

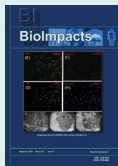


# Epigenetics of the blood pressure reactivity to salt: Is the salt sensitive phenotype correctable?

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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.



**H**ypertension (HT) is the most common chronic cardiovascular disease and an important contributor to morbidity and mortality.<sup>1</sup> Worldwide, nearly 30% of adults have blood pressures (BP)  $\geq 140/90$  mm Hg, and 45%  $\geq 130/80$  mm Hg.<sup>2</sup> 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,<sup>3</sup> and decreases in salt intake, from 142 to 65 mmol/day, with lower averages of 6.7/3.0 mm Hg.<sup>4</sup> 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.<sup>5,6</sup> Based on studies showing that between 30% to 50% of adult hypertensives are SS<sup>7,8</sup>; 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  $\geq 140/90$ , instead of  $\geq 130/80$  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-dependent HT and cannot account for the high prevalence of the SS phenotype.<sup>9</sup> 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,<sup>10</sup> Obesity contributes up to 75% of the risk for HT,<sup>11,12</sup> 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.<sup>11,13</sup> Pivotal studies revealed that the BP of patients with metabolic syndrome is highly reactive to salt.<sup>13,14</sup> The SS phenotype develops in parallel with the increase in BP, and the worsening of overweight/obesity, glucose abnormalities and dyslipidemia.<sup>15,16</sup> In 301 young adults with metabolic syndrome ( $41.5 \pm 0.7$  years of age), the SBP of young adult subjects increased in direct proportion with the number of traits present; increasing from  $115 \pm 1.1$  mm Hg in subjects with 1 or 2 traits, to  $124 \pm 1.5$  mm Hg in subjects with three traits, and to  $134 \pm 2.7$  mm Hg in those with four or five traits. Testing for the degree of SS, notoriously, reducing salt intake from usual levels ( $8.2 \pm 0.6$  g/day) to a low salt diet ( $2.3$  g/day), lowered the BP by  $2 \pm 0.6$  mm Hg in subjects with one and two traits, by  $6.0 \pm 1.1$  mm Hg in subjects with three traits, and by  $9.7 \pm 1.3$  mm Hg in subjects with four and five traits.<sup>15</sup> Besides, salt restriction decreased the percentage of subjects with BP  $>140/90$  mm Hg from 23.8% to 8.2%.<sup>15</sup> 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.<sup>17</sup> 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.<sup>18</sup> 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 chronic 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 metabolically healthy obese.<sup>19</sup> 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 ( $47.8 \pm 2$  vs.  $39.2 \pm 2.8$  years), and had higher BPs ( $129/82$  vs.  $115/76$

mm Hg) than the group of SR obese.<sup>18</sup> Further, when the SS and SR obese were exposed to a one-year lifestyle-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.<sup>18</sup> 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.<sup>20</sup> 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.<sup>20</sup> 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.<sup>21</sup> 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.<sup>22</sup> The mechanisms by which obesity triggers the SS phenotype has been extensively studied, in animal models of obesity.<sup>23,24</sup> 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.<sup>22-24</sup> 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.<sup>25</sup> 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.<sup>26</sup> 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.<sup>27,28</sup> Of interest, compared to lean rats, obese rats were more SS and had impaired NO production and greater oxidative stress in their renal medulla.<sup>29,30</sup>

## 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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