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Epigenetics of the blood pressure reactivity to salt: Is the salt sensitive phenotype correctable?

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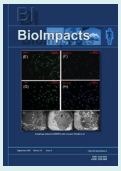

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Summary

Salt sensitivity defines a state characterized by a highly reactive blood pressure to changes in salt intake. The salt-sensitive phenotype is strongly associated with hypertension, visceral adiposity/metabolic syndrome, and ageing. Obesity accounts for around 70% of hypertension in young adults, and 30% to 50% of adult hypertensives carry the salt-sensitive phenotype. It is estimated that the salt-sensitive phenotype is responsible for high blood pressure in over 600 million adults. But is the salt-sensitive phenotype correctable? Interventional, controlled, clinical trials in obese adolescents and young obese adults, demonstrated that weight-reducing lifestyle modifications revert the salt-sensitive to the salt-resistant phenotype, and restored the faulty production of nitric oxide. Correction of the salt-sensitive phenotype lowers the blood pressure by reducing its reactivity to dietary salt. In a random sample of obese adults subjected to lifestyle modifications, those who were salt-resistant at baseline, were also normotensive and failed to further lower their blood pressure despite a 12% drop in body weight. The salt-resistant phenotype protects the metabolically healthy obese from hypertension, even if their salt consumption is comparable to that of salt-sensitive obese. In summary, at early stages, the elevated blood pressure of obesity, is determined by epigenetic changes leading to a state of salt-sensitivity.

Author's Biosketch

Dr. Luigi X. Cubeddu is an MD with a Ph.D. in Pharmacology. Dr. Cubeddu research interests include cardiovascular drug development, hypertension, and neuroendocrinology.

Hypertension (HT) is the most common chronic cardiovascular disease and an important contributor to morbidity and mortality.[1] Worldwide, nearly 30% of adults have blood pressures (BP) ≥140/90 mm Hg, and 45% ≥ 130/80 mm Hg.[2] Salt intake (sodium chloride) is a known risk factor for HT. In population studies, increases of 100-mmol in the daily urinary sodium excretion were associated with higher average for SBP/DBP of 6.0/2.5-mm Hg,[3] and decreases in salt intake, from 142 to 65 mmol/day, with lower averages of 6.7/3.0 mm Hg.[4] These population averages include on the extremes, salt sensitive individuals whose BP is highly responsive to salt (SS), and salt resistant (SR), whose BPs are mostly unreactive to salt. In between, are those with intermediate BP reactivity to salt. Presence of the SS phenotype increases the risk of HT and of cardiovascular and renal disease.[5,6] Based on studies showing that between 30% to 50% of adult hypertensives are SS[7,8]; it is expected that correction of the SS phenotype could prevent HT in over 600 million adults. These numbers are most likely an underestimate, since the threshold employed for defining HT prevalence was BP ≥140/90, instead of ≥130/80 mm Hg.

Despite its high prevalence, there is no simple test for determining SS in clinical practice, nor we understand the epigenetic modifications that trigger the SS phenotype. Although genetic and acquired factors may interplay, the Mendelian forms of SS HT are rare forms of salt-depended HT and cannot account for the high prevalence of the SS phenotype.[9] I propose that the high prevalence of the SS phenotype is largely due to its strong association with adiposity. In this article the term obesity includes overweight. It is estimated that approximately 40% of the world's population (2.9 billion people) has obesity,[10] Obesity contributes up to 75% of the risk for HT,[11,12] and in these subjects, the increase in BP is commonly associated with insulin resistance, atherosclerotic dyslipidemia, and glucose intolerance, a combination of traits known as

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the metabolic syndrome.[11,13] Pivotal studies revealed that the BP of patients with metabolic syndrome is highly reactive to salt.[13,14] The SS phenotype develops in parallel with the increase in BP, and the worsening of overweight/obesity, glucose abnormalities and dyslipidemia.[15,16] In 301 young adults with metabolic syndrome (41.5±0.7 years of age), the SBP of young adult subjects increased in direct proportion with the number of traits present; increasing from 115±1.1 mm Hg in subjects with 1 or 2 traits, to 124±1.5 mm Hg in subjects with three traits, and to 134±2.7 mm Hg in those with four or five traits. Testing for the degree of SS, notoriously, reducing salt intake from usual levels (8.2±0.6 g/day) to a low salt diet (2.3 g/day), lowered the BP by 2±0.6 mm Hg in subjects with one and two traits, by 6.0±1.1 mm Hg in subjects with three traits, and by 9.7±1.3 mm Hg in subjects with four and five traits.[15] Besides, salt restriction decreased the percentage of subjects with BP >140/90 mm Hg from 23.8% to 8.2%.[15] These findings suggest that the increased in BP observed in subjects with overweight and obesity results from the emergence of a SS phenotype, which like HT and its associated metabolic/inflammatory derangements, is not an all or none phenomenon, but a gradually developing condition.

If obesity causes the SS phenotype, would weight loss revert the SS to the SR phenotype? This question was first addressed in SS obese adolescents. It was observed that a 20-week program of caloric restriction without affecting dietary salt intake, achieved a mean 8% reduction in body weight, lowered the BP, and corrected the SS phenotype.[17] Subsequent studies in obese SS adults, demonstrated that a one-year intervention consisting of caloric restriction, increased physical activity and metformin, lowered the BP and corrected the SS phenotype.[18] The lifestyle-metformin intervention achieved an average 13% decrease in body weight and in waist circumference, lowered the SBP/DBP from 126/83 to 118/76 mm Hg, reverted the SS to the SR phenotype, and decreased triglycerides, insulin, and glucose levels. These interventional studies, although on small number of subjects, suggest that the epigenetic changes triggering the SS phenotype can be reversed with weight loss and improvement of its associated metabolic abnormalities. However, no studies on the reversibility on the SS phenotype are available in subjects with long standing obesity, chronic HT, in diabetics, and in individuals with significant chromic kidney disease.

Noteworthy, not all obese have elevated BP, insulin resistance, glucose intolerance, diabetes, and/or metabolic and inflammatory alterations; these subjects have been labelled as the metabolic healthy obese.[19] We propose that the metabolically healthy adults are normotensive because they harbor a SR phenotype. A study assessing the reactivity of the BP to salt in randomly selected obese adults, with comparable levels of obesity and salt intake, showed that the SS obese were older (47.8±2 vs. 39.2±2.8 years), and had higher BPs (129/82 vs.115/76 mm Hg) than the group of SR obese.[18] Further, when the SS and SR obese were exposed to a one-year life-style-metformin intervention, only those who were SS at baseline experienced significant BP lowering at the end of the intervention, despite comparable decreases in weight, and waist circumference in the SS and SR groups. The obese subjects whose BP was unreactive to dietary salt, had normal BPs at baseline and their BPs did not change despite correction of the obesity.[18] These findings suggest that the metabolically healthy obese adults are normotensive because they are phenotypically SR, either because they had not yet develop the epigenetic changes leading to the SS phenotype or because they are genetically protected. The SR phenotype protects the obese subjects from HT; whilst the development of the SS phenotype is responsible for the increase in BP in obese subjects. In summary, in obese SS subjects, the amount of dietary salt and the degree of SS are the major determinants of their BP levels.

The degree and duration of the obesity and of its associated metabolic/inflammatory derangements, may be the defining factors that trigger the change in phenotype. However, what is needed for the SS phenotype develops is unknown. Longitudinal studies assessing the conversion of the SR to the SS phenotype are unavailable, and research on the role of epigenetic changes determining the SS phenotype associated with obesity are just emerging.[20] A recent study revealed a strong expression of SS-related genes in adipose tissue, and a strong of co-expression of SS-related genes with obesity-related genes.[20] Further, in rats, introgression of the chromosome 1 from consomic non-obese SR Brown-Norway rats, into the genome of non-obese Dahl SS rats, significantly reduced SS and renal injury.[21] It would be of interest to establish if the SS phenotype induced by adiposity could be corrected by introgression of chromosome 1 from lean SR rats into the genome of obese SS rats.

In addition to obesity as a cause of SS, a greater prevalence of SS hypertension has also been reported with ageing, and in children of women who experience malnutrition during pregnancy; of interest, conditions associated with increased adiposity.[22] The mechanisms by which obesity triggers the SS phenotype has been extensively studied, in animal models of obesity.[23,24] Epigenetic modifications leading to endothelial dysfunction, imbalances between renal reactive oxygen species and nitric oxide generating systems, impaired renal vasodilation, increased sympathetic activity, adipocyte-derived aldosterone and aldosterone-releasing factors leading to increased aldosterone levels, increase intrarenal sympathetic activity and renin-angiotensin system activation, intrarenal macrophage infiltration and inflammation, and leptin resistance, are some of the proposed mechanisms triggering the SS phenotype in humans and animal models of obesity.[22-24] Epigenetic mechanisms such as increased levels of histone deacetylase

Research Highlights

What do we know?

√ Dietary salt intake increases BP, but the reactivity of BP to salt differs between subjects.

√ Salt sensitivity is defined as an increased reactivity of the individual's BP to salt, characterized by an exaggerated rise in BP with increases in salt intake and significant BP lowering with salt restriction.

√ Salt sensitivity is not an all-or-none phenomenon, but a continuous variable. Thus, the BP increases in direct relation to the amount of dietary salt and the degree of salt sensitivity.

√ Carrying the salt-sensitive phenotype increases the risk of developing HT and cardiovascular diseases.

What should we know?

√ The salt-sensitive phenotype is a highly prevalent condition, it is associated with obesity and HT and may be present in over 600 million subjects with HT.

√ Correction of the salt-sensitive phenotype may greatly reduce the prevalence of HT.

√ Visceral adiposity is a major cause of HT and accounts for nearly 70% of essential HT.

What did we learn?

√ The salt-sensitive phenotype is strongly associated with obesity and metabolic syndrome.

√ In young adults, the salt-sensitive phenotype associated with obesity is correctable by weight-reducing, lifestyle modifications.

√ The high BP in obese subjects is commonly due to the development of a salt-sensitive phenotype. The longer the duration and degree of obesity and its associated metabolic/inflammatory derangements, the greater the prevalence and degree of the SS phenotype.

√ The salt-sensitive phenotype increases the BP because the BP becomes sensitive to dietary salt. Reduced salt intake effectively decreases the BP in SS individuals.

√ The SR phenotype protects obese subjects from high BP. Not all obese have elevated BP or HT, and not all obese are salt sensitive. The BP of the metabolically healthy obese is protected because they harbor the salt-resistant phenotype.

What are we missing?

√ Understanding the epigenetic modifications that determine the salt-sensitive phenotype in human subjects.

√ Practical sensitive and specific tests to diagnose salt sensitivity in clinical medicine.

√ Longitudinal studies on salt-resistant and salt-sensitive phenotypes to determine phenotype changes and factors triggering such changes.

Clinical implications

√ In the absence of practical sensitive and specific tests for diagnosing salt sensitivity, low dietary salt must be prescribed for obese subjects with elevated BP.

√ Weight reduction/lifestyle modifications must be implemented in obese subjects with high BP. Reevaluation of need for salt restriction should be reassessed after weight loss.

√ Compliance with weight reduction prevents the deleterious effects of high BP, avoids unnecessary use of anti-HT medication, and reduces associated healthcare costs.

1 and acetylated histone H3 were observed in high-fat diet-induced obese HT mice.[25] Of interest, malnutrition during pregnancy through changes in DNA methylation, upregulates angiotensin II- AT1 receptor mRNA in the paraventricular nucleus of the hypothalamus. The overstimulation of the AT1 receptor increases renal sympathetic nerve activity leading to the postnatal development of SS hypertension.[26] Faulty NO production was demonstrated in overweight/obese SS human adults when exposed to a high-salt diet. Noteworthy, the faulty NO production was restored after correcting the obesity and reinstating the SR phenotype, by a caloric restriction and lifestyle-metformin intervention.[27,28] Of interest, compared to lean rats, obese rats were more SS and had impaired NO production and greater oxidative stress in their renal medulla.[29,30]

Concluding Remarks

The SS phenotype is strongly associated with overweight and obesity. The high prevalence of elevated BP in overweight/obese human subjects is mainly determined by the development of a SS phenotype. The BP, which is initially unresponsive to customary levels of dietary salt (SR phenotype), becomes responsive, rising in relation with degree of SS and the amount of dietary salt. At least for the race/ethnicities and age groups of the obese SS subjects studied, there is evidence that reductions in body weight revert the SS phenotype to the SR phenotype. In summary, at early stages, the epigenetic modifications that cause the SS phenotype in the obese subject, can be reverted with weight loss and correction of the metabolic and inflammatory abnormalities associated with obesity. In practice, reduced salt intake must be prescribed in obese subjects with elevated BP, and later reassessed after weight loss.

Competing Interests

There are no competing interests.

Ethical Statement

Not applicable.

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References

1. Lawes CM, Vander Hoorn S, Rodgers A. Global burden of blood-pressure-related disease, 2001. *Lancet* **2008**; 371: 1513-8. https://doi.org/10.1016/s0140-6736(08)60655-8
2. Carey RM, Whelton PK. Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Synopsis of the 2017 American College of Cardiology/American Heart Association Hypertension Guideline. *Ann Intern Med* **2018**; 168: 351-8. https://doi.org/10.7326/m17-3203
3. Elliott P, Stamler J, Nichols R, Dyer AR, Stamler R, Kesteloot H, *et al.* Intersalt revisited: further analyses of 24 hour sodium excretion and blood pressure within and across populations. Intersalt Cooperative Research Group. *BMJ* **1996**; 312: 1249-53. https://doi.org/10.1136/bmj.312.7041.1249
4. Sacks FM, Svetkey LP, Vollmer WM, Appel LJ, Bray GA, Harsha D,

et al. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group. *N Engl J Med* **2001**; 344: 3-10. https://doi.org/10.1056/nejm200101043440101
5. Weinberger MH, Fineberg NS, Fineberg SE, Weinberger M. Salt sensitivity, pulse pressure, and death in normal and hypertensive humans. *Hypertension* **2001**; 37: 429-32. https://doi.org/10.1161/01.hyp.37.2.429
6. Mu J, Zheng S, Lian Q, Liu F, Liu Z. Evolution of blood pressure from adolescents to youth in salt sensitivies: a 18-year follow-up study in Hanzhong children cohort. *Nutr J* **2012**; 11: 70. https://doi.org/10.1186/1475-2891-11-70
7. Weinberger MH. Salt sensitivity of blood pressure in humans. *Hypertension* **1996**; 27: 481-90. https://doi.org/10.1161/01.hyp.27.3.481
8. Kotchen TA, Cowley AW, Jr., Frohlich ED. Salt in health and disease--a delicate balance. *N Engl J Med* **2013**; 368: 1229-37. https://doi.org/10.1056/NEJMra1212606
9. Cowley AW Jr. The genetic dissection of essential hypertension. *Nat Rev Genet* **2006**; 7: 829-40. https://doi.org/10.1038/nrg1967
10. Powell-Wiley TM, Poirier P, Burke LE, Després JP, Gordon-Larsen P, Lavie CJ, *et al.* Obesity and Cardiovascular Disease: A Scientific Statement From the American Heart Association. *Circulation* **2021**; 143: e984-e1010. https://doi.org/10.1161/cir.0000000000000973
11. Wilson PW, D'Agostino RB, Sullivan L, Parise H, Kannel WB. Overweight and obesity as determinants of cardiovascular risk: the Framingham experience. *Arch Intern Med* **2002**; 162: 1867-72. https://doi.org/10.1001/archinte.162.16.1867
12. Garrison RJ, Kannel WB, Stokes J, 3rd, Castelli WP. Incidence and precursors of hypertension in young adults: the Framingham Offspring Study. *Prev Med* **1987**; 16: 235-51. https://doi.org/10.1016/0091-7435(87)90087-9
13. Hoffmann IS, Cubeddu LX. Clustering of silent cardiovascular risk factors in apparently healthy Hispanics. *J Hum Hypertens* **2002**; 16 Suppl 1: S137-41. https://doi.org/10.1038/sj.jhh.1001360
14. Uzu T, Kimura G, Yamauchi A, Kanasaki M, Isshiki K, Araki S, *et al.* Enhanced sodium sensitivity and disturbed circadian rhythm of blood pressure in essential hypertension. *J Hypertens* **2006**; 24: 1627-32. https://doi.org/10.1097/01.hjh.0000239299.71001.77
15. Hoffmann IS, Cubeddu LX. Increased blood pressure reactivity to dietary salt in patients with the metabolic syndrome. *J Hum Hypertens* **2007**; 21: 438-44. https://doi.org/10.1038/sj.jhh.1002153
16. Hoffmann IS, Cubeddu LX. Salt and the metabolic syndrome. *Nutr Metab Cardiovasc Dis* **2009**; 19: 123-8. https://doi.org/10.1016/j.numecd.2008.02.011
17. Rocchini AP, Key J, Bondie D, Chico R, Moorehead C, Katch V, *et al.* The effect of weight loss on the sensitivity of blood pressure to sodium in obese adolescents. *N Engl J Med* **1989**; 321: 580-5. https://doi.org/10.1056/nejm198908313210905
18. Hoffmann IS, Alfieri AB, Cubeddu LX. Salt-resistant and salt-sensitive phenotypes determine the sensitivity of blood pressure to weight loss in overweight/obese patients. *J Clin Hypertens (Greenwich)* **2008**; 10: 355-61. https://doi.org/10.1111/j.1751-7176.2008.07609.x
19. Fauchier G, Bisson A, Bodin A, Herbert J, Semaan C, Angoulvant D, *et al.* Metabolically healthy obesity and cardiovascular events: A nationwide cohort study. *Diabetes Obes Metab* **2021**; 23: 2492-501. https://doi.org/10.1111/dom.14492
20. Sabir JSM, El Omri A, Banaganapalli B, Aljuaid N, Omar AMS, Altaf A, *et al.* Unraveling the role of salt-sensitivity genes in obesity with integrated network biology and co-expression analysis. *PLoS One* **2020**; 15: e0228400. https://doi.org/10.1371/journal.pone.0228400
21. Potter JC, Whiles SA, Miles CB, Whiles JB, Mitchell MA, Biederman BE, *et al.* Salt-Sensitive Hypertension, Renal Injury, and Renal Vasodysfunction Associated With Dahl Salt-Sensitive Rats Are Abolished in Consomic SS.BN1 Rats. *J Am Heart Assoc* **2021**; 10: e020261. https://doi.org/10.1161/jaha.120.020261
22. Kawarazaki W, Fujita T. Kidney and epigenetic mechanisms of salt-sensitive hypertension. *Nat Rev Nephrol* **2021**; 17: 350-63. https://doi.org/10.1038/s41581-021-00399-2
23. Johnson RJ, Lanaspa MA, Gabriela Sánchez-Lozada L, Rodriguez-Iturbe B. The discovery of hypertension: evolving views on the role of the kidneys, and current hot topics. *Am J Physiol Renal Physiol* **2015**; 308: F167-78. https://doi.org/10.1152/ajprenal.00503.2014
24. Morris RC, Jr., Schmidlin O, Sebastian A, Tanaka M, Kurtz TW. Vasodysfunction That Involves Renal Vasodysfunction, Not Abnormally Increased Renal Retention of Sodium, Accounts for the Initiation of Salt-Induced Hypertension. *Circulation* **2016**; 133: 881-93. https://doi.org/10.1161/circulationaha.115.017923
25. Choi J, Park S, Kwon TK, Sohn SI, Park KM, Kim JI. Role of the histone deacetylase inhibitor valproic acid in high-fat diet-induced hypertension via inhibition of HDAC1/angiotensin II axis. *Int J Obes (Lond)* **2017**; 41: 1702-9. https://doi.org/10.1038/ijo.2017.166
26. Kawakami-Mori F, Nishimoto M, Reheman L, Kawarazaki W, Ayuzawa N, Ueda K, *et al.* Aberrant DNA methylation of hypothalamic angiotensin receptor in prenatal programmed hypertension. *JCI Insight* **2018**; 3. https://doi.org/10.1172/jci.insight.95625
27. Cubeddu LX, Alfieri AB, Hoffmann IS, Jimenez E, Roa CM, Cubeddu R, *et al.* Nitric oxide and salt sensitivity. *Am J Hypertens* **2000**; 13: 973-9. https://doi.org/10.1016/s0895-7061(00)00283-1
28. Hoffmann IS, Alfieri AB, Cubeddu LX. Effects of lifestyle changes and metformin on salt sensitivity and nitric oxide metabolism in obese salt-sensitive Hispanics. *J Hum Hypertens* **2007**; 21: 571-8. https://doi.org/10.1038/sj.jhh.1002182
29. Quigley JE, Elmarakby AA, Knight SF, Manhiani MM, Stepp DW, Olearzcyk JJ, *et al.* Obesity induced renal oxidative stress contributes to renal injury in salt-sensitive hypertension. *Clin Exp Pharmacol Physiol* **2009**; 36: 724-8. https://doi.org/10.1111/j.1440-1681.2009.05139.x
30. Cowley AW, Jr., Yang C, Zheleznova NN, Staruschenko A, Kurth T, Rein L, *et al.* Evidence of the Importance of Nox4 in Production of Hypertension in Dahl Salt-Sensitive Rats. *Hypertension* **2016**; 67: 440-50. https://doi.org/10.1161/hypertensionaha.115.06280