Heart Assoc., 2017, 6: e005653

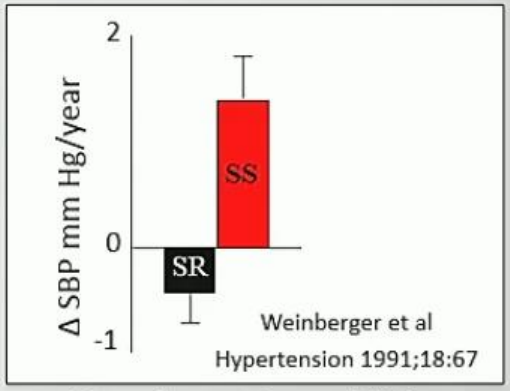
Clinical phenotype and prevalence of salt-sensitivity

Clinical Phenotype and Prevalence

African American - Elderly - Obese

Lack of Nocturnal Dipping of BP

Predicts HTN in Normotensives

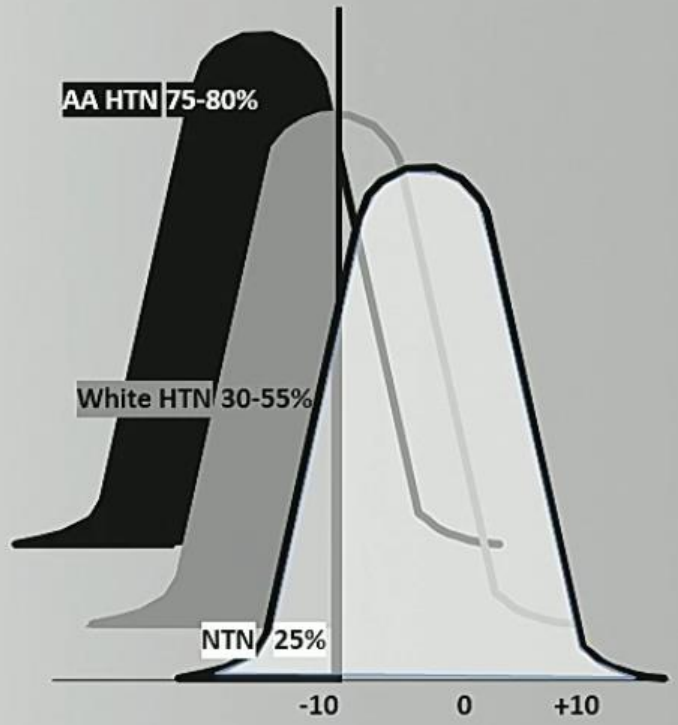


More Stroke - Renal Disease

More LVH and LV Dysfunction

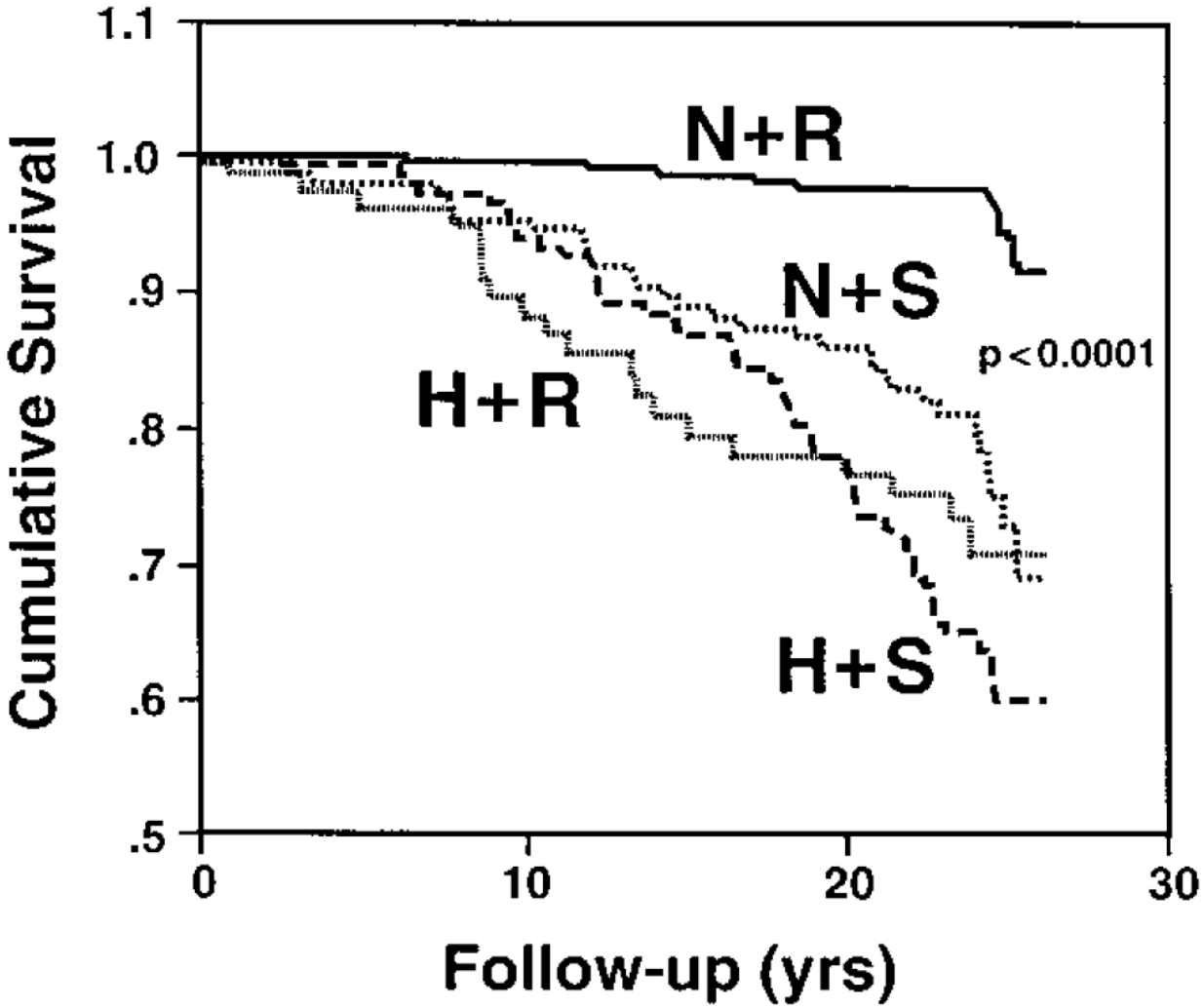
Less ischemic heart disease

More insulin resistant



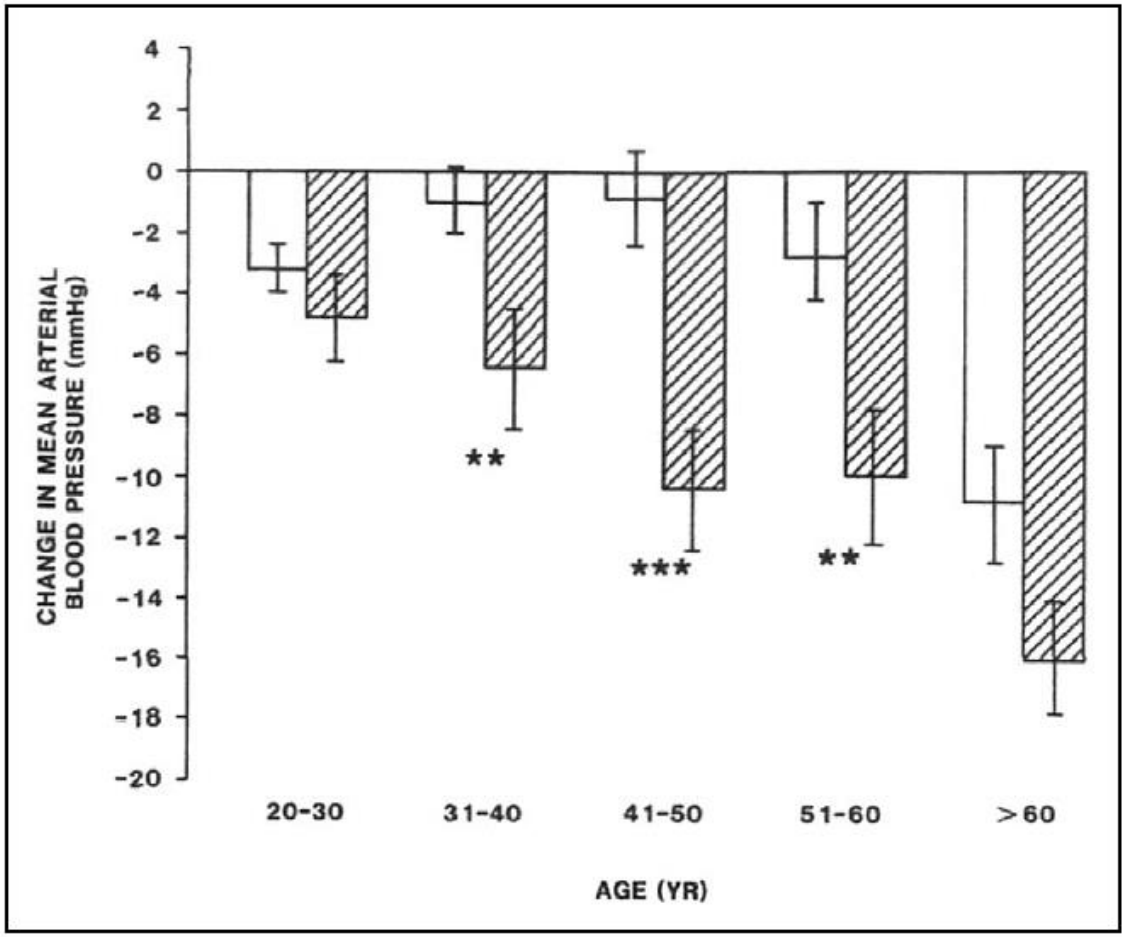
Fernando Elijovich, MD, FAHA. Vanderbilt University

Survival in relation to salt-sensitivity and presence of hypertension



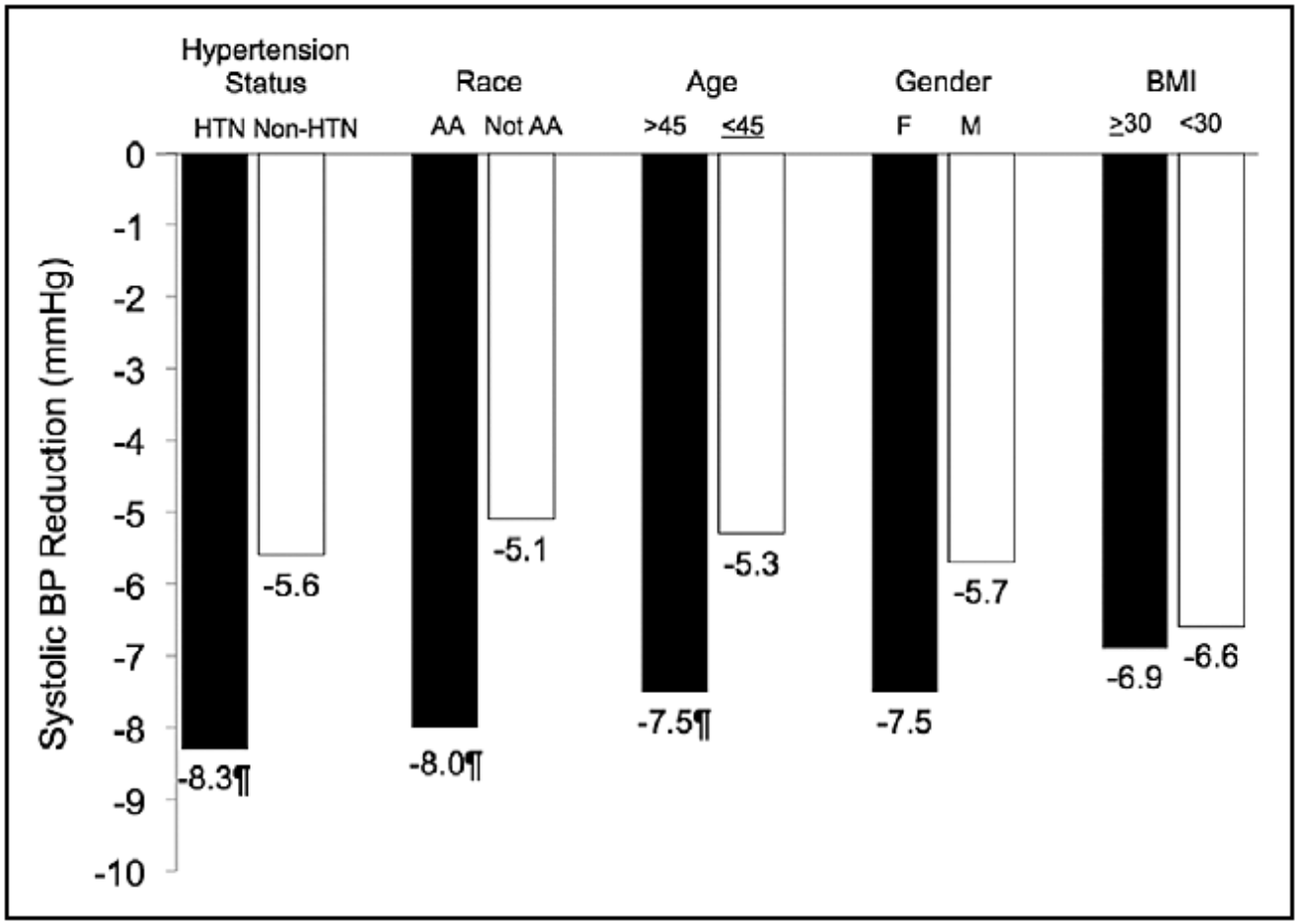
Hypertension, 2001

Mean arterial pressure decreases in response to salt depletion in normotensive (open bars) and hypertensive (hatched bars) individuals at different age decades



Elijovich F. et al. Hypertension, 2016, 68, e7 - e46

Effects of sodium reduction (from high to low sodium levels in the control diet) on systolic blood pressure by subgroup in the **Dietary Approaches to Stop Hypertension (DASH)- sodium trial**



Elijovich F. et al. Hypertension, 2016, 68, e7 - e46

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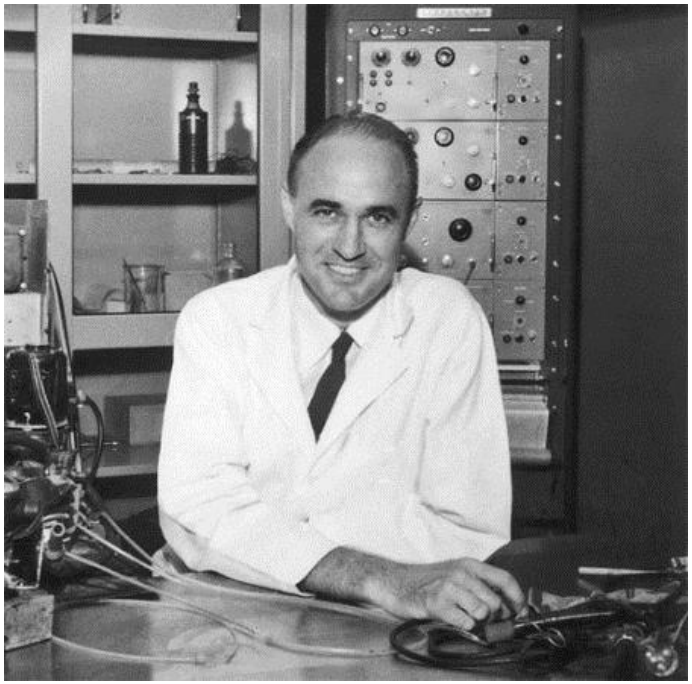
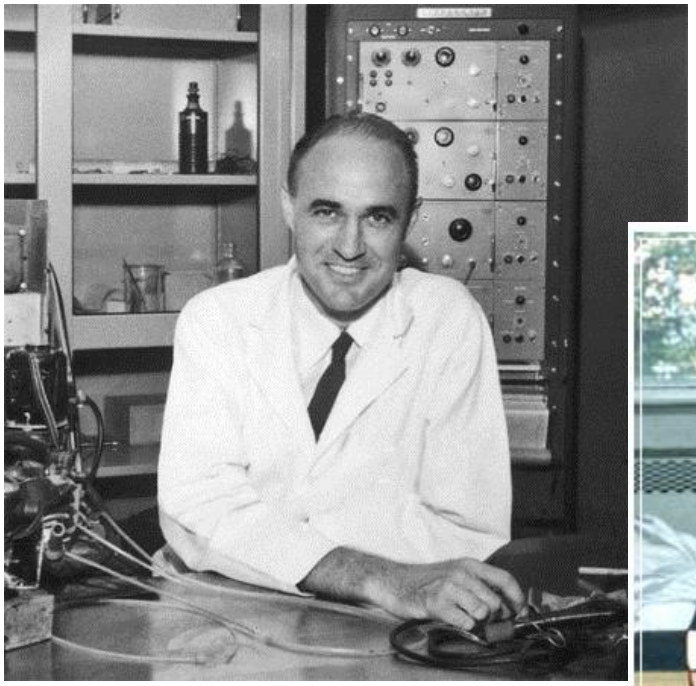
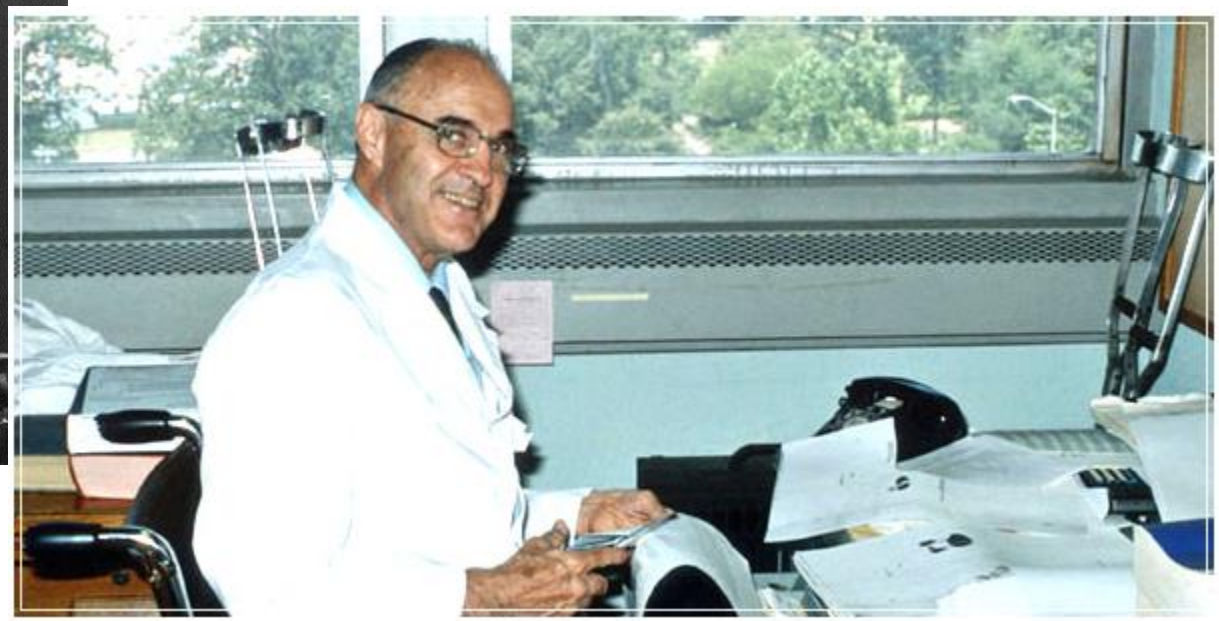
Arthur Guyton (1919 – 2003) – American physiologist author of the pressure-natriuresis theory

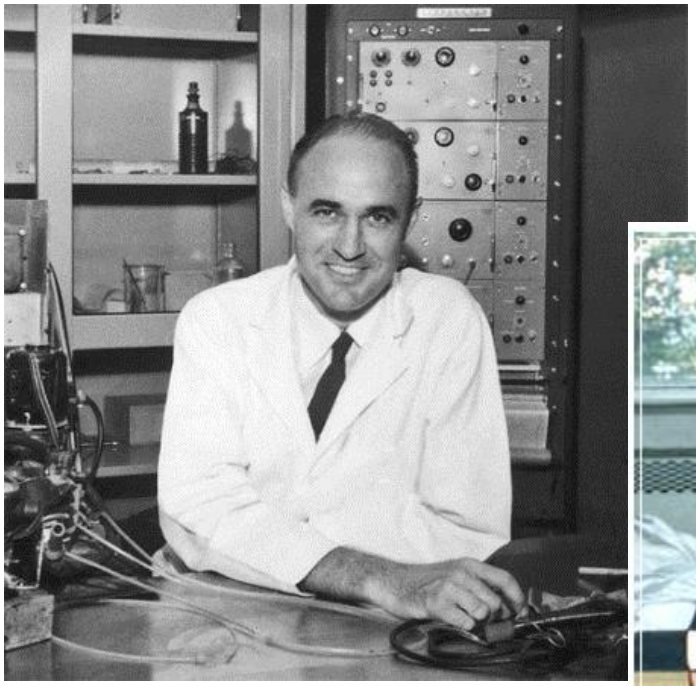


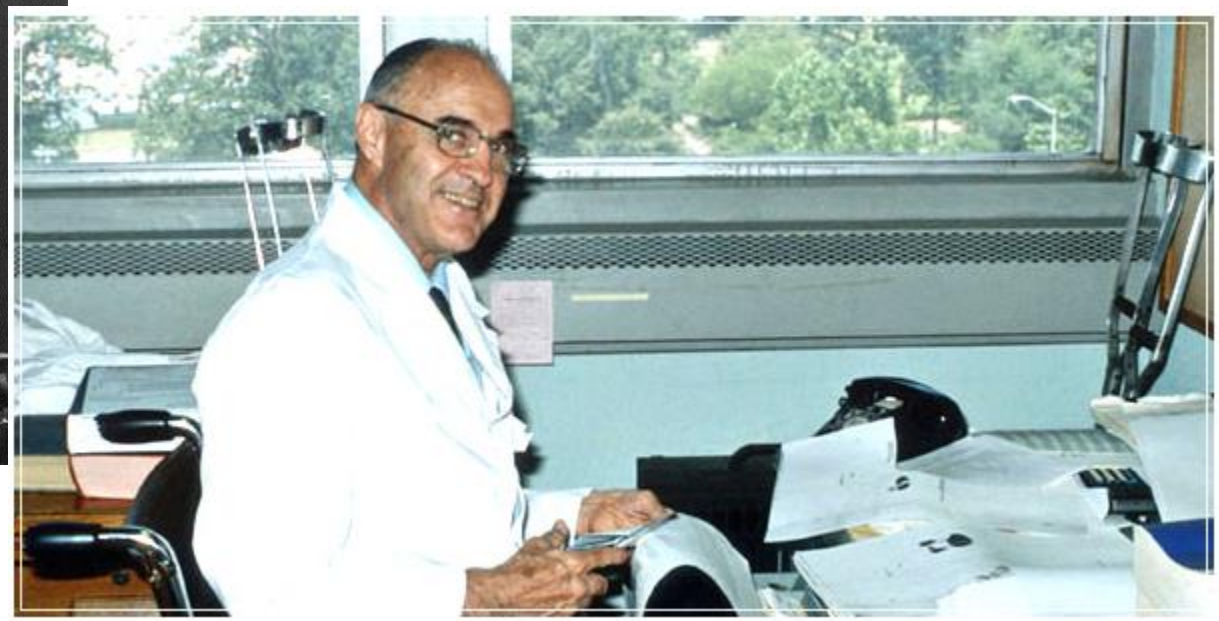
Arthur Guyton (1919 – 2003) – American physiologist author of the pressure-natriuresis theory





Arthur Guyton (1919 – 2003) – American physiologist author of the pressure-natriuresis theory



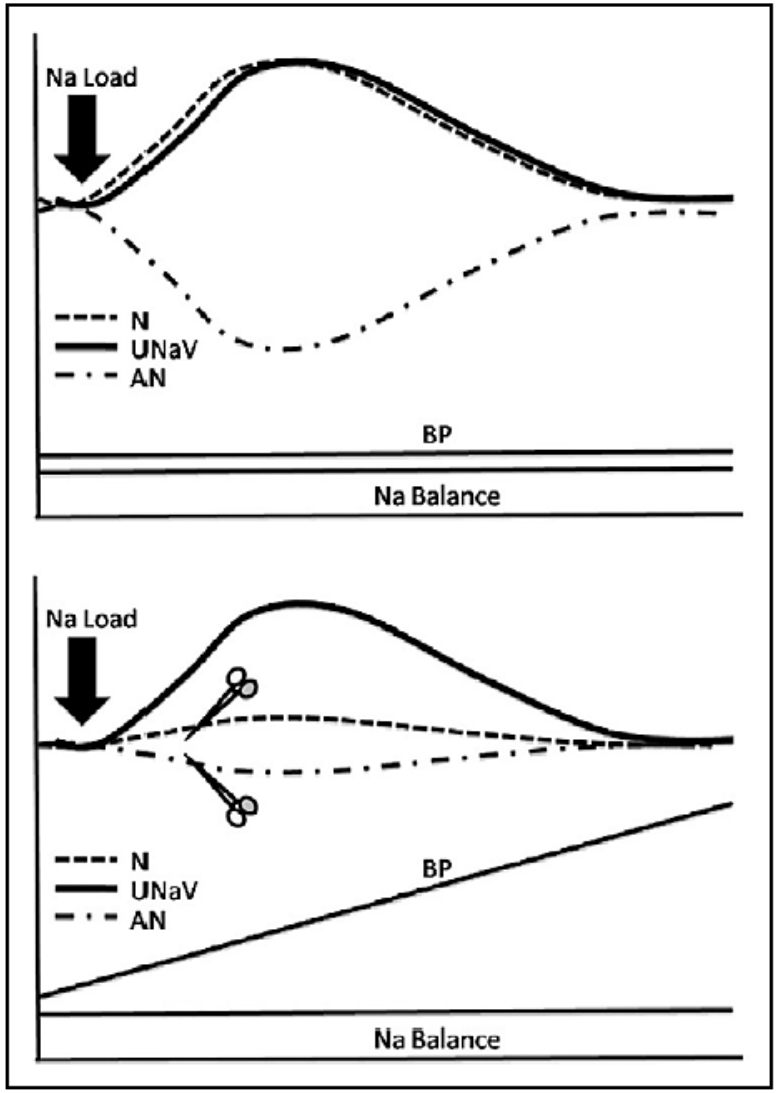


By 1955, Dr. Guyton had used wheelchair and crutches since 1947 because of the residual paralysis of polio which he contracted as a surgical resident at Massachusetts General Hospital in October 1946.

Arthur Guyton (1919 – 2003) and Ruth Guyton (1922-2003)

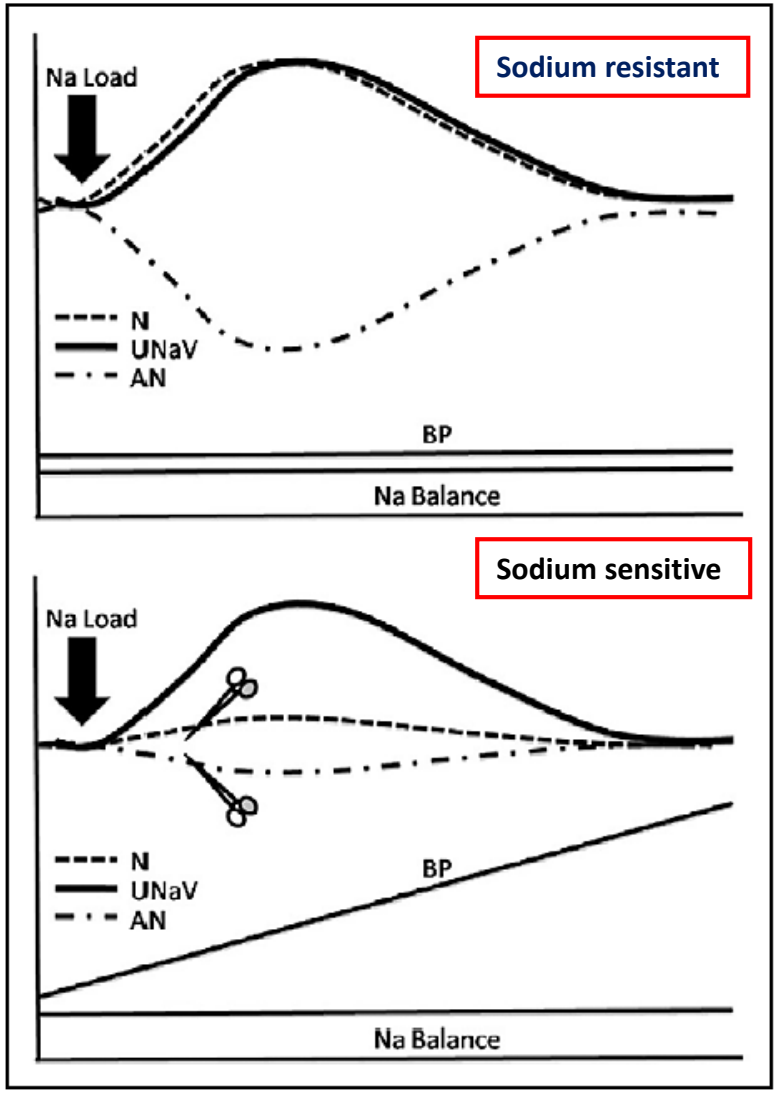
All 10 of the Guyton children went into medical school, received M.D. degrees and went into academic or private practice

Interaction between sodium load, natriuretic and antinatriuretic systems, natriuresis and blood pressure



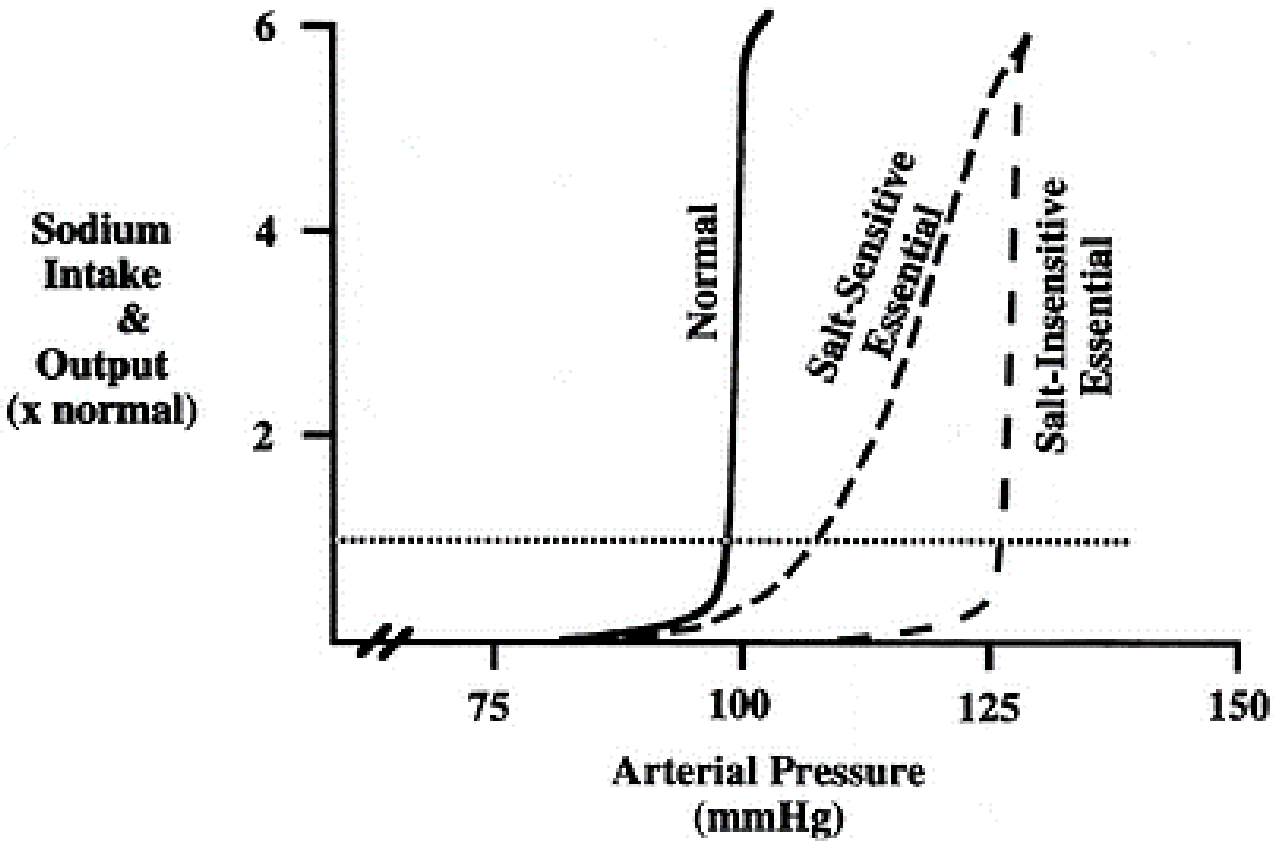
Elijovich F. et al. Hypertension, 2016, 68, e7 - e46

Interaction between sodium load, natriuretic and antinatriuretic systems, natriuresis and blood pressure



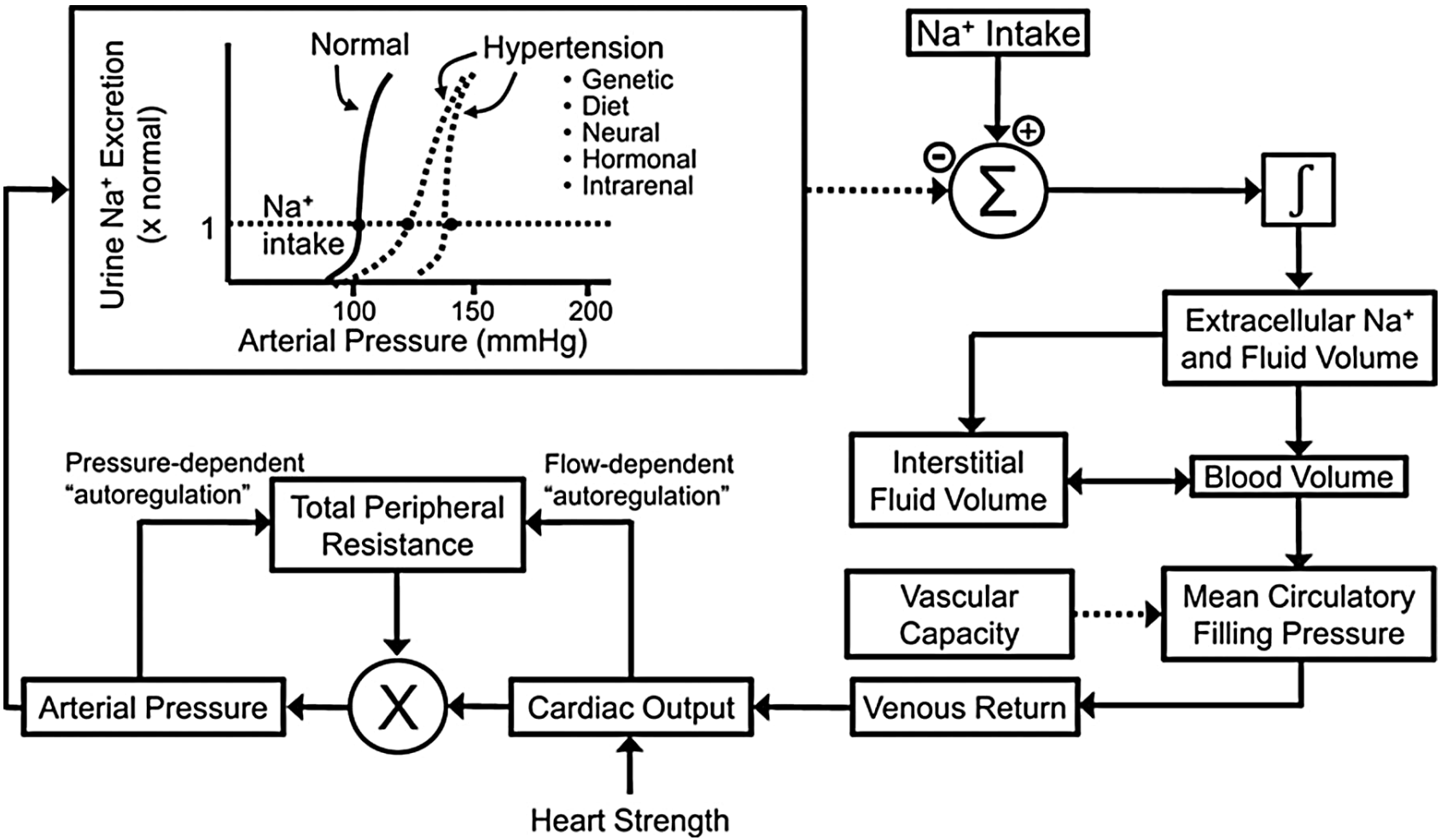
Elijovich F. et al. Hypertension, 2016, 68, e7 - e46

Pressure-natriuresis relationship in normotensive and hypertensive subjects



Hall J.E. et al. J. Am. Soc. Nephrol., 1999, 10, 258-265

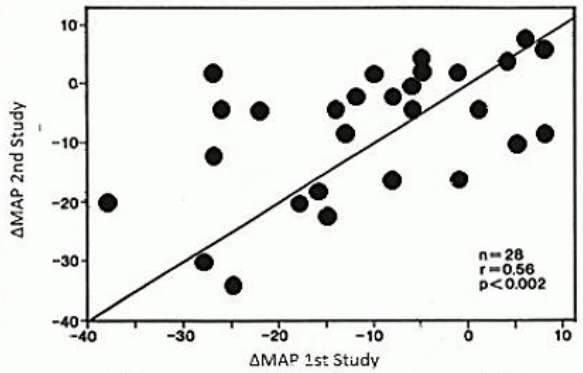
Pressure-natriuresis relationship in normotensive and hypertensive subjects - Guyton concept



Salt sensitivity is a phenotype, genetically determined

It is a phenotype, not a random occurrence

Reproducible over time

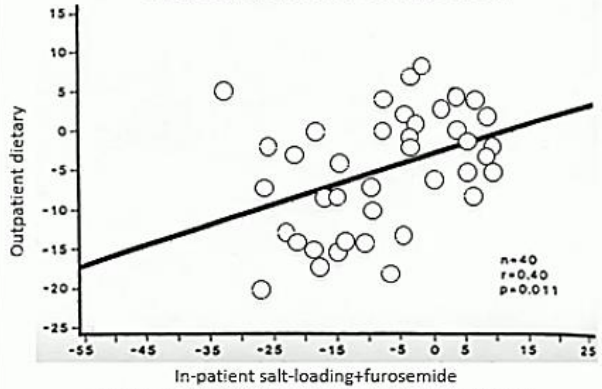


Weinberger et al Hypertension 1991;18:67

Associated in sibs and twins

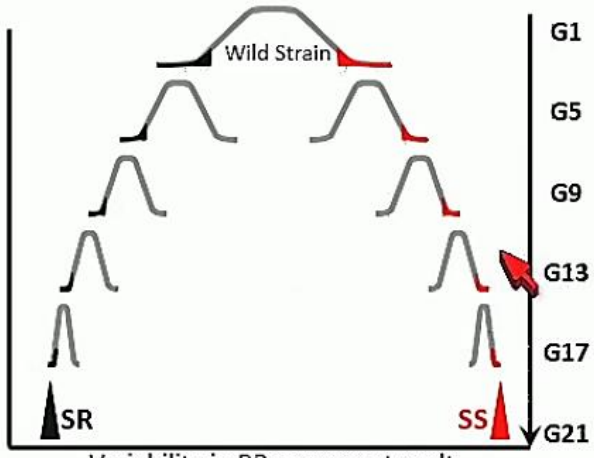
Grim et al Hypertension 1980;2:I34

Reproducible with two methods



Weinberger et al Am J Hypertens 1993;6:179

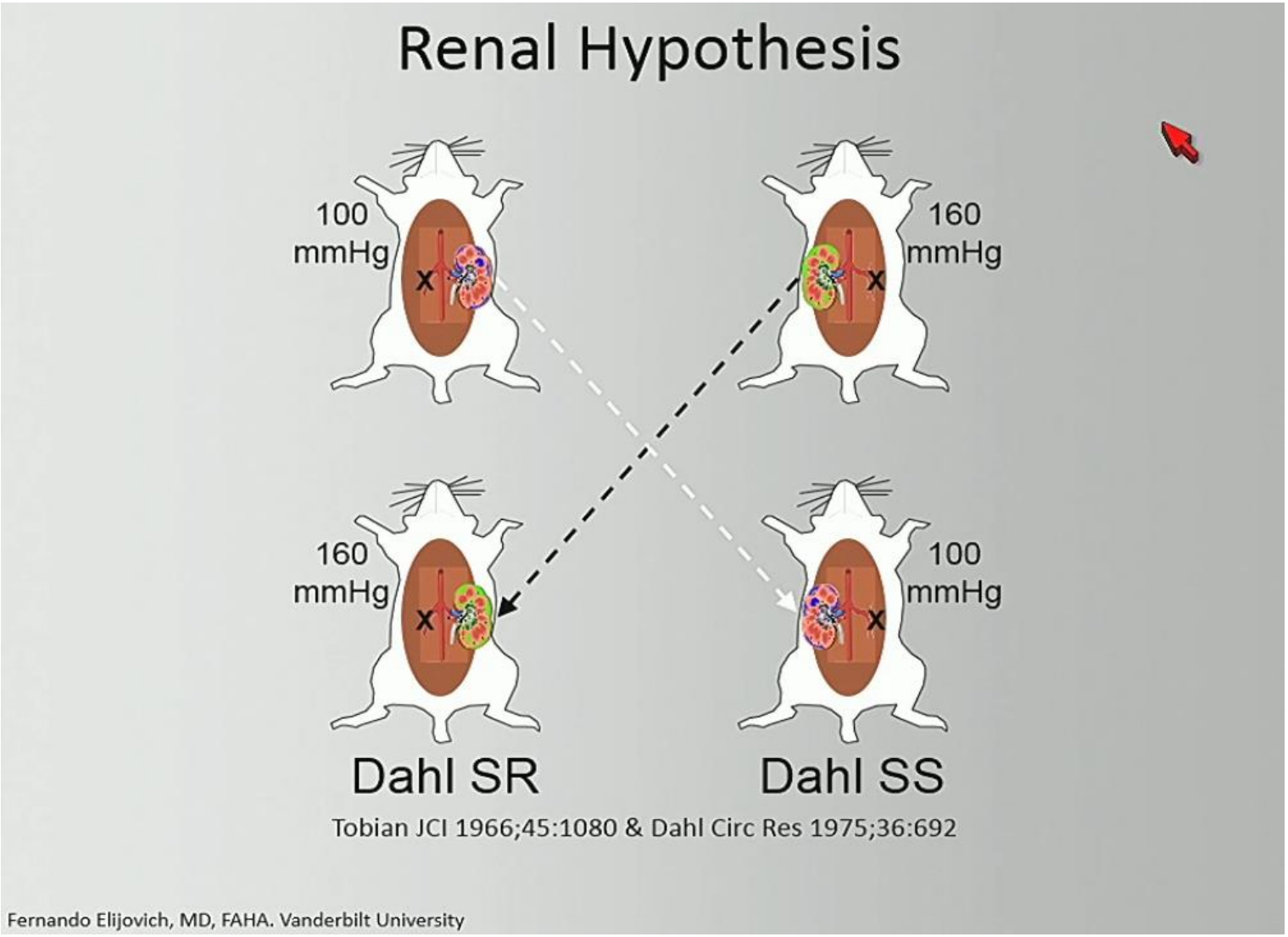
Can be in-bred in animals:
Dahl, Milan, Sabra, SS-SHR



Variability in BP response to salt

Fernando Elijovich, MD, FAHA. Vanderbilt University

Role of the kidneys in the pathogenesis of salt sensitive hypertension



Role of genetic factors in the pathogenesis of salt sensitivity

Summary

- Salt-sensitivity is common in human populations.
- Genetic factors play an important role in determining salt-sensitivity.
- Candidate genes in the renin-angiotensin-aldosterone system, sodium channels/transporters, natriuretic peptide system, sympathetic nervous system, signal transduction pathways, endothelin and adhesion molecules might all be involved in the regulation of salt-sensitivity.
- Genome-wide association studies have identified novel genetic variants for salt-sensitivity.
- Whole genome sequencing (WGS) and whole exome sequencing (WES) might identify functional variants for salt-sensitivity.

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REVIEW

CURRENT OPINION

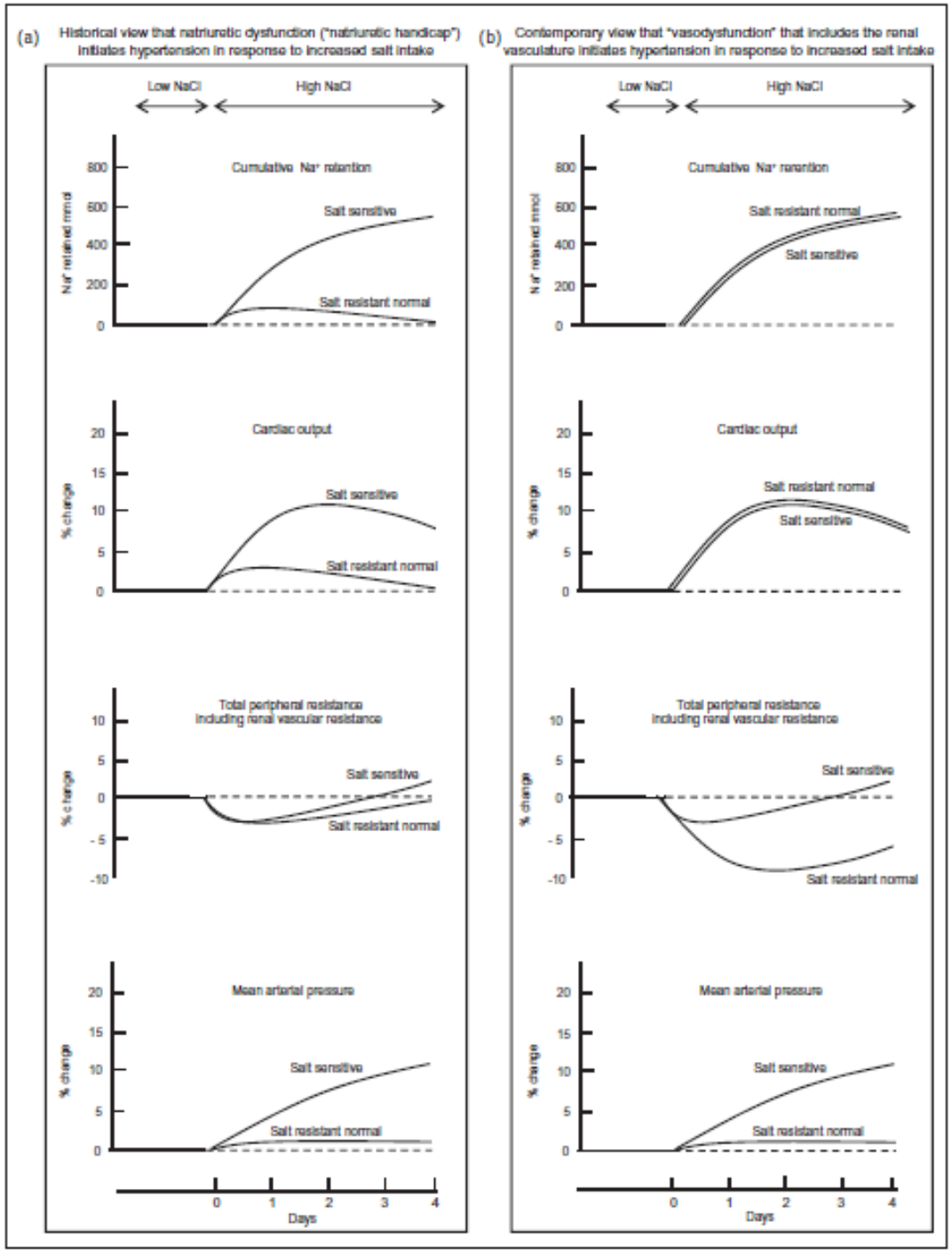
The pivotal role of renal vasodysfunction in salt sensitivity and the initiation of salt-induced hypertension

Theodore W. Kurtz[a], Stephen E. DiCarlo[b], Michal Pravenec[c], and R. Curtis Morris Jr.[d]

Purpose of review

For decades, it has been widely accepted that initiation of salt-induced hypertension involves a type of kidney dysfunction (natriuretic handicap), which causes salt-sensitive subjects to initially excrete less of a sodium load than normal subjects and undergo abnormal increases in cardiac output, and therefore blood pressure. Here we discuss emerging views that renal vasodysfunction, not natriuretic dysfunction (subnormal sodium excretion), is usually a critical factor initiating salt-induced hypertension.

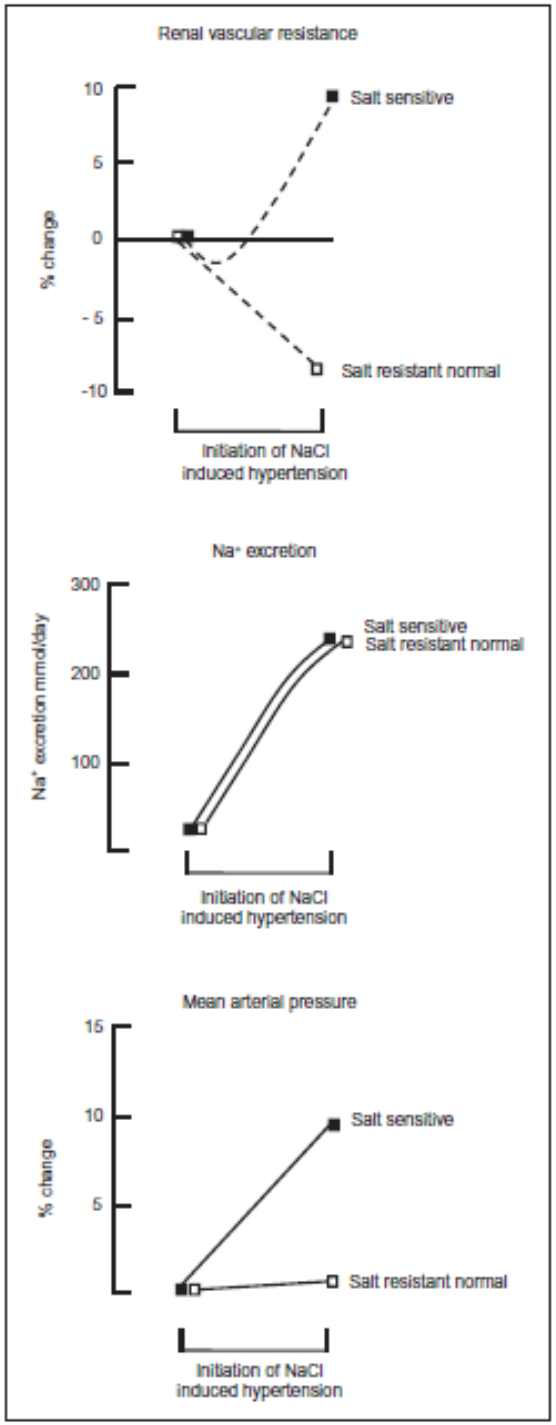
Kurtz T. W. et al., Curr. Opin. Nephrol. Hypertens., 2018, 27, 83 - 92



Historical and new concept of salt-induced hypertension

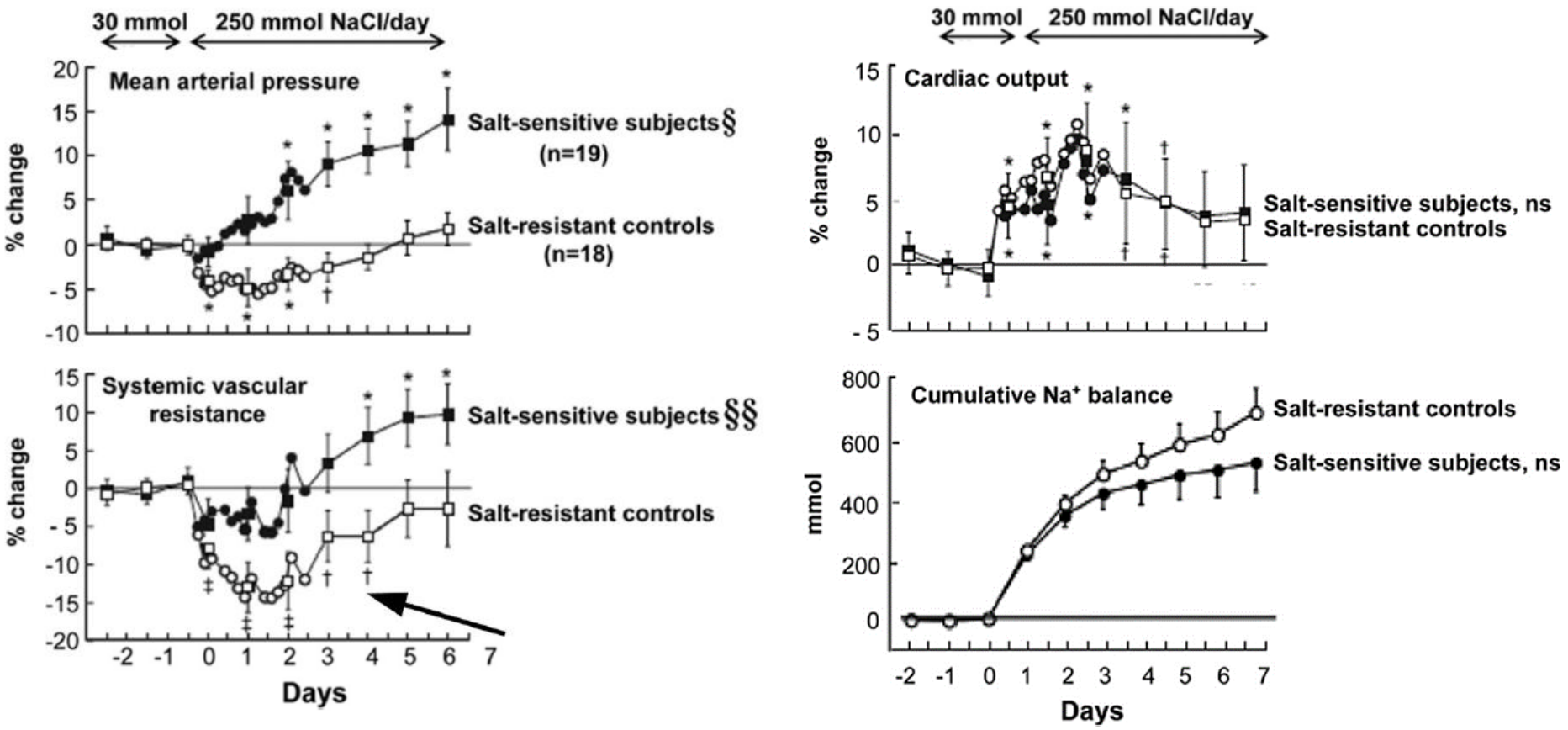
Kurtz T. W. et al., Curr. Opin. Nephrol. Hypertens., 2018, 27, 83 - 92

Changes in renal vascular resistance, sodium excretion and blood pressure during initiation of salt-induced hypertension



Kurtz T. W. et al.,
Curr. Opin. Nephrol. Hypertens., 2018, 27, 83 - 92

Haemodynamic changes induced by 7 days of high sodium diet in sodium sensitive and sodium resistant subjects



Morris R.C. et al. Circulation, 2016, 133, 881 - 893

Role of the increased vascular resistance in the pathogenesis of salt sensitivity

TABLE 1. Examples of contemporary theories on mechanistic abnormalities causing salt sensitivity

Neurogenic dysfunction theories [24–27]
Brain Aldo-ENaC-EO-α_2 Na^+ pump-ANG II theory [28–30]
Mechanogenic theory[a] [31]
Vasopressin-related theories [32–35]
Vascular angiotensin II dysregulation theory [36]
TGF-β/NO – endothelial dysfunction theory [37,39,40]
Skin Na^+ storage and MPS-driven TonEBP/VEGF-C dysfunction theory [44–46]
Endothelial glycocalyx and EnNaC-mediated vascular dysfunction theory [47–51]
ADMA/NO-mediated vasodysfunction theory [12,52,53]
Oxidative stress theories[b] [41–43]

Kurtz T. W. et al., J. Hypertens., 2017, 35, 2214 - 2225

Endothelial responses to high salt intake affect arteriolar vasodilation and BP

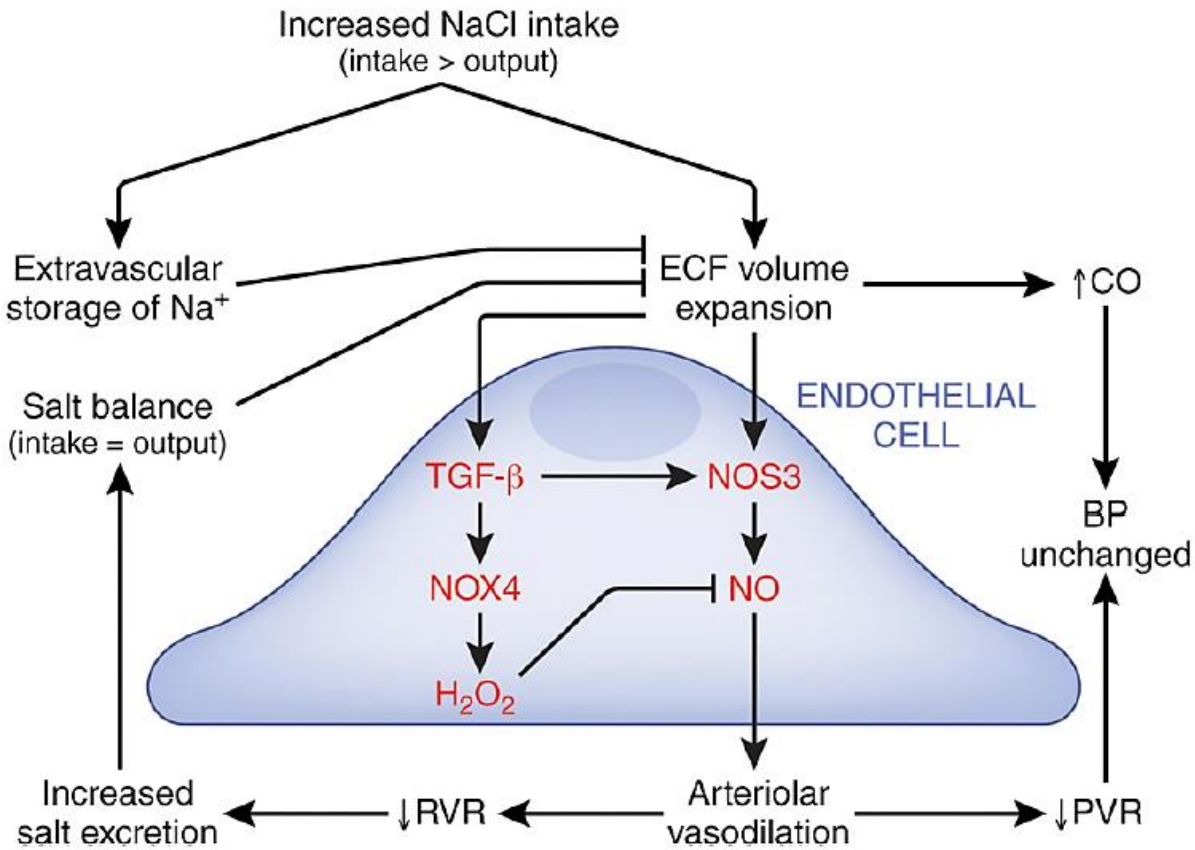


Figure 5. Endothelial responses to high salt intake affect arteriolar vasodilation and BP.

Feng W. et al., J. Am. Soc. Nephrol., 2017, 28, 1362 - 1369

High salt – induced production of NO is impaired in the Dahl SS rats

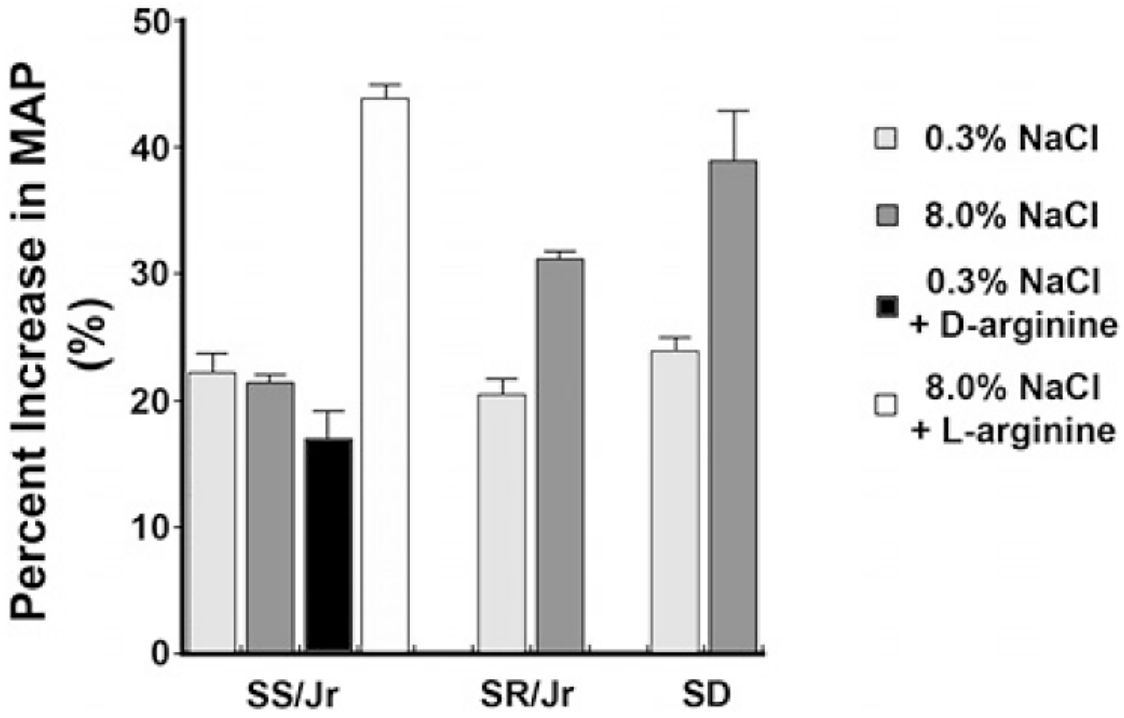
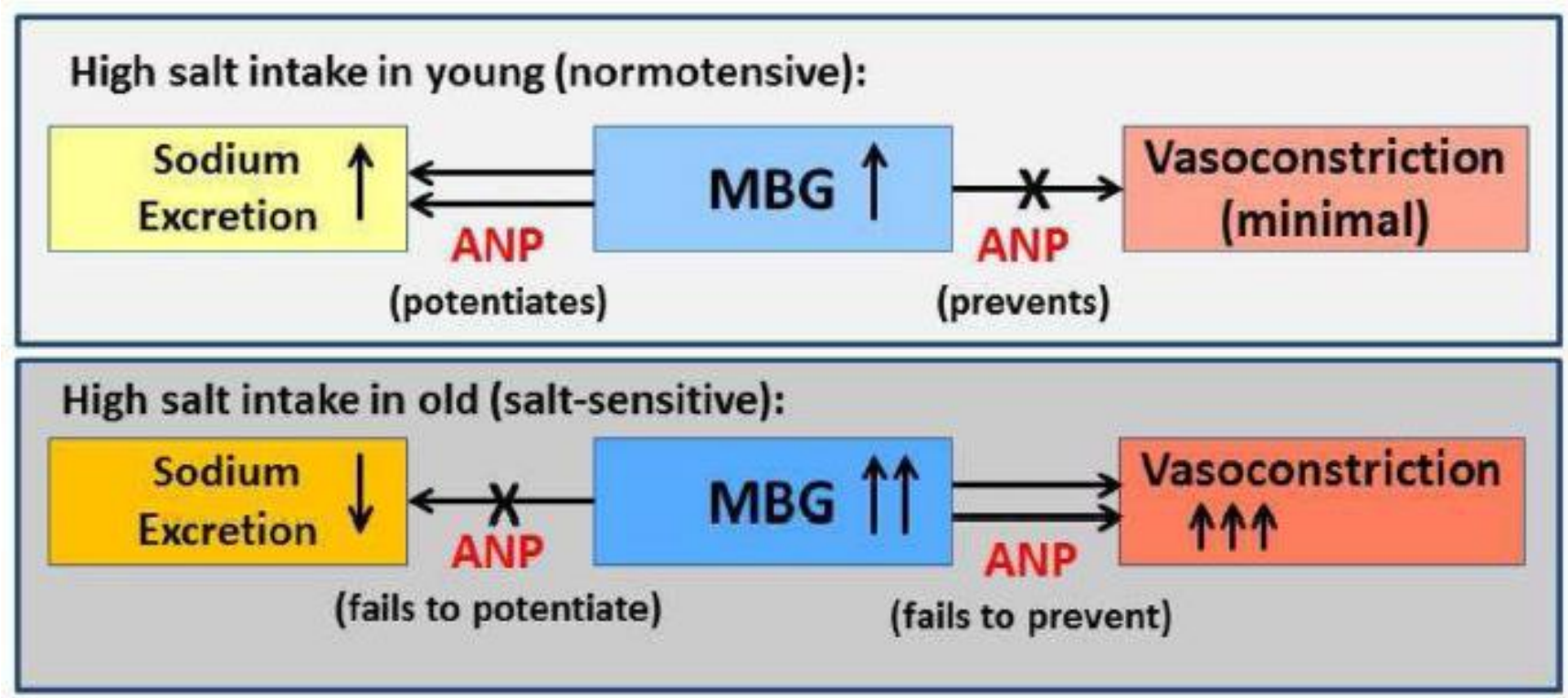


Figure 1. High salt–induced production of NO is impaired in the Dahl/Rapp SS rat.

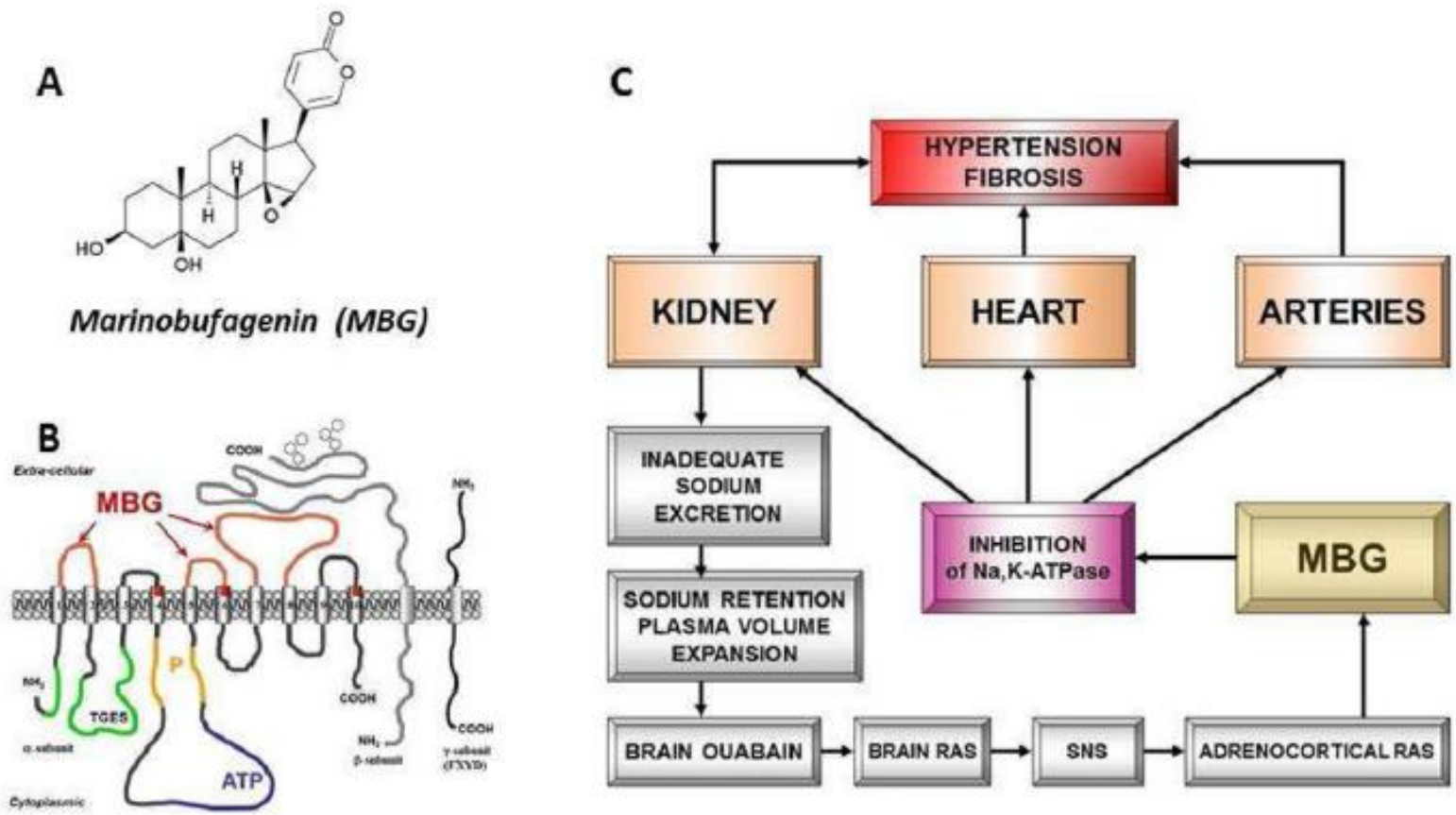
Feng W. et al., J. Am. Soc. Nephrol., 2017, 28, 1362 - 1369

Age-associated shift of the modulation of renal and vascular effects of MBG by ANP



AlGhatrif M. et al., Med. Clin. North. Am., 2017, 101, 81 - 101

Structure of marinobufagenin (MBG) (A) and Na/K- ATPase with binding sites for MBG (B). Interaction between RAAS and MBG in the pathogenesis of salt-sensitive hypertension (C)



AlGhatrif M. et al. Med. Clin. North Am., 2017, 10, 81 - 101

BRIEF REVIEW www.jasn.org

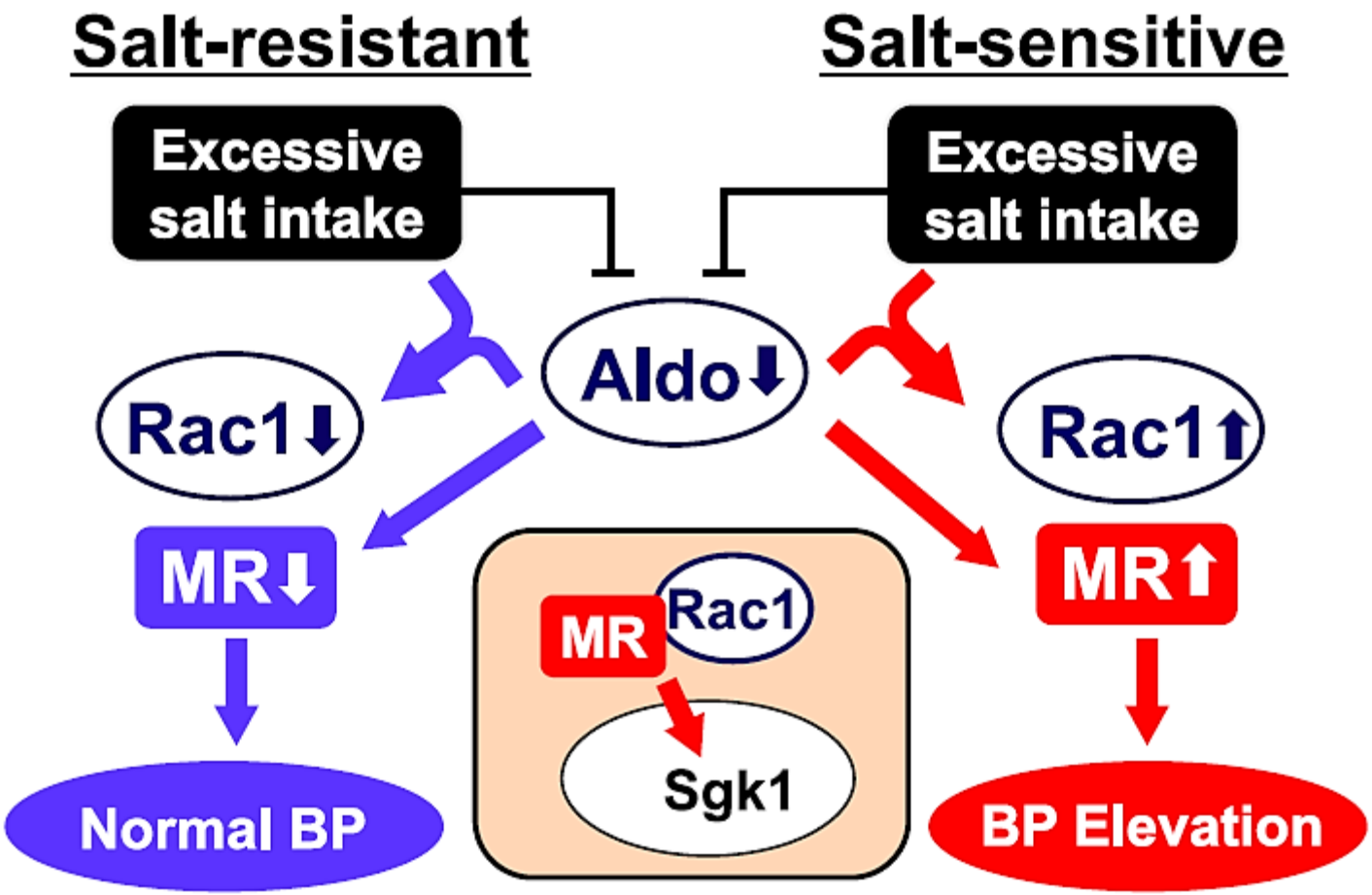
Mechanism of Salt-Sensitive Hypertension: Focus on Adrenal and Sympathetic Nervous Systems

Toshiro Fujita

Department of Clinical Epigenetics, Research Center for Advanced Science and Technology, The University of Tokyo, Tokyo, Japan; and CREST, Tokyo, Japan

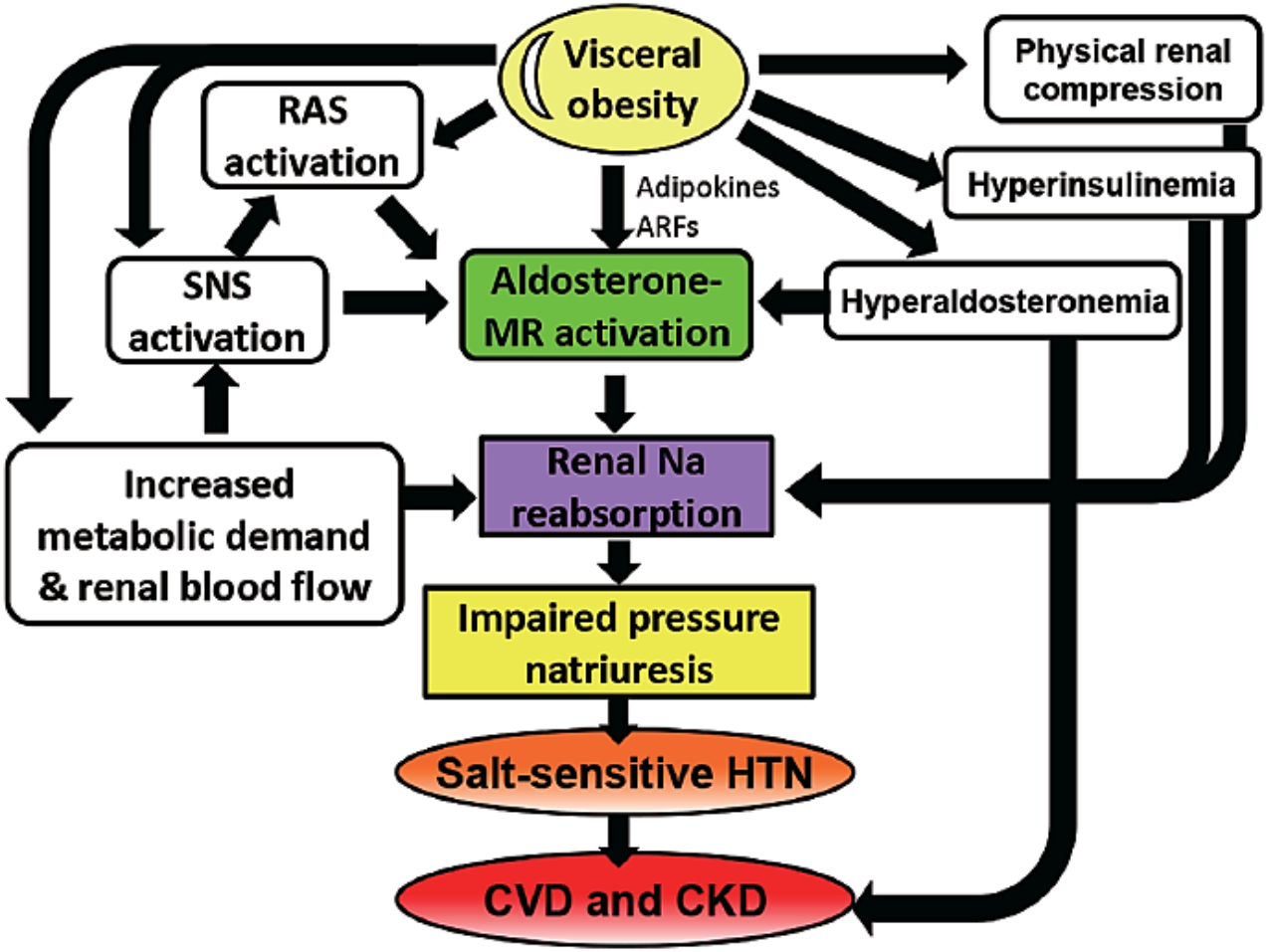
Fujita T., J. Am. Soc. Nephrol., 2014, 25, 1148-1155

Rac 1 is a modulator of MR activity and serves as a determinator of salt-sensitive hypertension



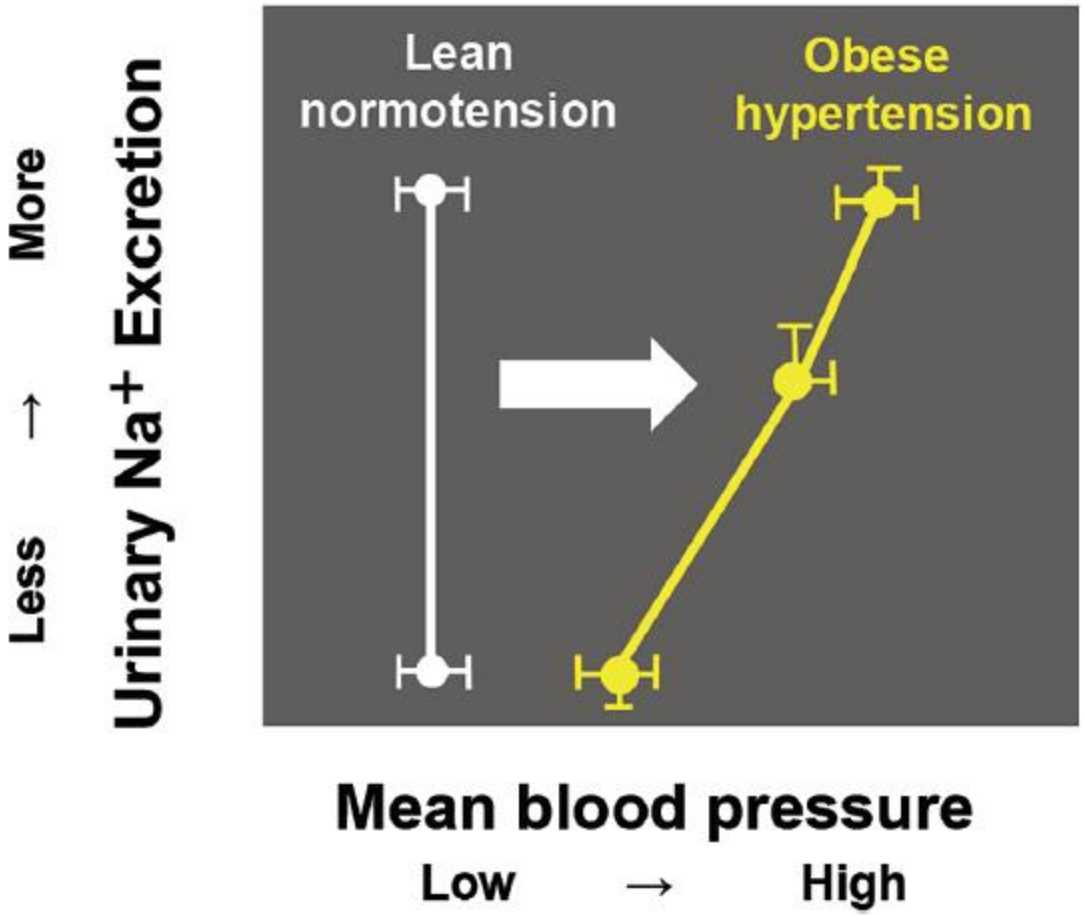
Fujita T., J. Am. Soc. Nephrol., 2014, 25, 1148-1155

The mechanism underlying obesity – related hypertension and kidney impairment



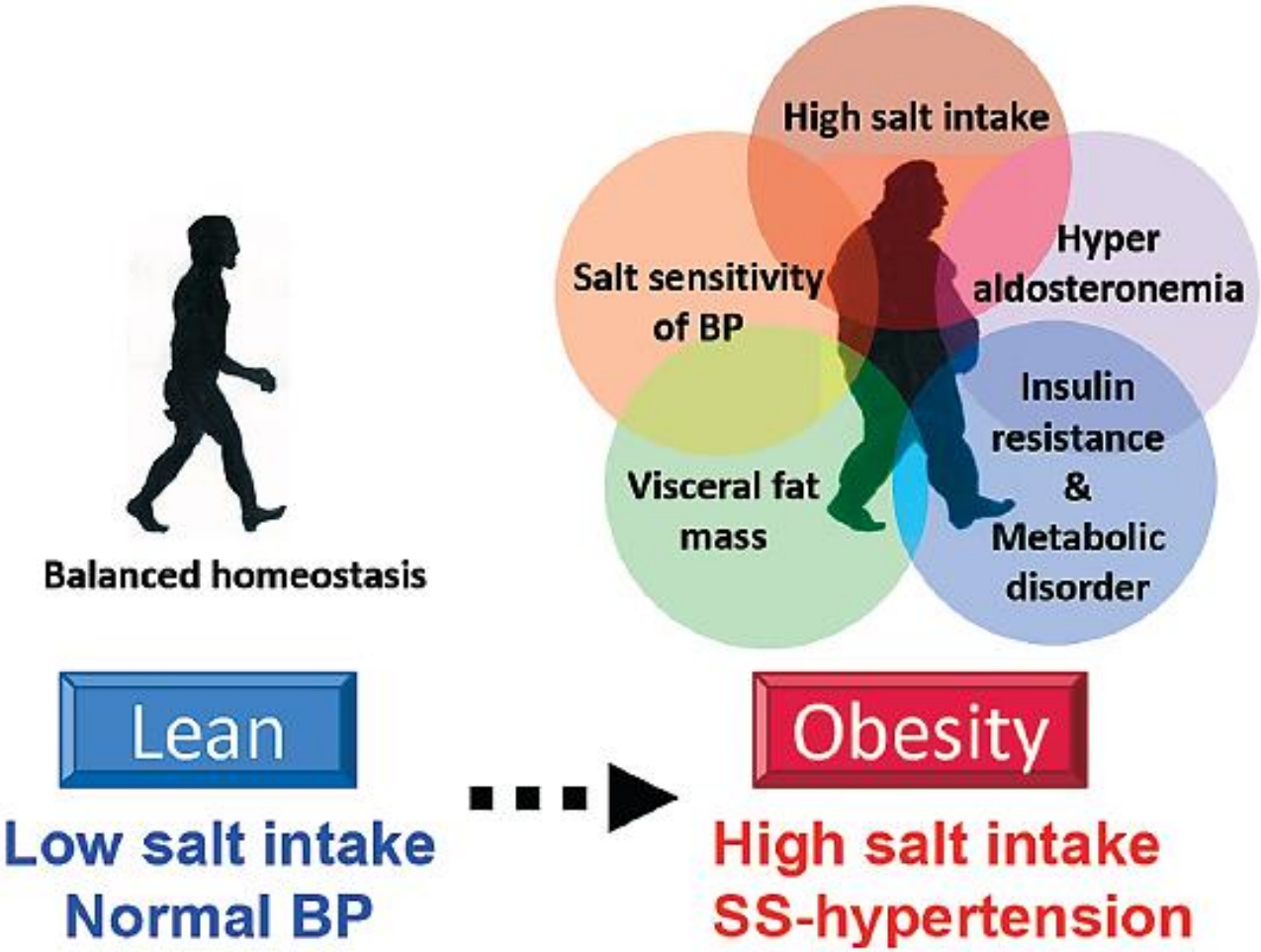
Kawarazaki W. and Fujita T., Am. J. Hypertens., 2016, 29, 415 - 423

The BP-natriuresis curve is slanted and shifted to the right, in obese subjects indicating impaired renal-pressure natriuresis



Kawarazaki W. and Fujita T., Am. J. Hypertens., 2016, 29, 415 - 423

High salt intake increases the risk of obesity



Kawarazaki W. and Fujita T., Am. J. Hypertens., 2016, 29, 415 - 423

Physiological Reports

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Physiological Reports ISSN 2051-817X

ORIGINAL RESEARCH

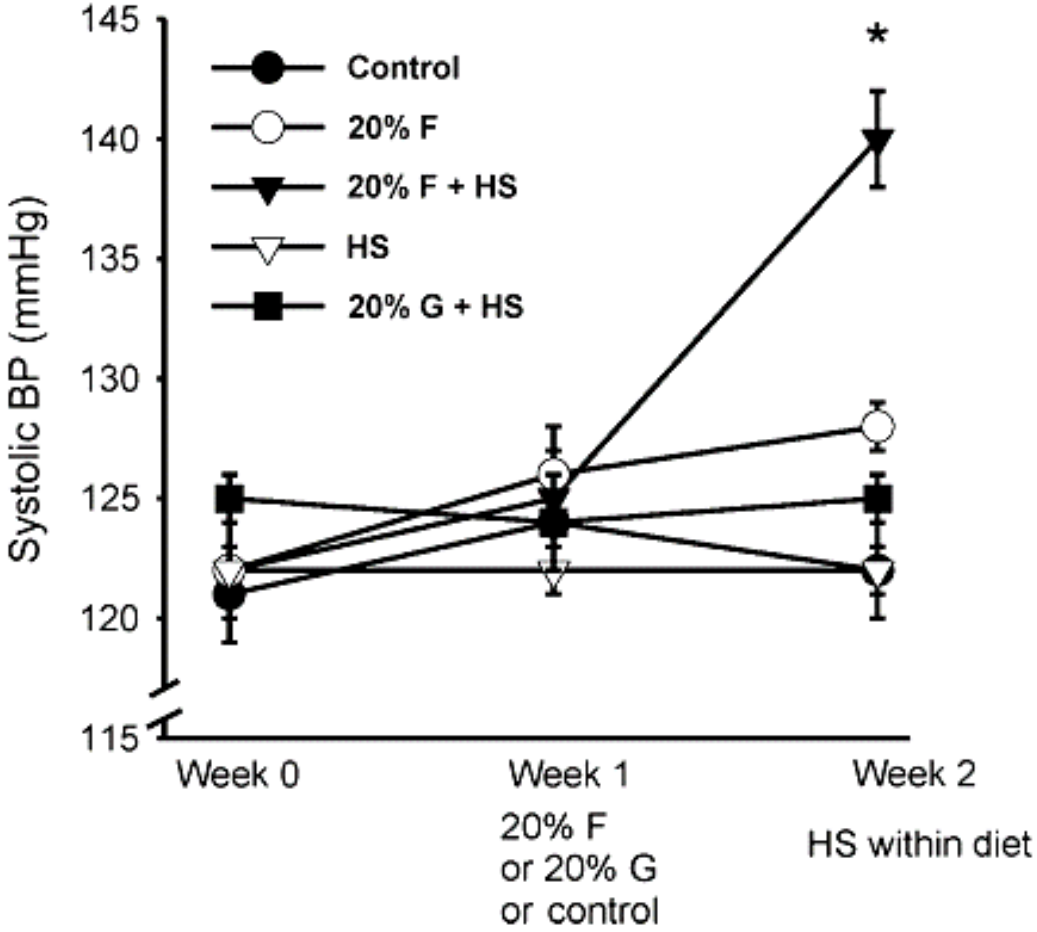
Moderate (20%) fructose-enriched diet stimulates salt-sensitive hypertension with increased salt retention and decreased renal nitric oxide

Kevin L. Gordish[1], Kamal M. Kassem[2], Pablo A. Ortiz[1,2] & William H. Beierwaltes[1,2]

1 Department of Physiology, Wayne State School of Medicine, Detroit, Michigan
2 Department of Internal Medicine, Hypertension and Vascular Research Division, Henry Ford Hospital, Detroit, Michigan

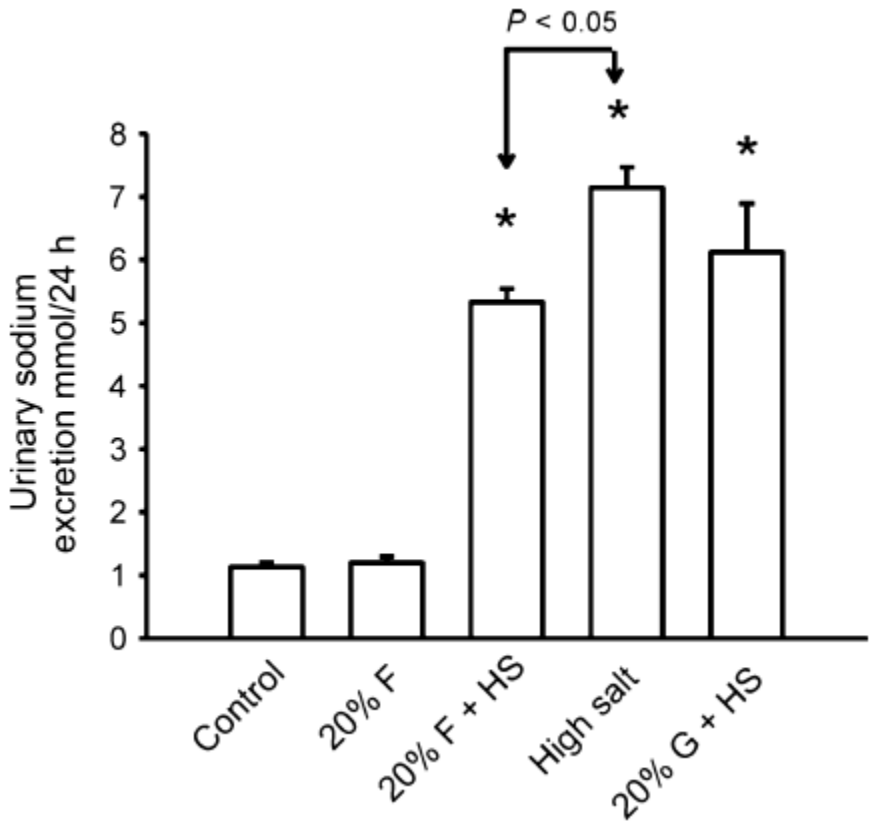
Physiol. Rep., 2017, 5(7), e13162

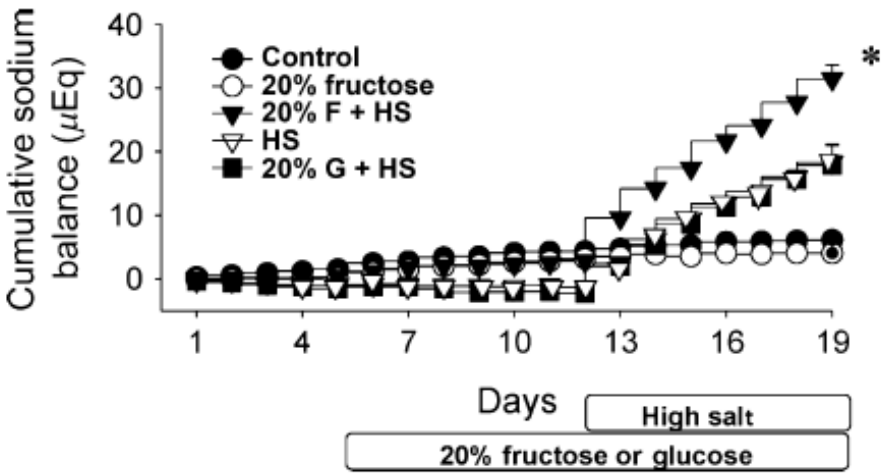
Increased blood pressure in rats receiving high salt diet with 20% of fructose



Gordish K.L. et al., Physiol. Rep., 2017, 5(7), e13162

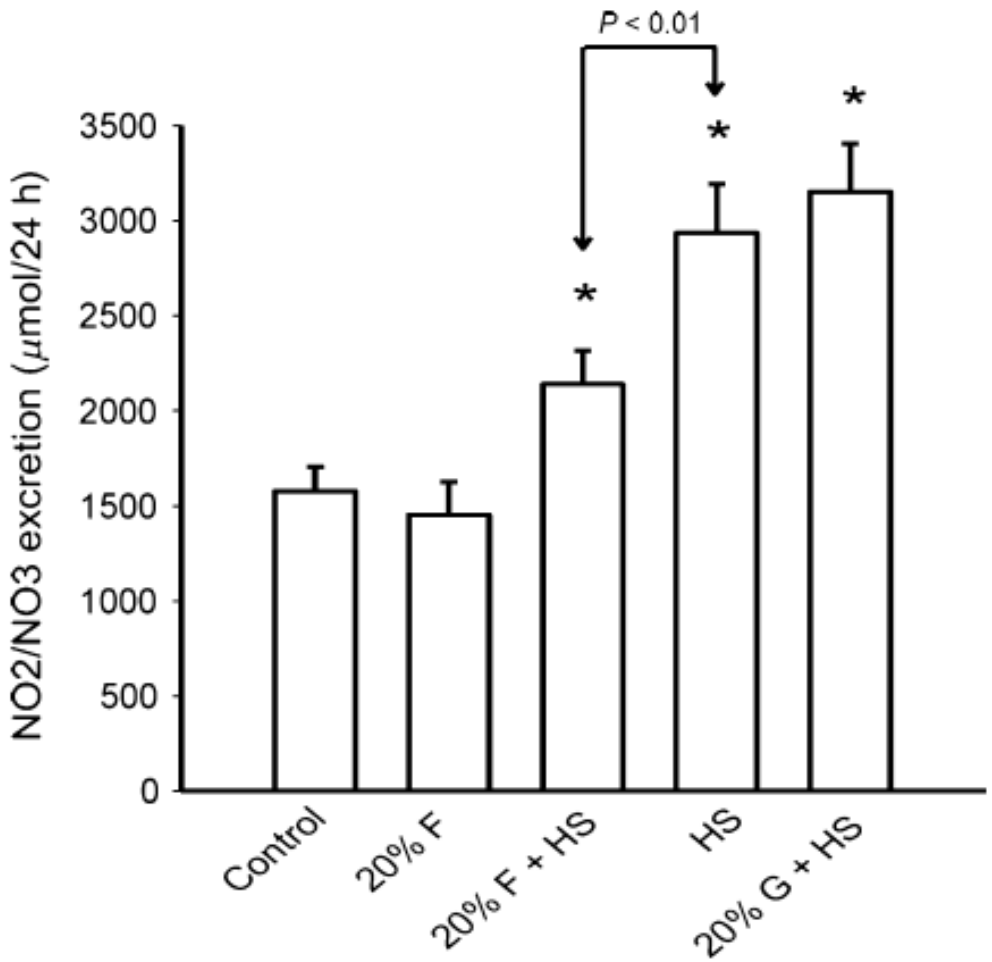
Increased sodium excreation is blunted in rats receiving 20% fructose plus high sodium diet





Gordish K.L. et al., Physiol. Rep., 2017, 5(7), e13162

NO2/NO3 excretion (marker of NO synthesis) is blunted in rats receiving high salt diet and 20% fructose



Gordish K.L. et al., Physiol. Rep., 2017, 5(7), e13162

Role of gut microbiome in the pathogenesis of salt sensitive hypertension

ARTICLE

doi:10.1038/nature24628

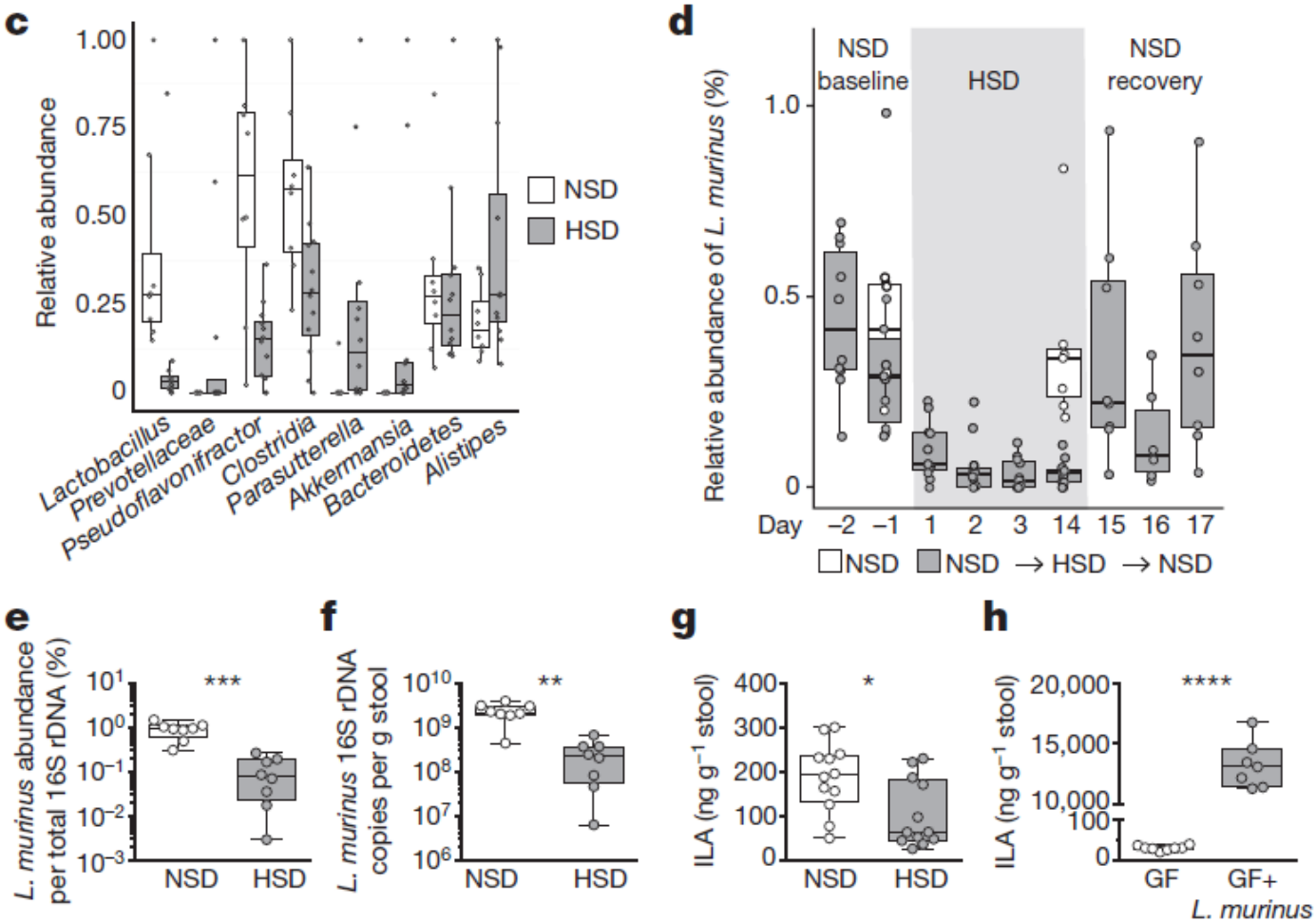
Salt-responsive gut commensal modulates T_H17 axis and disease

Nicola Wilck[1,2,3,4,5], Mariana G. Matus[6,7], Sean M. Kearney[6], Scott W. Olesen[6], Kristoffer Forslund[8], Hendrik Bartolomaeus[1,2,3,4], Stefanie Haase[9], Anja Mähler[1,5], András Balogh[1,2,3,4,5], Lajos Markó[1,2,3,4,5], Olga Vvedenskaya[3,10,11], Friedrich H. Kleiner[1], Dmitry Tsvetkov[1,2], Lars Klug[1,5], Paul I. Costea[8], Shinichi Sunagawa[8,12], Lisa Maier[13], Natalia Rakova[1,9], Valentin Schatz[14], Patrick Neubert[14], Christian Frätzer[15], Alexander Krannich[5], Maik Gollasch[1,2,3], Diana A. Grohme[16], Beatriz F. Côrte-Real[17], Roman G. Gerlach[18], Marijana Basic[19], Athanasios Typas[13], Chuan Wu[20], Jens M. Titze[21], Jonathan Jantsch[14], Michael Boschmann[1,5], Ralf Dechend[1,2,5], Markus Kleinewietfeld[16,17,22], Stefan Kempa[3,5,10], Peer Bork[3,8,23,24], Ralf A. Linker[9]§, Eric J. Alm[6]§ & Dominik N. Müller[1,2,3,4,5]§

A Western lifestyle with high salt consumption can lead to hypertension and cardiovascular disease. High salt may additionally drive autoimmunity by inducing T helper 17 (T_H17) cells, which can also contribute to hypertension. Induction of T_H17 cells depends on gut microbiota; however, the effect of salt on the gut microbiome is unknown. Here we show that high salt intake affects the gut microbiome in mice, particularly by depleting *Lactobacillus murinus*. Consequently, treatment of mice with *L. murinus* prevented salt-induced aggravation of actively induced experimental autoimmune encephalomyelitis and salt-sensitive hypertension by modulating T_H17 cells. In line with these findings, a moderate high-salt challenge in a pilot study in humans reduced intestinal survival of *Lactobacillus* spp., increased T_H17 cells and increased blood pressure. Our results connect high salt intake to the gut-immune axis and highlight the gut microbiome as a potential therapeutic target to counteract salt-sensitive conditions.

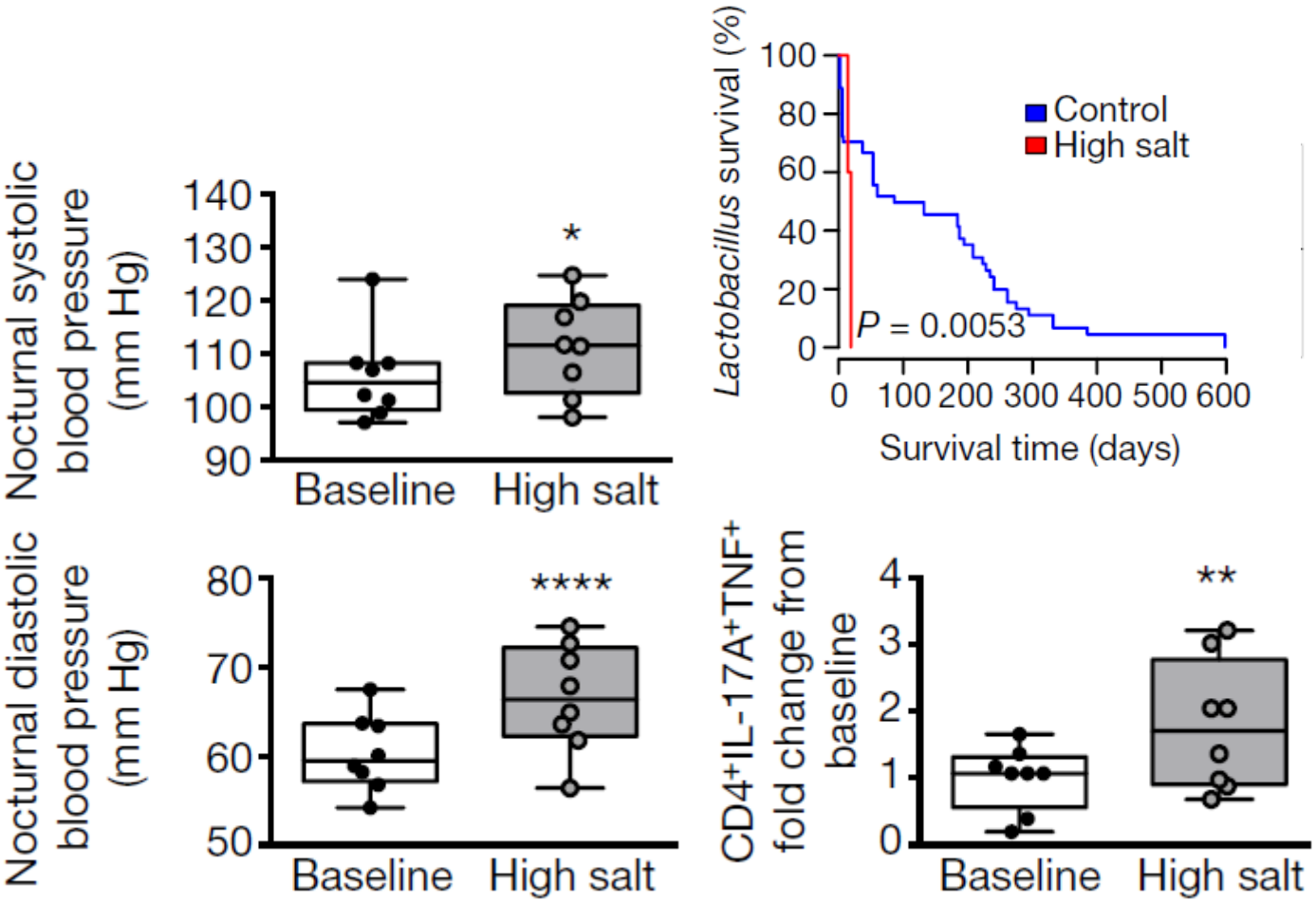
Wilck N. et al., Nature, 2017, 551, 585-589

High salt diet (HSD) alters the faecal microbiome and depletes Lactobacillus murinus



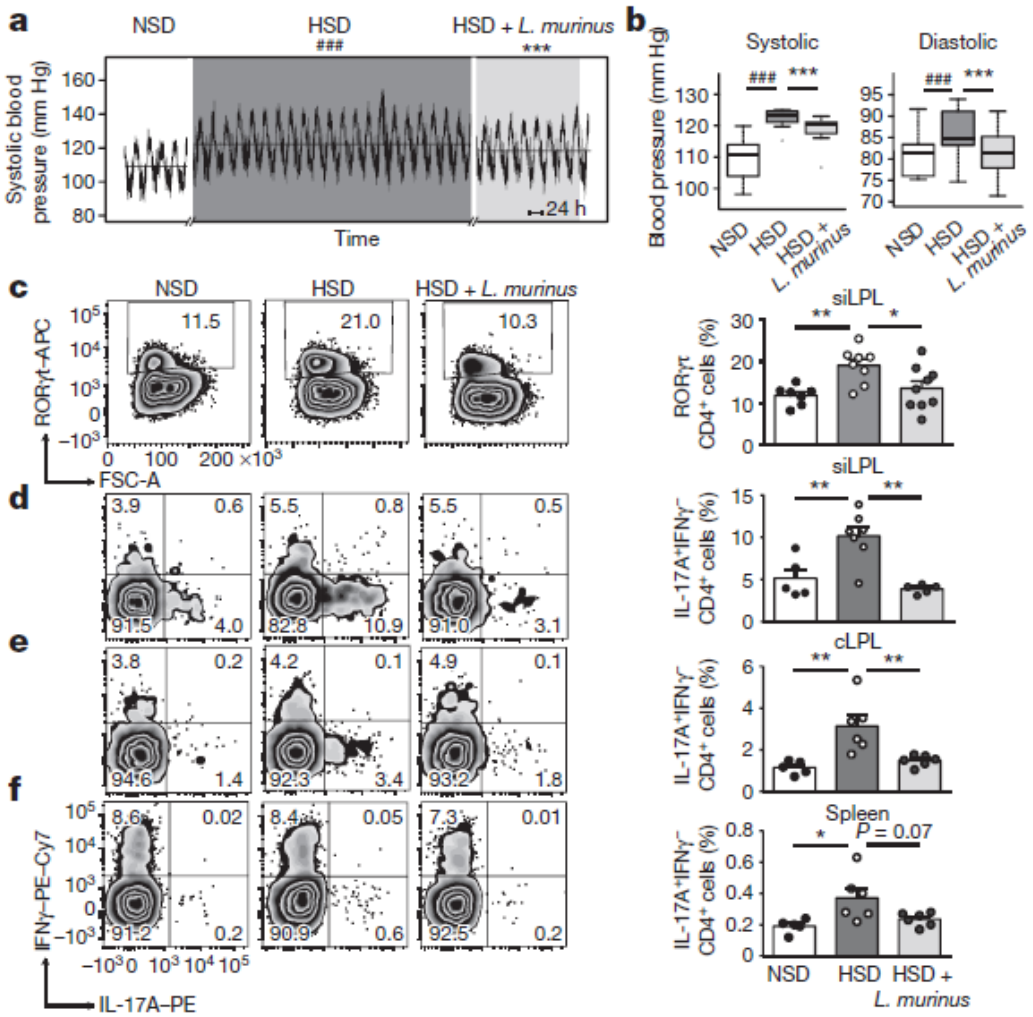
Wilck N. et al., Nature, 2017, 551, 585-589

High salt diet affects blood pressure, TH17 cells and Lactobacillus species in healthy humans



Wilck N. et al., Nature, 2017, 551, 585-589

Treatment with Lactobacillus ameliorates salt -sensitive hypertension and reduces the number of Th17 cells



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ARTICLE

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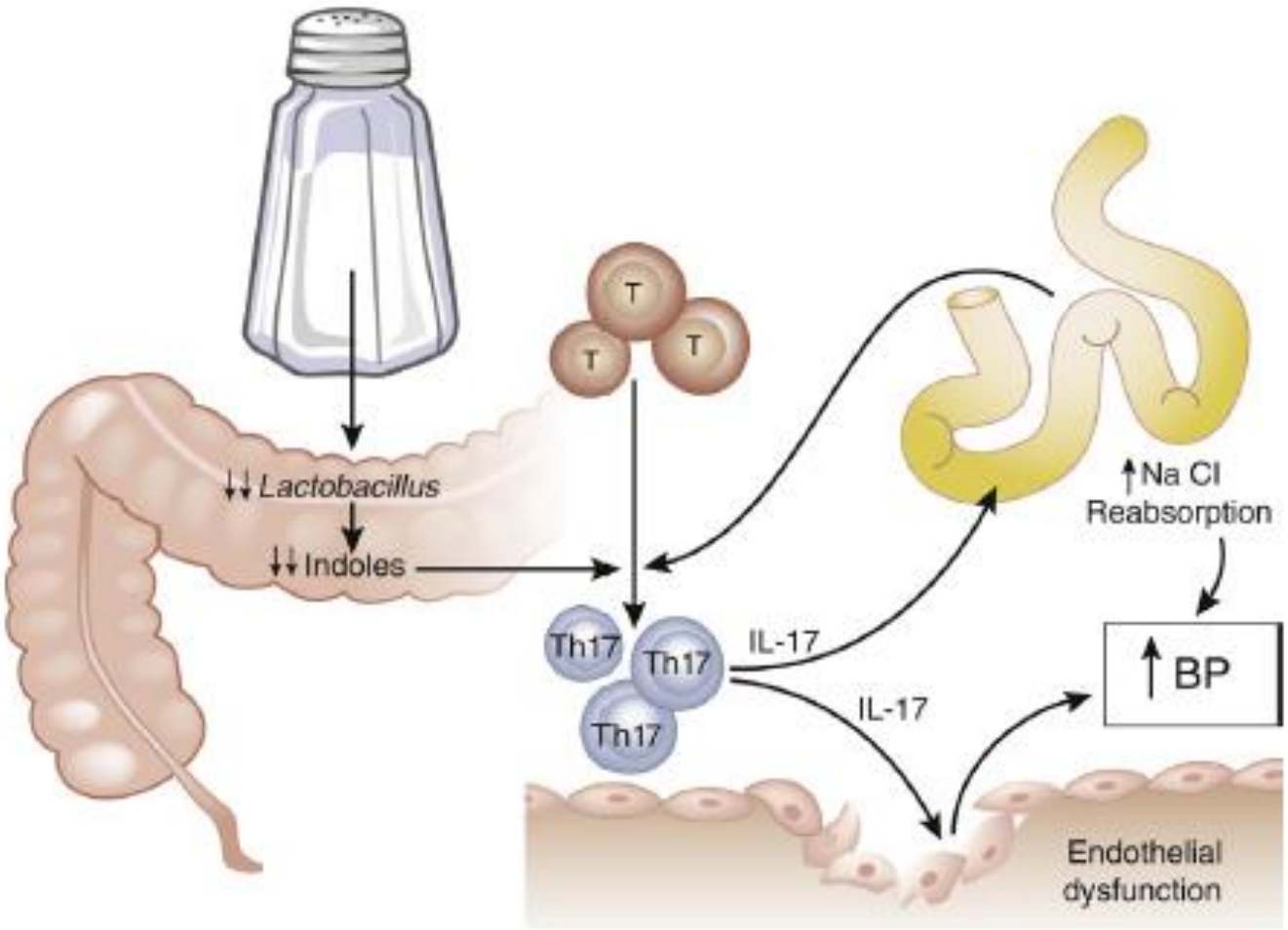
Salt-responsive gut commensal modulates T_H17 axis and disease

Nicola Wilck[1,2,3,4,5], Mariana G. Matus[6,7], Sean M. Kearney[6], Scott W. Olesen[6], Kristoffer Forslund[8], Hendrik Bartolomaeus[1,2,3,4], Stefanie Haase[9], Anja Mähler[1,5], András Balogh[1,2,3,4,5], Lajos Markó[1,2,3,4,5], Olga Vvedenskaya[3,10,11], Friedrich H. Kleiner[1], Dmitry Tsvetkov[1,2], Lars Klug[1,5], Paul I. Costea[8], Shinichi Sunagawa[8,12], Lisa Maier[13], Natalia Rakova[1,9], Valentin Schatz[14], Patrick Neubert[14], Christian Frätzer[15], Alexander Krannich[5], Maik Gollasch[1,2,3], Diana A. Grohme[16], Beatriz F. Côrte-Real[17], Roman G. Gerlach[18], Marijana Basic[19], Athanasios Typas[13], Chuan Wu[20], Jens M. Titze[21], Jonathan Jantsch[14], Michael Boschmann[1,5], Ralf Dechend[1,2,5], Markus Kleinewietfeld[16,17,22], Stefan Kempa[3,5,10], Peer Bork[3,8,23,24], Ralf A. Linker[9]§, Eric J. Alm[6]§ & Dominik N. Müller[1,2,3,4,5]§

Our experimental data in mice suggest that the gut microbiota might serve as a potential target to counteract salt-sensitive conditions. The identification of *Lactobacillus* as a 'natural inhibitor' of high salt-induced T_H17 cells in mice could serve as a basis for the development of novel prevention and treatment strategies. It is up to randomized controlled trials in humans with diseases to test this hypothesis. Moreover, any future dietary salt intervention trial should thus consider monitoring the microbiome to expand on our observations.

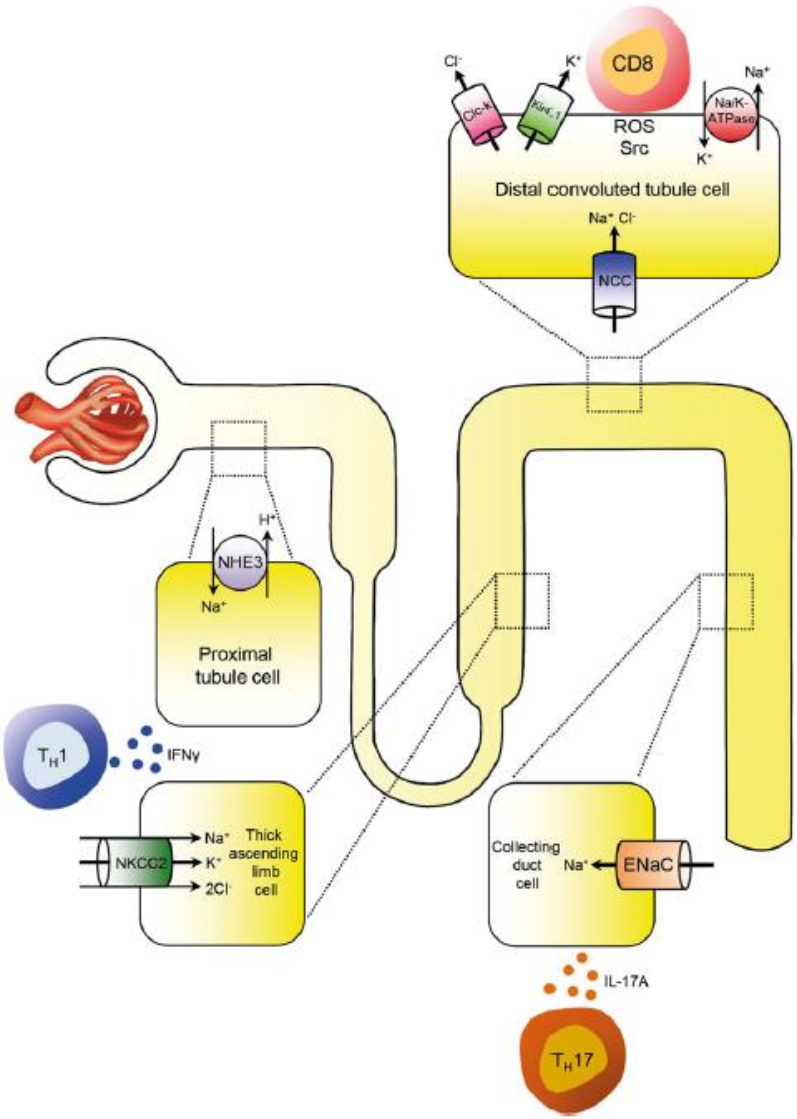
Wilck N. et al., Nature, 2017, 551, 585-589

Proposed mechanisms of salt-sensitive hypertension



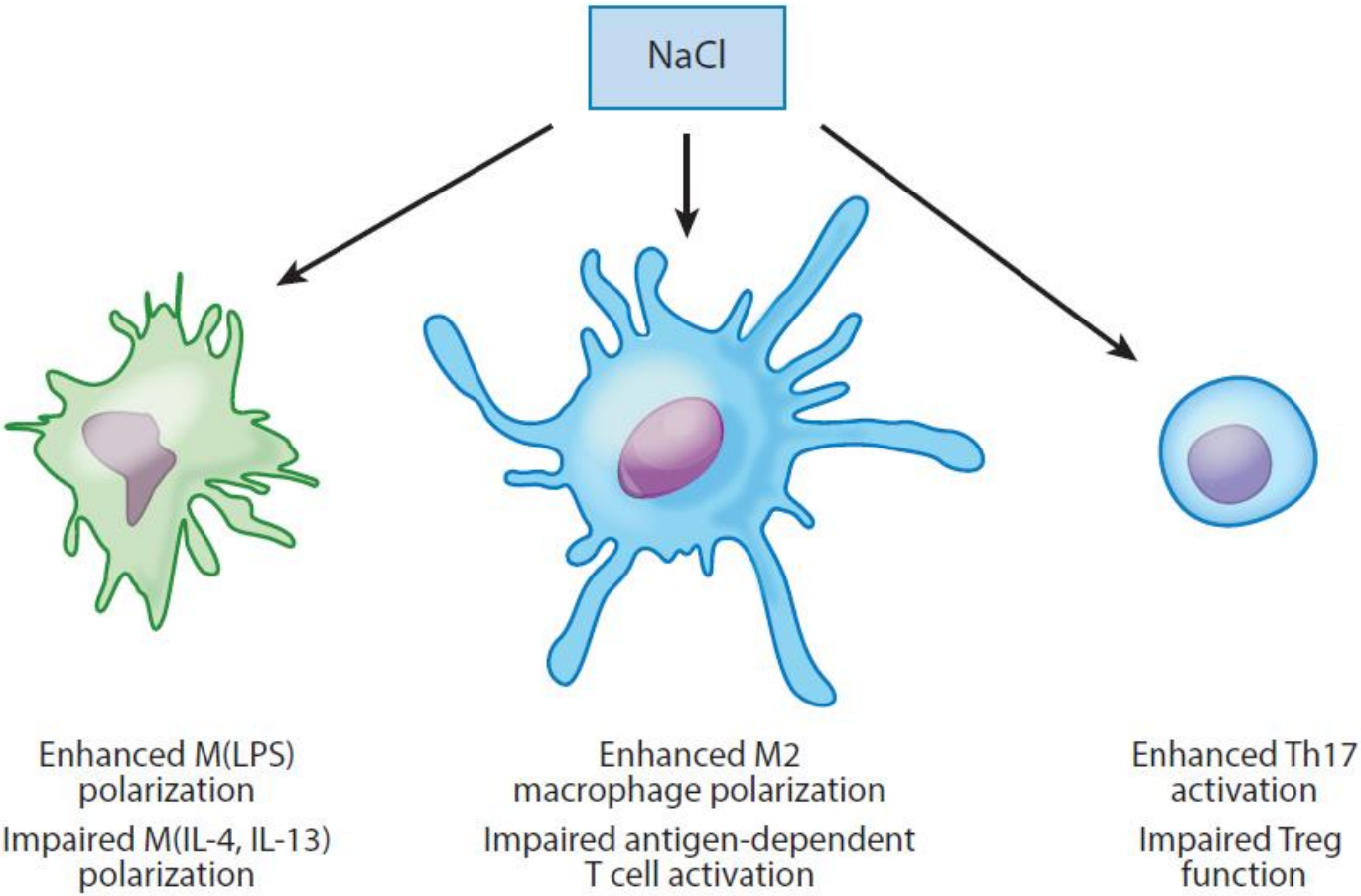
Wyatt C. Y. and Crowley S. M. Kidney Int., 2018, 93, 532 - 534

Inflammation and renal sodium transporters



Wenzel U.O. et al., Br. J. Pharmacol., 2018, in press

Effects of salt on the immune cell phenotype



Rucker A.J. et al., Annu. Rev. Physiol., 2018, 80, 283 - 307

Salt affects immune system and promotes hypertension

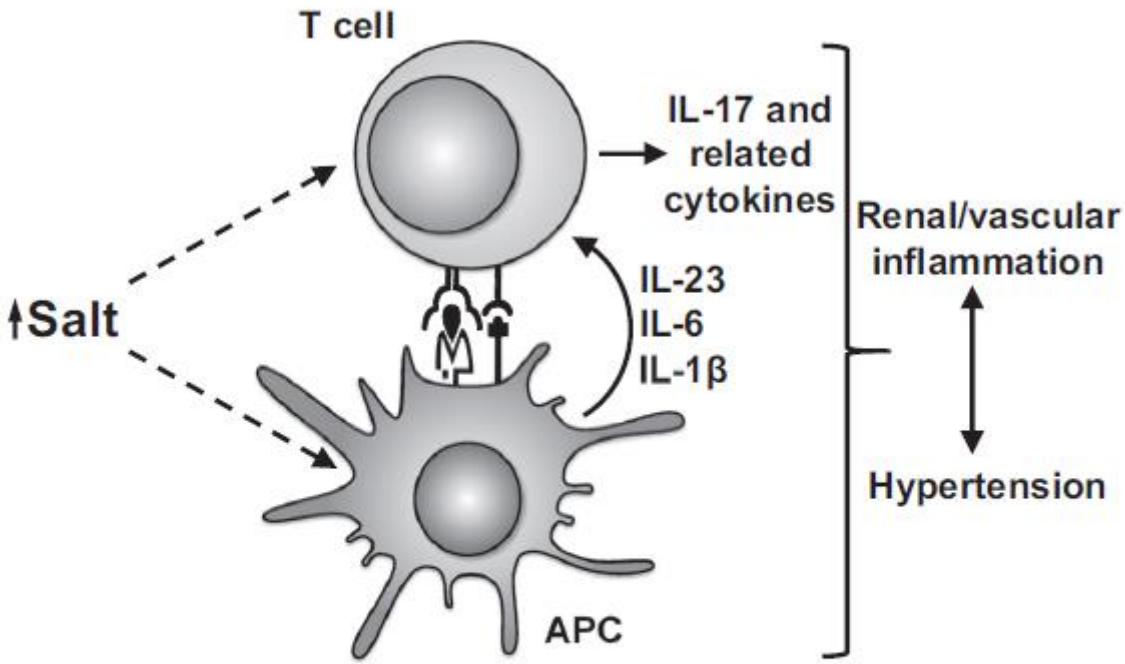
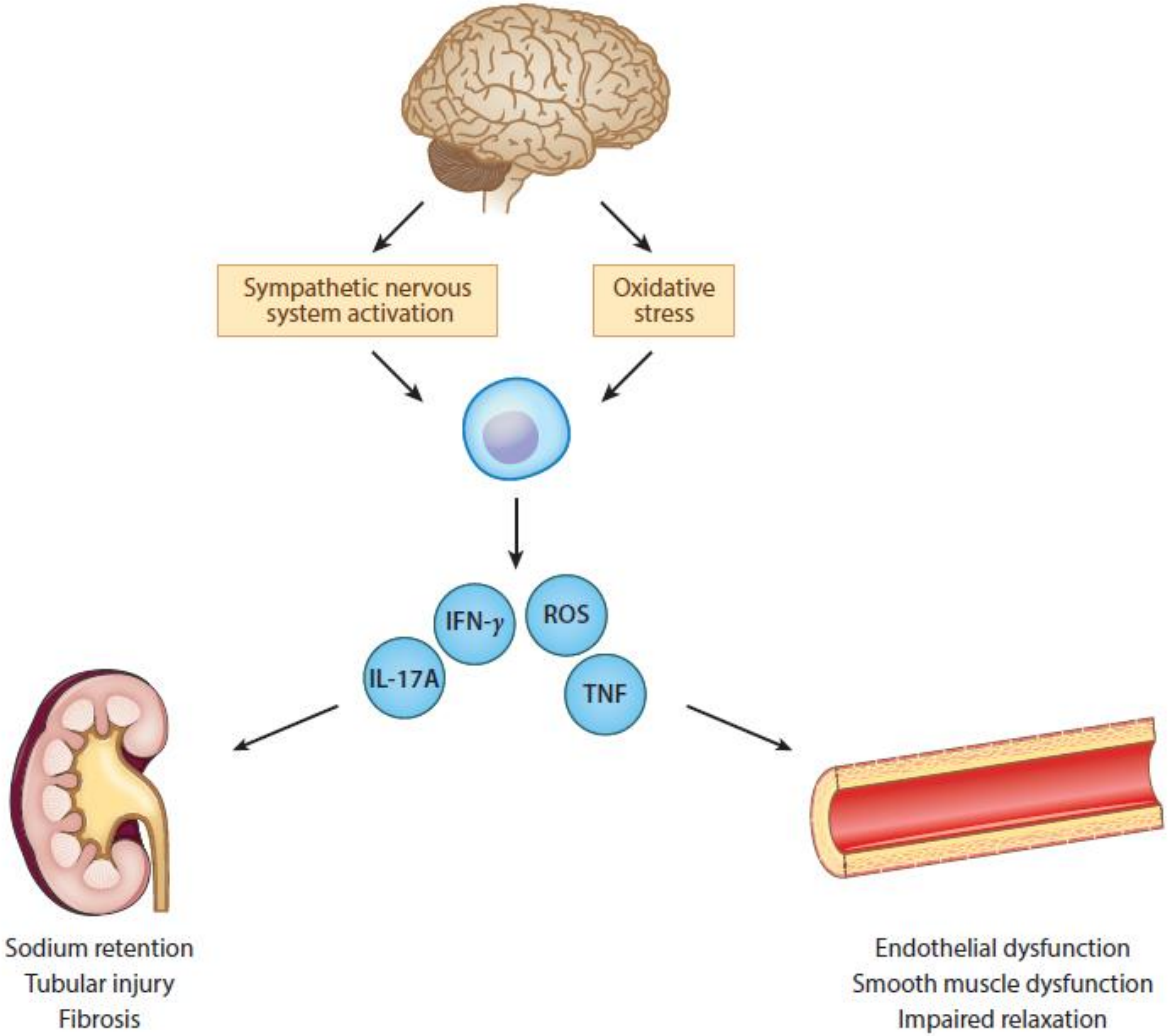


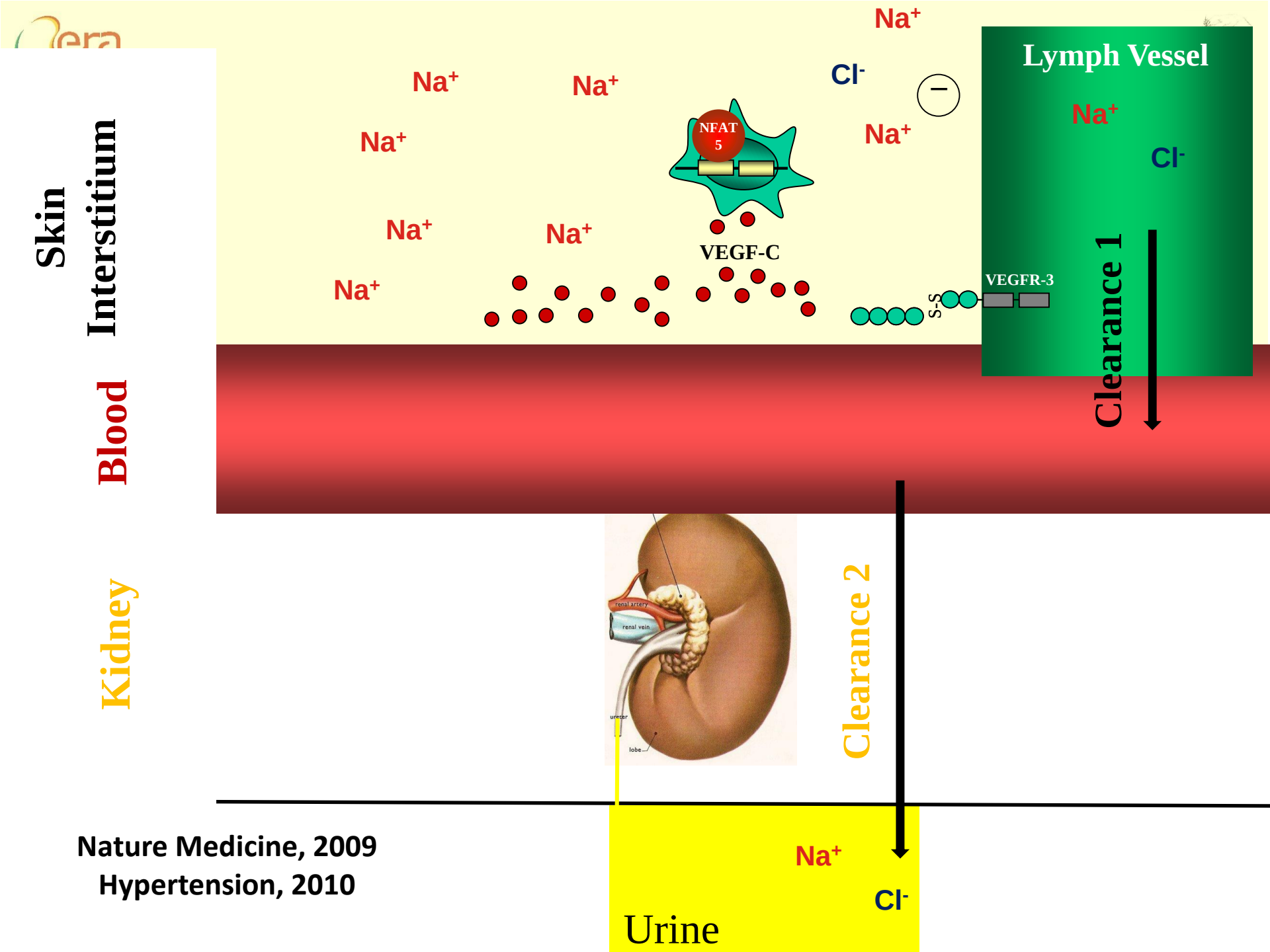
Fig. 1. Paradigm illustrating how salt may affect immune cells to promote hypertension. High salt drives T cells toward a prohypertensive IL-17 phenotype, both directly and indirectly through activation of antigen-presenting cells (APC), such as monocytes, macrophages, and dendritic cells. This T-cell activation leads to renal and vascular inflammation, dysfunction of the kidneys and vasculature, and ultimately hypertension.

Foss J.D. et al., Am. J. Physiol., 2017, 312, R1 - R4

Proposed roles of T- lymphocytes in hypertension and salt sensitivity

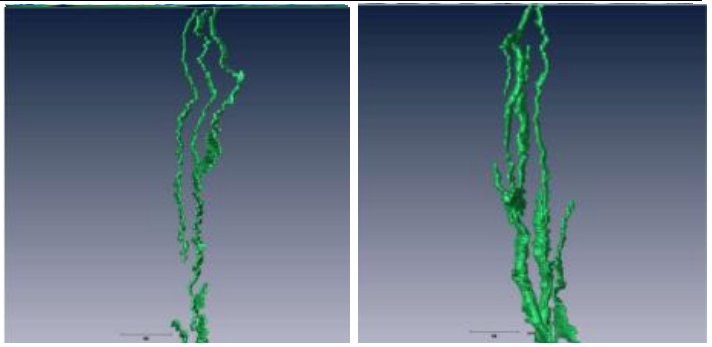


Rucker A.J. et al., Annu. Rev. Physiol., 2018, 80, 283 - 307

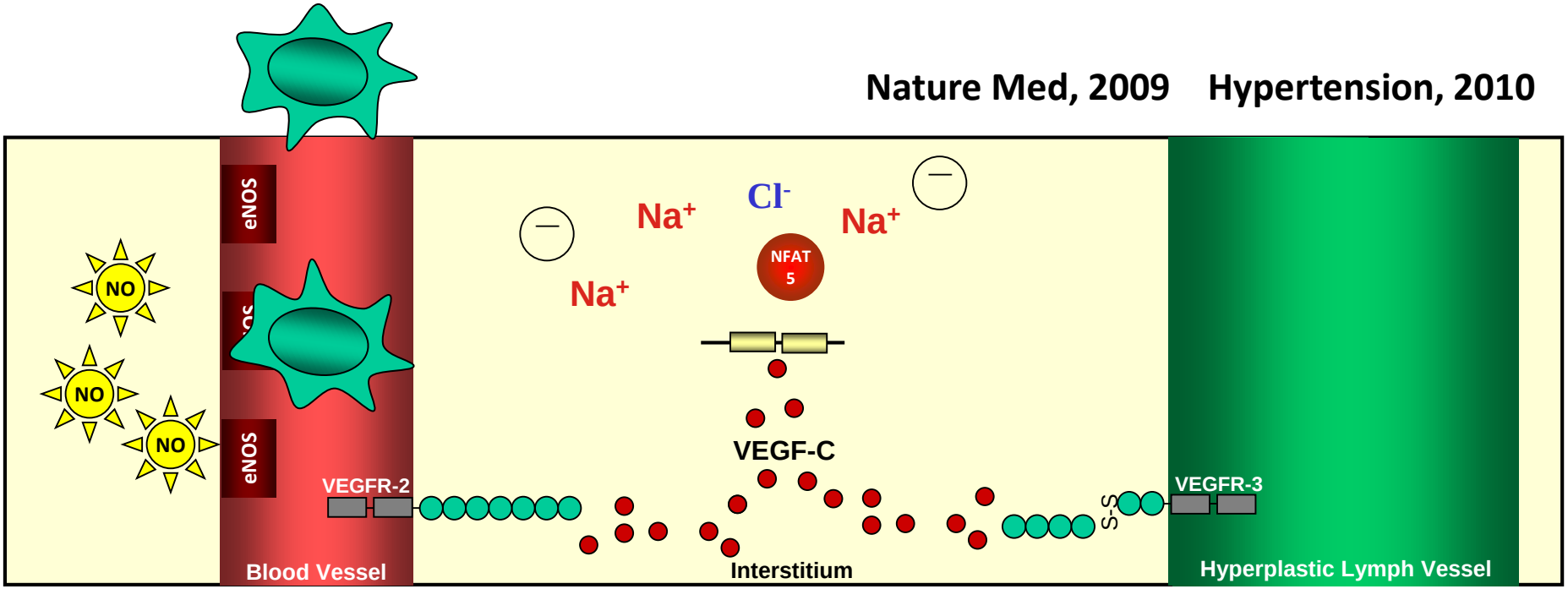


Nature Medicine, 2009
Hypertension, 2010

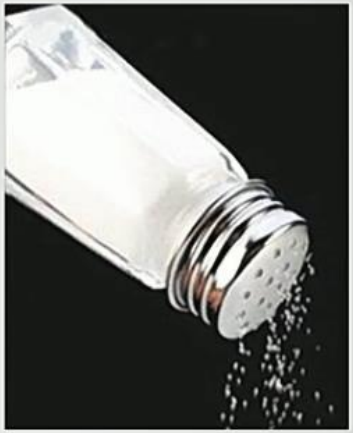
	LSD	HSD
Blood: [$Na^+ + K^+$]	143 ± 2 mM	145 ± 2 mM
Skin: [$Na^+ + K^+$]	177 ± 8 mM	191 ± 7 * mM



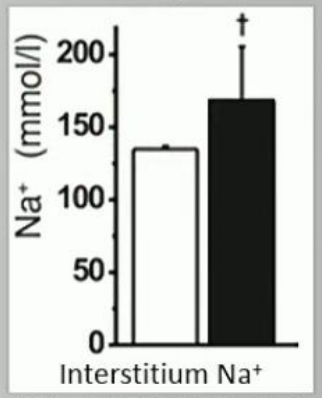
Nature Med, 2009 Hypertension, 2010



Imcreased sodium content in the skin, assesed by the MRI method



Increased skin Na^+, not reflected in plasma

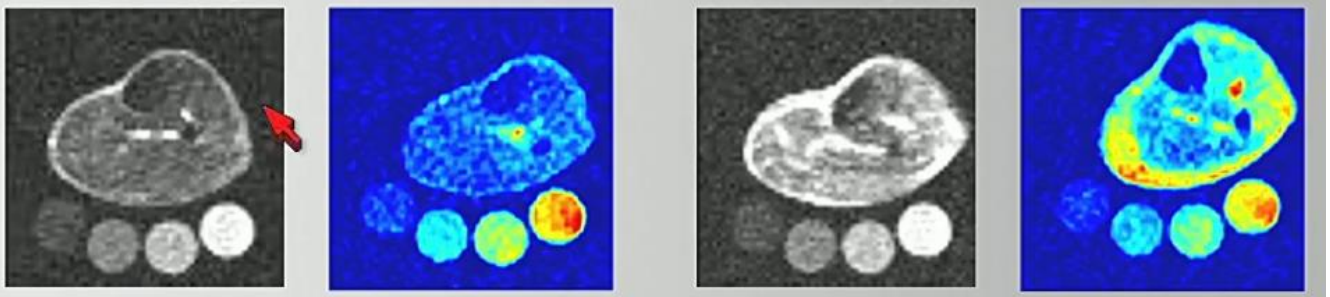


Wiig et al JCI 2013;123:2803

24 yo healthy man

85 yo hypertensive man

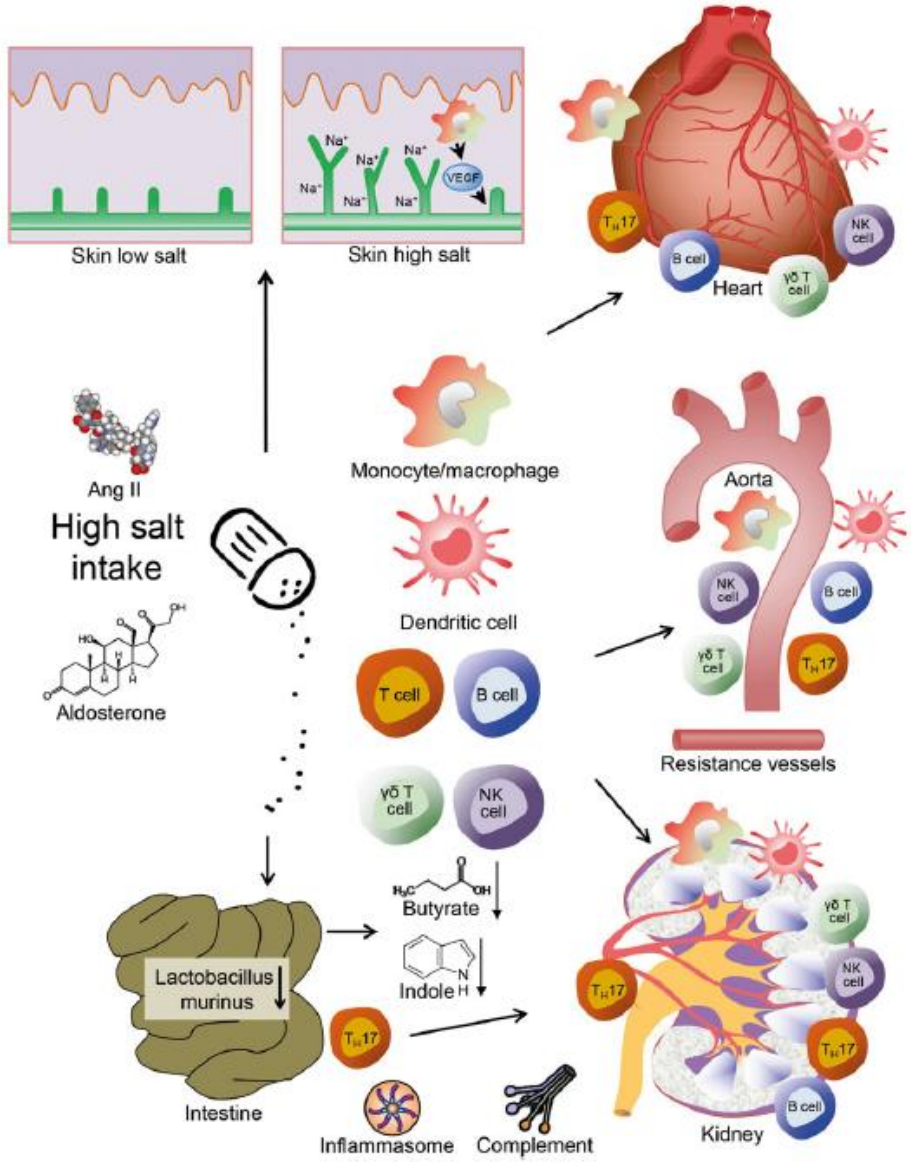
^{23}Na-MRI



Kopp et al Hypertension. 2013;61:635

Fernando Elijovich, MD, FAHA. Vanderbilt University

Salt and hypertension – new concepts



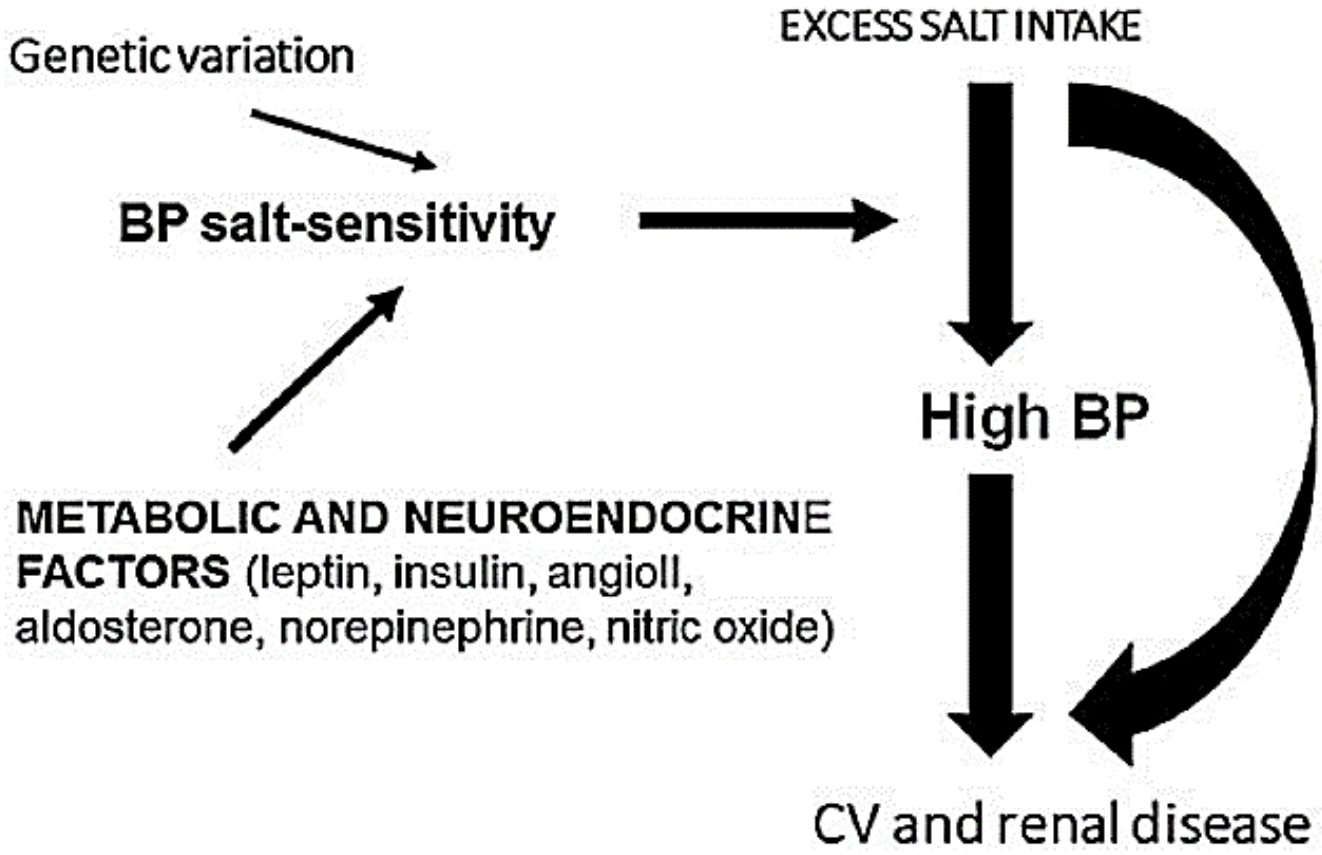
Hypertension and end organ damage

Wenzel U.O et al., Br. J. Pharmacol., 2018, in press

Outline of the lecture

- Definition of the salt – sensitive hypertension
- Pathogenesis (classical) of the salt - sensitive hypertension
- New concepts of the salt - sensitive hypertension
- Salt - sensitive hypertension and the risk of CKD development
- Summary of the lecture

Zależność pomiędzy sodo-zależnym nadciśnieniem tętniczym a występowaniem powikłań sercowo-naczyniowych i nerkowych



Galletti F. and Strazzullo P., Nephrol. Dial. Transplant., 2016, 31, 1386 - 1391

AHA Scientific Statement

Salt Sensitivity of Blood Pressure

A Scientific Statement From the American Heart Association

Fernando Elijovich, MD, FAHA, Vice Chair; Myron H. Weinberger, MD, FAHA, Vice Chair;
Cheryl A.M. Anderson, PhD; Lawrence J. Appel, MD, MPH, FAHA;
Michael Bursztyn, MD, FAHA; Nancy R. Cook, ScD; Richard A. Dart, MD, FAHA;
Christopher H. Newton-Cheh, MD, MPH; Frank M. Sacks, MD;
Cheryl L. Laffer, MD, PhD, FAHA, Chair; on behalf of the American Heart
Association Professional and Public Education Committee of the Council on Hypertension;
Council on Functional Genomics and Translational Biology; and Stroke Council

The original SS and subsequent DS/Jr rats developed fulminant hypertension when exposed to a high-salt (8%) diet and died by the age of 8 weeks. They had a plethora of vascular lesions, renal fibrosis, and cardiac hypertrophy. Several investigators reported a variety of physiological abnormalities contributing to hypertension in DS/Jr rats, among them differences in cellular ion transport and concentration, enhanced sympathetic activity and blunted baroreflexes, reduced renal medullary blood flow, disturbed balance between vasoconstrictors and vasodilators with a special role for nitric oxide (NO), enhanced oxidative stress, and activated Rac1 GTPase mineralocorticoid receptor interaction.[17]

Elijovich F. et al. Hypertension, 2016, 68, e7 - e46

High salt loading induces tubular injury and renal interstitial fibrosis in Dahl SS rats

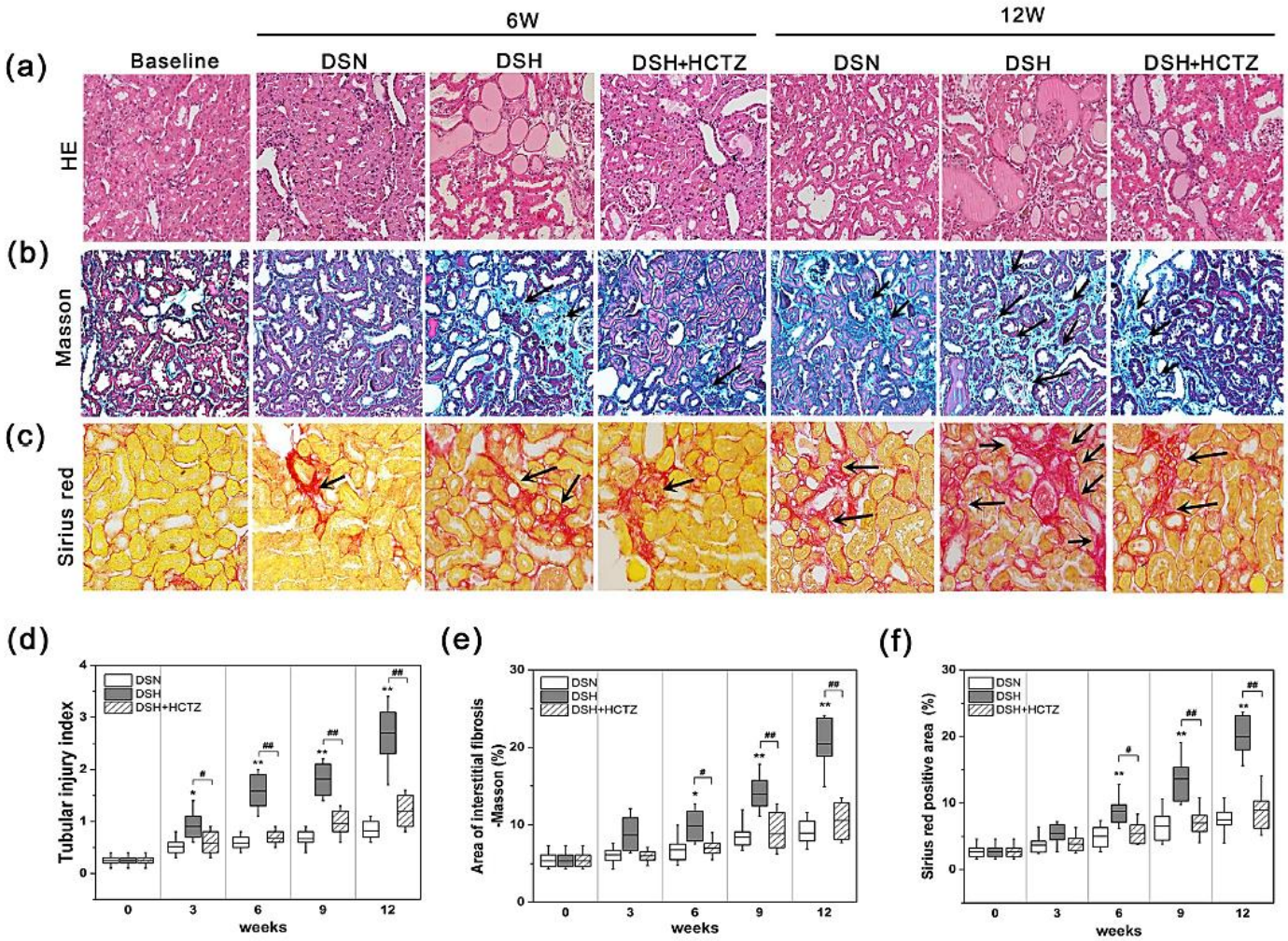


Figure 2. High salt loading induces tubular injury and renal interstitial fibrosis in DS rats. (a)

Wei S.Y. et al., SCIENTIFIC REPORTS/7:45952/

High salt loading induces glomerular injury with progressive glomerulosclerosis in Dahl SS rats

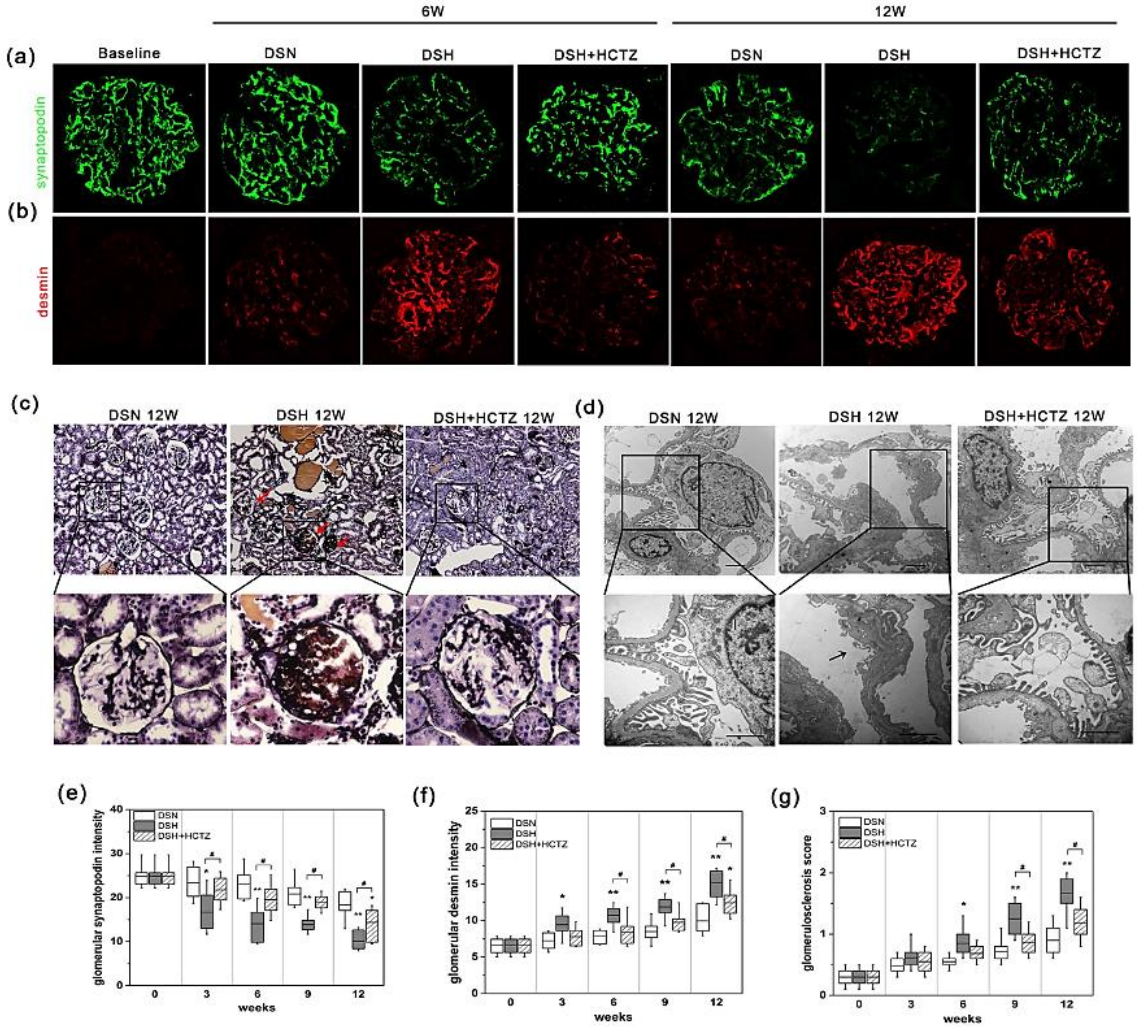


Figure 3. High salt loading induces glomerular injury with progressive glomerulosclerosis in DS

Wei S.Y. et al., SCIENTIFIC REPORTS/7:45952/

SCIENTIFIC REPORTS

OPEN

Renal Tumor Necrosis Factor α Contributes to Hypertension in Dahl Salt-Sensitive Rats

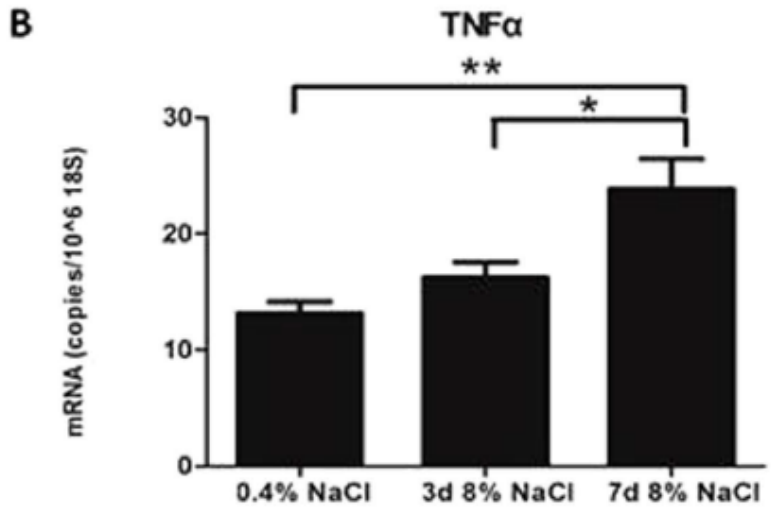
Received: 03 September 2015
Accepted: 03 February 2016
Published: 26 February 2016

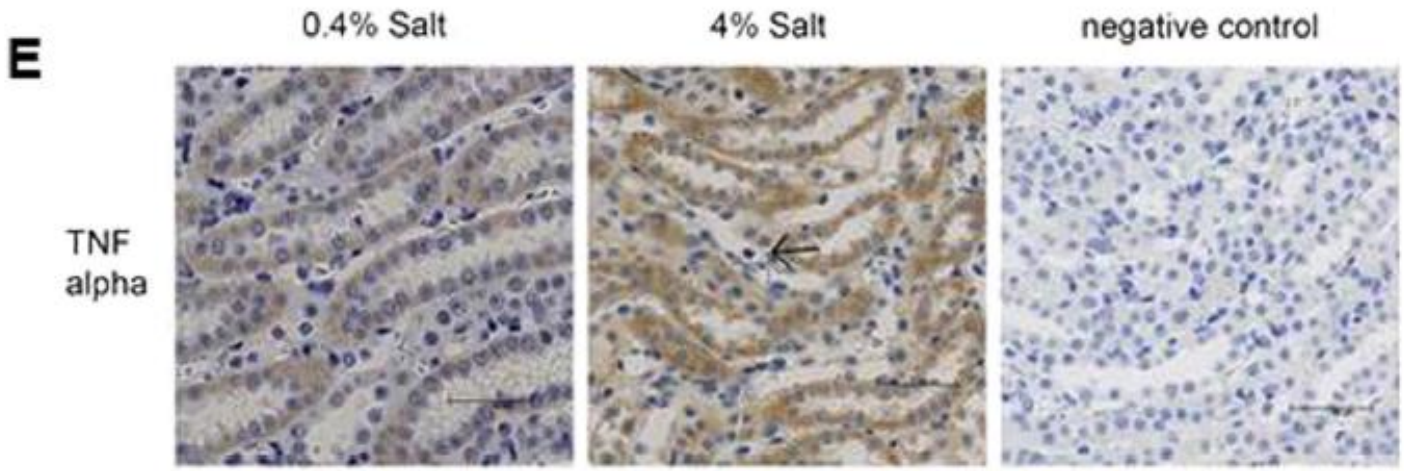
Baorui Huang[1,2,4], Yuan Cheng[3,4,5], Kristie Usa[3,4], Yong Liu[3,4], Maria Angeles Baker[3,4], David L. Mattson[4], Yongcheng He[5], Niansong Wang[1] & Mingyu Liang[3,4]

Tumor necrosis factor α (TNFα) is a major proinflammatory cytokine and its level is elevated in hypertensive states. Inflammation occurs in the kidneys during the development of hypertension. We hypothesized that TNFα specifically in the kidney contributes to the development of hypertension and renal injury in Dahl salt-sensitive (SS) rats, a widely used model of human salt-sensitive hypertension and renal injury. SS rats were chronically instrumented for renal interstitial infusion and blood pressure measurement in conscious, freely moving state. Gene expression was measured using real-time PCR and renal injury assessed with histological analysis. The abundance of TNFα in the renal medulla of SS rats, but not the salt-insensitive congenic SS.13^{BN26} rats, was significantly increased when rats had been fed a high-salt diet for 7 days ($n = 6$ or 9, $p < 0.01$). The abundance of TNFα receptors in the renal medulla was significantly higher in SS rats than SS.13^{BN26} rats. Renal interstitial administration of Etanercept, an inhibitor of TNFα, significantly attenuated the development of hypertension in SS rats on a high-salt diet ($n = 7–8$, $p < 0.05$). Glomerulosclerosis and interstitial fibrosis were also significantly ameliorated. These findings indicate intrarenal TNFα contributes to the development of hypertension and renal injury in SS rats.

Huang B. et al., SCIENTIFIC REPORTS/6/21960

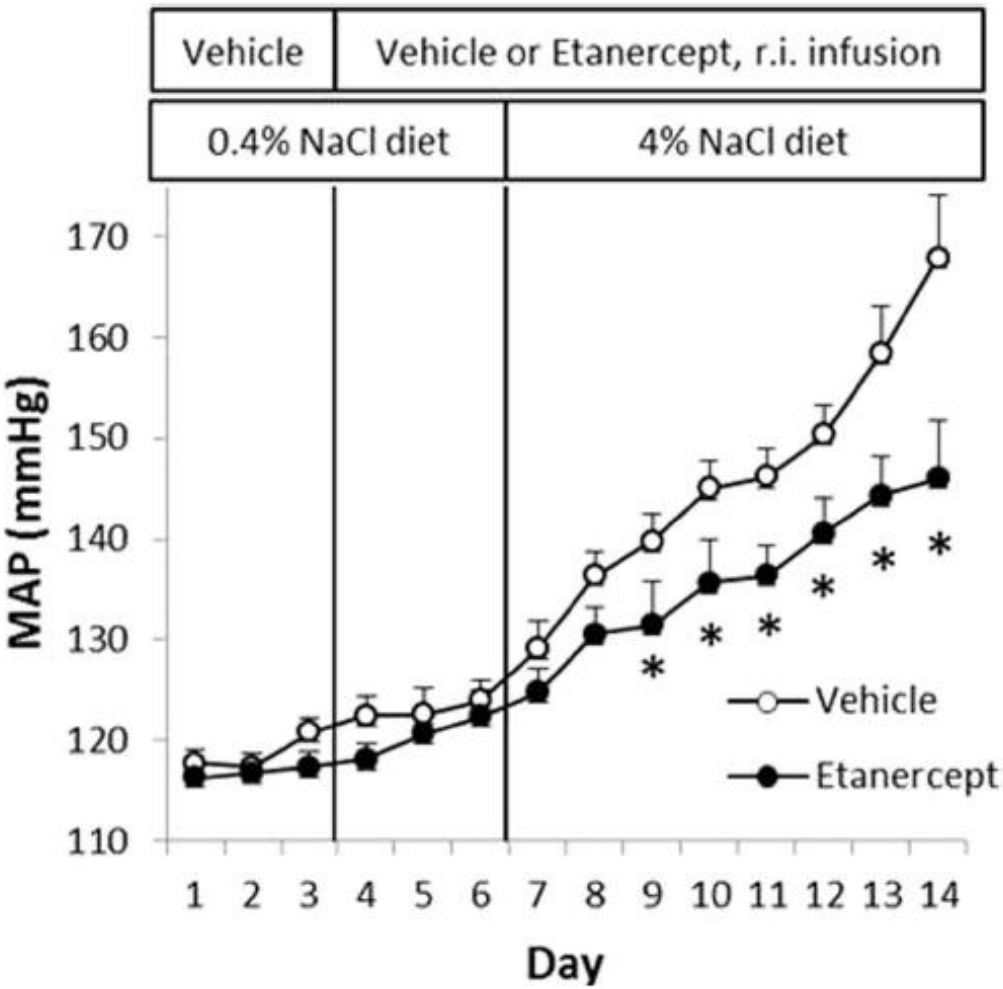
Increased TNF alfa secretion and abundance of TNF alfa in the renal medulla in salt sensitive rats





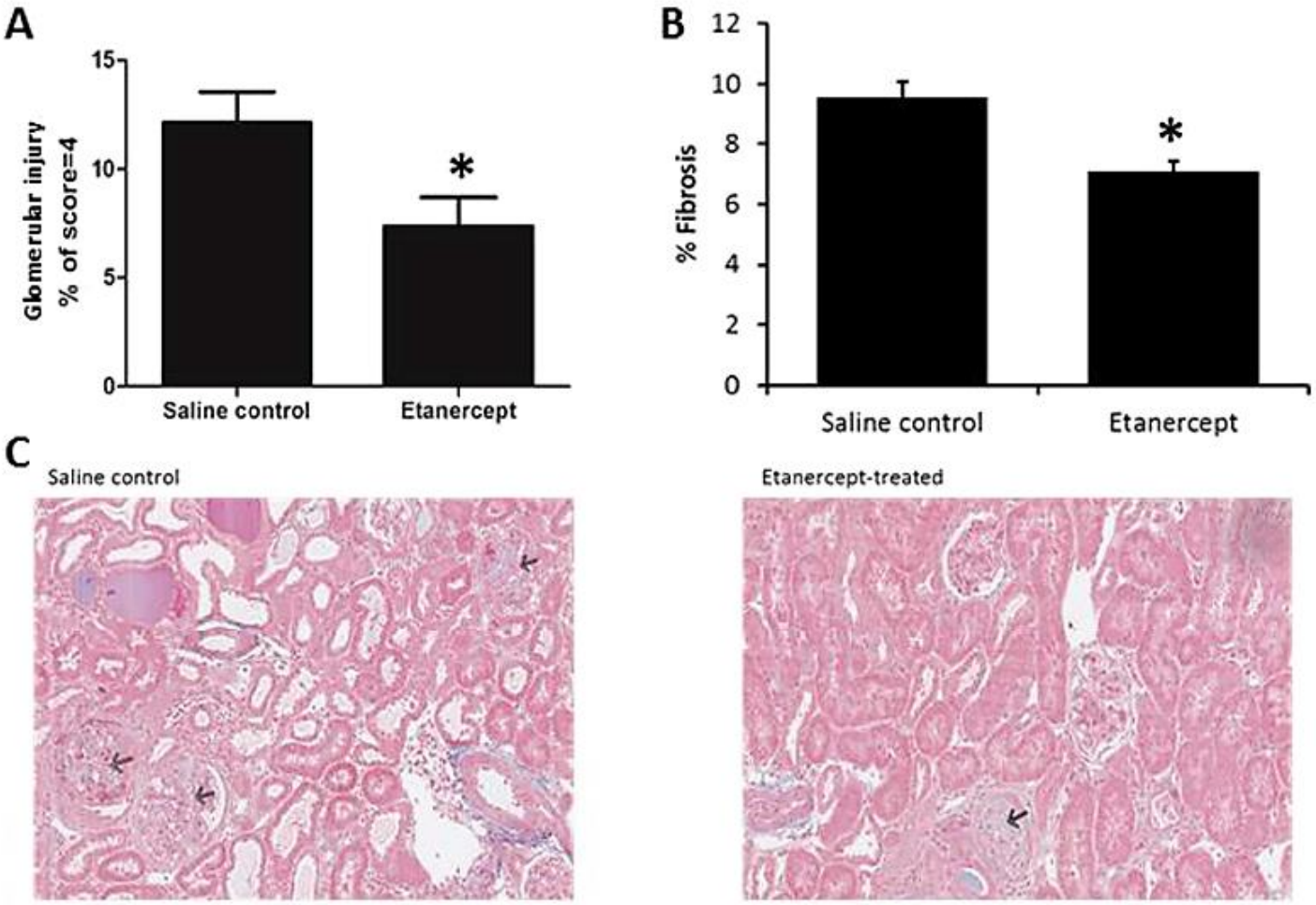
Huang B. et al., SCIENTIFIC REPORTS/6/21960

Etanercept infused directly to the kidney recuses blood pressure in rats with salt sensitive hypertension



Huang B. et al., SCIENTIFIC REPORTS/6/21960

Etanercept infused directly to the kidney reduces glomerular injury and interstitial fibrosis in rats with salt sensitive hypertension



Huang B. et al., SCIENTIFIC REPORTS/6/21960

Ets in the Kidney—Unraveling the Molecular Mechanism Underlying Renal Damage in Salt-Sensitive Hypertension

Joseph C. Gigliotti* and Thu H. Le†

*Department of Integrated Physiology and Pharmacology, Liberty University College of Osteopathic Medicine, Lynchburg, Virginia; and †Department of Medicine, University of Virginia, Charlottesville, Virginia

J Am Soc Nephrol 28: 3131–3133, 2017.
doi: https://doi.org/10.1681/ASN.2017080917

Potential involvement of Ets -1 in the pathogenesis of hypertension associated kidney disease

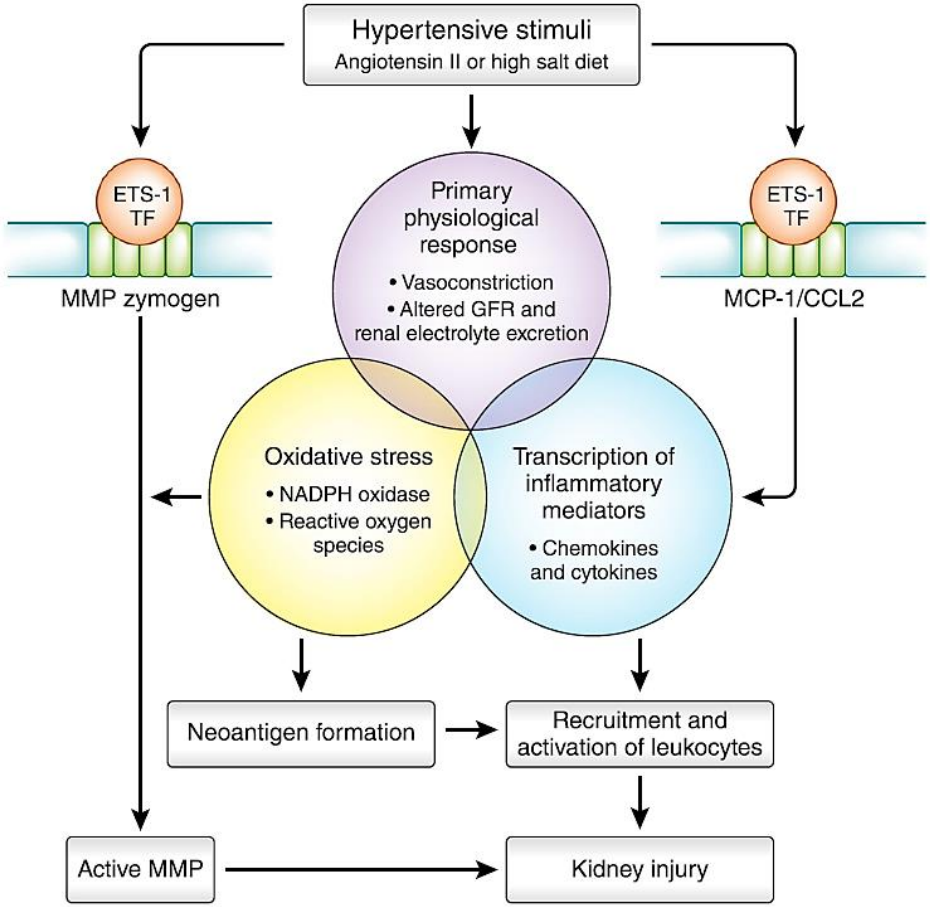


Figure 1. Potential involvement of ETS-1 in the emerging paradigm of the pathophysiology of hypertension-associated kidney injury.

Gigliotti J.C. and Le Th.H, J. Am.Soc. Nephrol., 2017, 28, 3131-3133

BASIC RESEARCH www.jasn.org

Haploinsufficiency of the Transcription Factor *Ets-1* Is Renoprotective in Dahl Salt-Sensitive Rats

Wenguang Feng,* Bo Chen,† Dongqi Xing,* Xingsheng Li,* Huma Fatima,† Edgar A. Jaimes,§ and Paul W. Sanders*‡¶

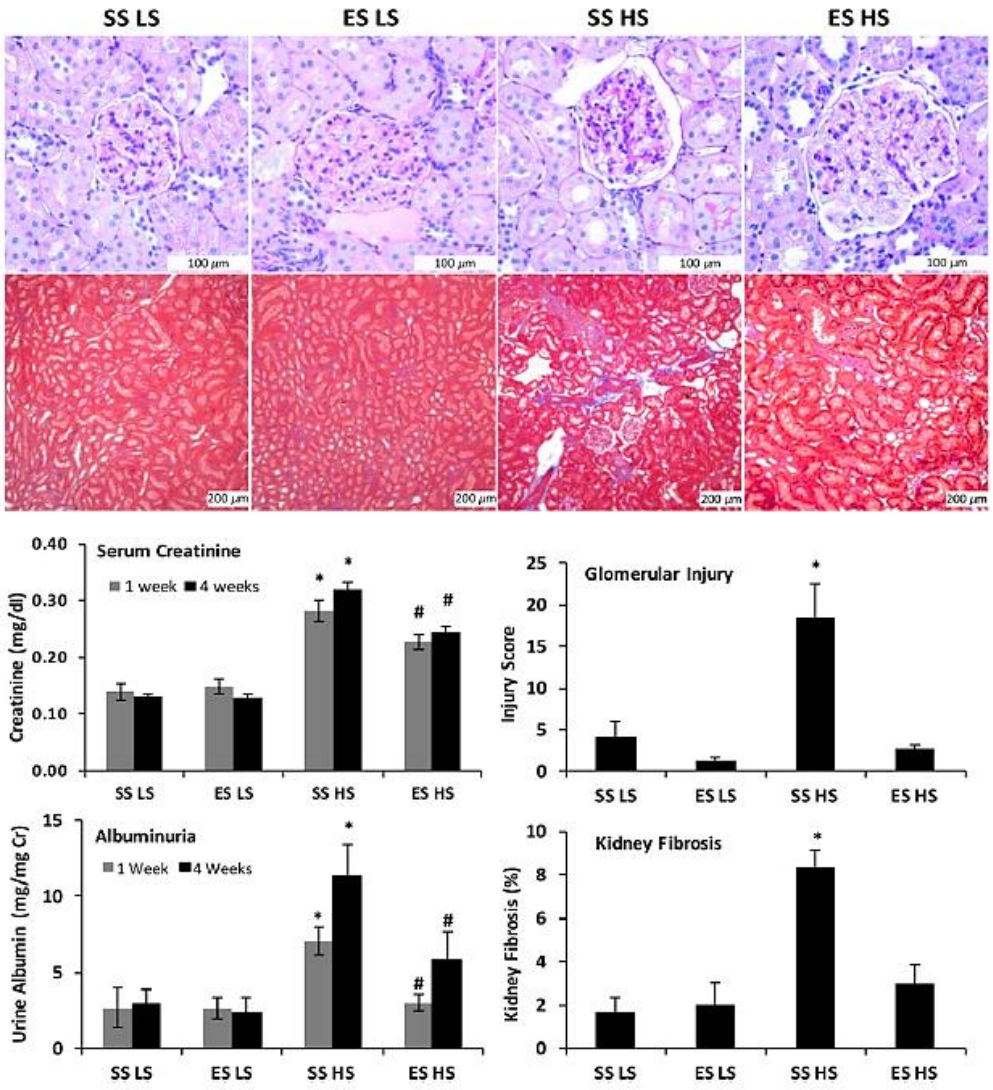
Divisions of Nephrology and Cardiovascular Disease, Departments of *Medicine, †Pathology and ‡Cell, Developmental and Integrative Biology, University of Alabama at Birmingham, Birmingham, Alabama; §Renal Service, Memorial Sloan Kettering Cancer Center, New York, New York; and ¶Department of Medicine, Veterans Affairs Medical Center, Birmingham, Alabama

ABSTRACT

Studies using Dahl salt-sensitive (SS) rats identified specific quantitative trait loci that predispose animals to hypertension-associated albuminuria and kidney injury. We explored the hypothesis that kidney-specific expression of the transcription factor *Ets-1*, located within one of these loci on chromosome 8, mediates glomerular injury in SS hypertension. During the first week on a high-salt diet, SS rats and SS rats with only one functioning *Ets-1* gene (ES rats) demonstrated similar increases in BP. However, serum creatinine concentration, albuminuria, and glomerular expression of ETS-1 and two ETS-1 targets, MCP-1 and MMP2, did not increase as substantially in ES rats as in SS rats. Mean BP subsequently increased further in SS rats and remained higher than that of ES rats for the rest of the study. After 4 weeks of high-salt intake, ES rats still showed a lower mean serum creatinine concentration and less albuminuria, as well as less histologic evidence of glomerular injury and kidney fibrosis, than SS rats did. To investigate the specific contribution of renal *Ets-1*, we transplanted kidneys from ES or SS rats into salt-resistant SS-Chr $13^{BN/McwiCrl}$ (SS-13BN) rats. Within 10 days on a high-salt diet, BP increased similarly in ES and SS allograft recipients, becoming significantly higher than the BP of control isograft recipients. However, mean serum creatinine concentration and albuminuria remained lower in ES allograft recipients than in SS allograft recipients at 2 weeks, and ES allografts showed less glomerular injury and interstitial fibrosis. In conclusion, reduced renal expression of ETS-1 prevented hypertension-associated kidney injury in SS rats.

J. Am. Soc. Nephrol., 2017, 28, 3239 - 3250

Ets-1 mutation significantly reduced kidney injury and improves kidney function during salt-sensitive rats.



Feng W. et al., J. Am. Soc. Nephrol., 2017, 28, 3239 - 3250

Outline of the lecture

- Definition of the salt – sensitive hypertension
- Pathogenesis (classical) of the salt - sensitive hypertension
- New concepts of the salt - sensitive hypertension
- Salt - sensitive hypertension and the risk of CKD development
- Summary of the lecture

Summary

- During the last years several new concepts of salt sensitivity was generated:

1. Skin as a buffer for high salt loading
2. Role of inflammation in the pathogenesis of salt sensitivity
3. Influence of salt on gut microbioma
4. Role of salt in the cytokines production (like TGF alfa) and kidney fibrosis

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Under the Auspices of
ISN, ERA-EDTA, RPS, IFKF and **ISP**

26 - 31 August, 2018

Thank you very much for your attention !!!

Prof. Andrzej Wiecek

Department of Nephrology, Transplantation and Internal Medicine
Medical University of Silesia, Katowice, Poland

e-mail: awiecek@sum.edu.pl