Salt-sensitivity of blood pressure: a paradigm of gene-environment interaction

Pasquale Strazzullo, Alfonso Siani*, Paola Russo*

*Department of Clinical and Experimental Medicine, "Federico II" University of Naples Medical School, Naples, *Institute of Food Science and Technology, National Research Council, Avellino, Italy*

(Ital Heart J 2000; 1 (Suppl 3): S15-S19)

Address:

Prof. Pasquale Strazzullo

Dipartimento di Medicina Clinica e Sperimentale Università degli Studi "Federico II" Via S. Pansini, 5 80131 Napoli E-mail: strazzul@unina.it

The multifactorial origins of hypertension

Arterial hypertension is not a disease in itself but rather a powerful risk factor for cardiovascular and renal disease. The risk associated with hypertension is graded and continuous, starting with blood pressure levels well below the clinically useful but arbitrary definition of hypertension given by the guidelines for the physician[1,2]. While it is true that the higher the blood pressure the greater the individual relative risk of cardiovascular and renal complications, on epidemiological grounds and with regard to public health, the population attributable risk is of even greater interest. In fact, by multiplying the relative risk associated with a certain blood pressure level by the number of people exposed to that level, it may be found that the large number of people affected by the mildest forms of hypertension or just having high-normal blood pressure levels contribute to a large proportion of cardiovascular morbidity and mortality. This is, for instance, the lesson coming from the analysis carried out by the Multiple Risk Factor Intervention Trial Investigators[3]. Accordingly, the study of the genetic causes of hypertension should not focus solely on patients and families with severe forms of hypertension but should aim to unveil the genetic contribution to population blood pressure variability all over the blood pressure range[4].

The growing interest in a number of genes coding for proteins involved at various levels in the metabolic handling of dietary sodium chloride has to be seen within this intellectual framework.

Dietary salt intake as a risk factor for hypertension

The relationship between dietary salt and blood pressure is supported by overwhelming evidence from epidemiological, clinical and experimental studies[5]. The earliest observations on this subject are found in the history of Chinese medicine and date back to about one thousand years BC[6]. A dramatic switch from a low-salt to a progressively salt-enriched diet is believed to have taken place when mankind made the transition from hunting and collecting food to food producing. The agricultural man learned to use salt to preserve food, particularly meat, for long periods of time, with sodium chloride acting as a dehydrator and a preservative against bacterial growth[7,8].

These anthropological considerations led to the concept of maladaptation of blood pressure homeostasis in the face of a major environmental modification which occurred over a relatively short span of human evolution[7]. It is conceivable that a genetic array that had been biologically appropriate for what used to be a low-salt environment became unfavorable once the dietary intake of salt started to rise, in as much as the prevailing physiological challenge for the kidney was no longer conservation but rather quantitative elimination of excess salt.

Although the clinician s interest in dietary salt intake focuses on its role as a determinant of arterial hypertension , the issue of excess salt intake contribution to population variability of blood pressure is scientifically more sound and far more attractive for the clinical geneticist.

Definition and determinants of salt-sensitivity

Salt-sensitivity can be defined as the measurable effect of a sodium chloride load on individual blood pressure levels. The interest in salt-sensitivity stems from the observation that the effect of sodium chloride on blood pressure is heterogeneous within the hypertensive population[9,10] and also among normotensive individuals[11]. Similarly to what has been said for blood pressure, it is quite arbitrary to classify an individual as salt-sensitive or salt-resistant for the very reason that the blood pressure response to a sodium load (or to salt restriction) follows a typical Gaussian curve. Thus, the classifications adopted in most published clinical studies, based on a pre-defined cut-off, fail to provide the correct perception of a truly quantitative phenomenon[9,10]. Several studies have been conducted in an attempt to identify predictors of blood pressure salt-sensitivity, for the assessment of which these studies have relied on either short-term dietary trials or acute sodium loads and volume expansion maneuvers[11].

Although several organs are presumably involved in the blood pressure response to salt, the kidney is both the final track and the fine modulator of the response. According to the well known theory proposed by De Wardener et al.[12], sodium-dependent hypertension is the consequence of an inherited and/or acquired inability of the kidney to excrete a sodium load. In a high sodium environment, the renal defect would determine an increase in extracellular fluid and intrathoracic blood volume that in time may induce an increase in blood pressure.

A number of factors are able to impair the natriuretic ability of the kidney and shift the pressure-natriuresis curve to the right. Hyperactivity of the sympathetic nervous system or of the renin-angiotensin-aldosterone axis, insulin resistance, reduced production of atrial natriuretic peptides and other natriuretic substances, functional alterations of renal tubular ion transport systems, are among the factors involved in renal sodium handling acknowledged as potential acquired contributors to salt-sensitivity of blood pressure. The excess sympathetic activity associated with stressful lifestyles and the reduced sensitivity to insulin associated with overweight or obesity are good examples of these mechanistic pathways. Excess noradrenaline released at the sympathetic end-terminals within the kidney as well as the hyperinsulinemia associated with insulin resistance have the power to enhance tubular sodium reabsorption and shift the pressure-natriuresis curve to the right.

Genetic versus acquired causes of salt-sensitivity and their interaction

An intriguing question one has to ask is to what extent these factors are acquired causes of impairment in renal natriuretic capacity, as it appears, and to what degree they are under the influence of genetic variation. The Trp64Arg polymorphism in the beta$_3$-adrenergic receptor, for instance, is associated with predisposition to abdominal adiposity, hypertension and possibly insulin resistance[13,14]. In turn, the reduction in renal sodium excretory ability consequent to insulin resistance, hyperinsulinemia and sympathetic activation may be seen, at least to some extent, as genetically determined.

Hypertension due to single gene abnormalities is a rare condition; nevertheless, a number of monogenic forms following a Mendelian type of inheritance have been described. Classic linkage analysis has located the genes implicated in glucocorticoid-remediable aldosteronism[15], in Liddle s syndrome[16] and in the apparent mineralocorticoid excess syndrome[17]. It is noteworthy that all these forms of monogenic hypertension, due to well characterized genetic abnormalities, are related to an altered renal sodium handling. Much more frequently arterial hypertension is caused by the synergistic action of multiple environmental and genetic factors. Thus, its phenotypic expression derives from the interaction between a large number of susceptibility genes (polygenes) of variable penetrance (Table I)[18-46] and various other influences partly related to lifestyle (e.g. nutritional factors, physical activity, etc.). Considerable and growing efforts are being made in order to identify candidate genes ; as a consequence, the number of polymorphic variants of genes possibly implicated in high blood pressure is continuously in-

Table I. Candidate genes for arterial hypertension.

Angiotensin-converting enzyme*[18,19]
Angiotensinogen*[20,21]
Angiotensin II type 1 receptor[22]
Atrial natriuretic peptide*[23]
Natriuretic peptide clearance receptor*[24]
Aldosterone synthase*[25,26]
Na^+/K^+ ATPase*[27]
β subunit epithelial sodium channel*[28]
α-adducin*[29,30]
α_{1B}-adrenergic receptor[31]
α_2-adrenergic receptor*[32]
β_2-adrenergic receptor*[33]
β_3-adrenergic receptor*[13,34]
Glucocorticoid receptor[35]
Insulin receptor[36]
Glucagon receptor*[37]
Lipoprotein lipase[38]
Pancreatic phospholipase[39]
Growth hormone[40]
Complement C3F[41]
Type 1A dopamine receptor[31]
Endothelial nitric oxide synthase*[42]
SA gene[43]
G-protein β_3 subunit*[44]
Prostacyclin synthase[45]
Hp1-haptoglobin*[46]

* genes more likely to be involved in the salt-sensitivity of blood pressure.

creasing. Many of these variants are associated with a functional alteration.

The interaction between functional mutations associated with altered renal sodium handling and changes in dietary sodium intake represents a paradigm for the study of gene-environment interaction. Figure 1 shows a schematic frame of the complex multifactorial interactions between genes, environment, demographic and metabolic factors implicated in salt-sensitivity of blood pressure. A reasonable working hypothesis is that each one of a number of less severe mutations in genes directly or indirectly related to renal sodium handling gives a contribution to the individual blood pressure sensitivity to changes in sodium intake.

Candidate genes possibly contributing to salt-sensitivity are listed in table I[18-46]. Attention has been focused on genes involved in the regulation of the renin-angiotensin axis, in transmembrane ion exchange, in the modulation of sympathetic activity and in other metabolic pathways relevant to sodium handling. In a study of over 1500 subjects participating in the phase II of the Trials of Hypertension Prevention, Hunt et al.[21] showed that individuals homozygous for a mutation in the angiotensinogen gene had a significantly better response to sodium restriction as compared to individuals with the wild-type genotype. The frequence of the insertion allele of the angiotensin-converting enzyme gene was higher in salt-sensitive than in salt-resistant Japanese hypertensive patients[19]. An increased frequence of polymorphic variants of the atrial natriuretic peptide gene has been identified among hypertensive African-Americans, supporting the hypothesis that a deficient atrial natriuretic peptide secretion contributes to elevated salt-sensitivity in people of African descent[23]. Recently, Sarzani et al.[24] detected, in a population of obese hypertensive Caucasian patients, a biallelic (A/C) polymorphism at position 55 of the promoter of the natriuretic peptide clearance receptor: the C(-55) variant was associated with lower atrial natriuretic peptide levels and higher blood pressure levels.

The association between polymorphic variants of α- and β-adrenergic receptors and salt-sensitivity has been the object of investigation. A linkage between the β_2-adrenergic receptor locus and the blood pressure response to sodium load was suggested by Svetkey et al.[33] in a study on Afro-American families; moreover, Lockette et al.[32] showed a significant difference in a restriction fragment length polymorphism for the α_2-adrenoceptor between black and white hypertensive patients. In a large population sample of middle aged men (The Olivetti Prospective Heart Study), we have recently observed that the carriers of the Trp64Arg polymorphism of the β_3-adrenergic receptor had significantly higher levels of plasma aldosterone in comparison with the carriers of the wild type Arg64Arg allele[13]. In the same population sample, we have also found that the Gly40Ser mutation of the glucagon receptor gene was associated with significantly increased sodium reabsorption at the proximal tubule and high blood pressure (Strazzullo P. et al., unpublished data).

Bianchi and coworkers[29,30] have reported convincing evidence for a role of genetic variants of the α-adducin gene associated with functional alterations of the Na^+-K^+ pump, higher blood pressure and enhanced sensitivity to diuretics. Evidence is also accumulating in favor of a significant contribution by variants of the epithelial sodium channel gene at least in some populations[28], leading to the conclusion that the renal tubule might be the site of multiple dysfunction potentially relevant to salt-sensitivity of blood pressure.

This very brief and inevitably incomplete review of the multifaceted background of blood pressure salt-sensitivity supports the contention of a complex interaction between a number of genes influencing renal sodium handling and several metabolic, nutritional and neurohormonal factors converging on the same final pathway[47]: the final result of these multiple interactions is an impairment in the natriuretic ability of the kidney with a resultant shift in the pressure-natriuresis curve to the right[48]. The elucidation of the precise role of the gene products involved in this process is a promising approach to the comprehension of the molecular bases of blood pressure regulation.

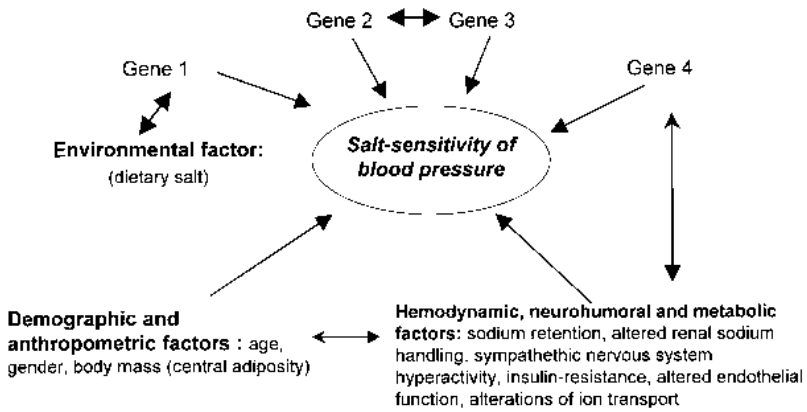

Figure 1. *Interaction between genetic and acquired factors associated with salt-sensitivity of blood pressure.*

References

1. International Task Force for Prevention of Coronary Heart Disease. Coronary heart disease: reducing the risk. Nutr Metab Cardiovasc Dis 1998; 8: 205-71.
2. WHO-ISH Guidelines Subcommittee. 1999 World Health Organization-International Society of Hypertension Guidelines for the management of hypertension. J Hypertens 1999; 17: 151-83.
3. Stamler J, Stamler R, Neaton JD. Blood pressure, systolic and diastolic, and cardiovascular risks: US population data. Arch Intern Med 1993; 153: 598-615.
4. Harrap SB. Genetics. In: Oparil S, Weber MA, eds. Hypertension: a companion to Brenner and Rector s The Kidney. Philadelphia, PA: WB Saunders, 2000: 29-42.
5. Siani A, Guglielmucci F, Farinaro E, Strazzullo P. Increasing evidence for the role of salt and salt-sensitivity in hypertension. Nutr Metab Cardiovasc Dis 2000; 10: 93-100.
6. Huang Ti Nei Ching Su Wen (1000 BC) from the translation by Wang Ping (AD 762).
7. Eaton SB, Konner M. Paleolithic nutrition. A consideration of its nature and current implications. N Engl J Med 1985; 312: 283-9.
8. Blyth WB. Salt and water in culture and medicine. N Engl J Med 1994; 330: 1909-10.
9. Luft FC, Weinberger MH. Heterogeneous responses to changes in dietary salt intake: the salt-sensitivity paradigm. Am J Clin Nutr 1997; 65 (Suppl): 612S-617S.
10. Galletti F, Ferrara I, Stinga F, Iacone R, Noviello F, Strazzullo P. Evaluation of a rapid protocol for the assessment of salt sensitivity against the blood pressure response to dietary sodium chloride restriction. Am J Hypertens 1997; 10: 462-6.
11. Miller JZ, Weinberger MH, Dougherty SA, Fineberg NS, Christian GC, Grim CE. Heterogeneity of blood pressure response to dietary sodium restriction in normotensive adults. J Chron Dis 1987; 40: 245-50.
12. De Wardener HE, Clarkson EM, Bitensky L, MacGregor GA, Alaghband- Zadeh J, Chayen J. Effect of sodium intake on ability of human plasma to inhibit renal Na^+-K^+-adenosine triphosphatase in vitro. Lancet 1981; 1: 411-2.
13. Strazzullo P, Siani A, Barba G, et al. Relationship between plasma aldosterone, insulin resistance and beta$_3$-AR Trp64Arg gene polymorphism in a 20-year follow-up study. (abstr) In: Proceedings of the 10th European Meeting on Hypertension. Goteborg, 2000: S121.
14. Arner P, Hoffstedt J. Adrenoceptor genes in human obesity. J Intern Med 1999; 245: 667-72.
15. Lifton RP, Dluhy RG, Powers M, et al. A chimeric 11 beta-hydroxylase/aldosterone synthase gene causes glucocorticoid-remediable aldosteronism and human hypertension. Nature 1992; 355: 262-5.
16. Shimkets RA, Warnock DG, Bositis CM, et al. Liddle s syndrome: heritable human hypertension caused by mutations in the beta sub-unit of the epithelial sodium channel. Cell 1994; 79: 407-14.
17. Mune T, Rogerson FM, Nikkila H, Agarwal AK, White PC. Human hypertension caused by mutations in the kidney isozyme of 11 beta-hydroxysteroid dehydrogenase. Nat Genet 1995; 10: 394-9.
18. Fornage M, Amos CI, Kardia S, Sing CF, Turner ST, Boerwinkle E. Variation in the region of the angiotensin-converting enzyme gene influences inter-individual differences in blood pressure levels in young white males. Circulation 1991; 97: 1773-9.
19. Hiraga H, Oshima T, Watanabe M, et al. Angiotensin I converting enzyme gene polymorphism and salt sensitivity in essential hypertension. Hypertension 1999; 27: 569-72.
20. Jeunemaitre X, Soubrier F, Kotelevtsev YV, et al. Molecular basis of human hypertension: role of angiotensinogen. Cell 1992; 71: 169-80.
21. Hunt SC, Cook NR, Oberman A, et al. Angiotensinogen genotype, sodium reduction, weight loss, and prevention of hypertension. Trials of Hypertension Prevention, phase II. Hypertension 1998; 32: 393-401.
22. Bonnardeaux A, Davies E, Jeunemaitre X, et al. Angiotensin II type 1 receptor gene polymorphisms in human essential hypertension. Hypertension 1994; 24: 63-9.
23. Rutledge DR, Sun Y, Ross EA. Polymorphism within the atrial natriuretic peptide gene in essential hypertension. J Hypertens 1995; 13: 953-5.
24. Sarzani R, Dess -Fulgheri P, Salvi F, et al. A novel promoter variant of the natriuretic peptide clearance receptor gene is associated with lower atrial natriuretic peptide and higher blood pressure in obese hypertensives. J Hypertens 1999; 17: 1301-5.
25. Holland OB, Carr B. Modulation of aldosterone synthase messenger ribonucleic acid levels by dietary sodium and potassium and by adrenocorticotropin. Endocrinology 1993; 132: 2666-73.
26. Brand E, Schorr U, Ringel J, Beige J, Distler A, Sharma AM. Aldosterone synthase gene (CYP11B2) C-344T polymorphism in Caucasians from the Berlin Salt-Sensitivity Trial (BeSST). J Hypertens 1999; 17: 1563-7.
27. Perusse L, Deriaz O, Dionne FT, et al. Association and linkage analyses of the alpha and beta genes of the sodium-potassium ATPase with age-related changes in blood pressure. (abstr) Am J Hum Genet 1994; 55: 199A.
28. Baker EH, Dong YB, Sagnella GA, et al. Association of hypertension with T594M mutation in beta subunit of epithelial sodium channels in black people resident in London. Lancet 1998; 351: 1388-92.
29. Casari G, Barlassina C, Cusi D, et al. Association of the alpha-adducin locus with essential hypertension. Hypertension 1995; 25: 320-6.
30. Glorioso N, Manunta P, Filigheddu F, et al. The role of α-adducin polymorphism in blood pressure and sodium handling regulation may not be excluded by a negative association study. Hypertension 1999; 34: 649-54.
31. Krushkal J, Xiong M, Ferrel R, et al. Linkage and association of adrenergic and dopamine receptor genes in the distal portion of the long arm of chromosome 5 with systolic blood pressure variation. Hum Mol Genet 1991; 7: 1379-83.
32. Lockette W, Ghosh S, Farrow S, et al. Alpha$_2$ adrenergic receptor gene polymorphism and hypertension in blacks. Am J Hypertens 1995; 4: 390-4.
33. Svetkey LP, Chen YT, McKeown SP, Preis L, Wilson AF. Preliminary evidence of linkage of salt sensitivity in black Americans at the β_2-adrenergic receptor locus. Hypertension 1997; 29: 918-22.
34. Fujisawa T, Ikegami H, Yamato E, et al. Trp64Arg mutation of β_3-adrenergic receptor in essential hypertension. Insulin resistance and the adrenergic system. Am J Hypertens 1997; 10: 101-5.
35. Watt GC, Harrap SB, Foy CJ, et al. Abnormalities of glucocorticoid metabolism and the renin-angiotensin system: a four corners approach to the identification of genetic determinants of blood pressure. J Hypertens 1992; 10: 473-82.
36. Ying LH, Zee RY, Griffiths LR, Morris BJ. Association of a RFLP for the insulin receptor gene, but not insulin, with essential hypertension. Biophys Biochem Res Commun 1991; 181: 486-92.
37. Brand E, Bankir L, Plouin PF, Soubrier F. Glucagon receptor gene mutation (Gly40Ser) in human essential hypertension: the PEGASE study. Hypertension 1999; 34: 15-7.
38. Wu DA, Ku X, Warden CH, et al. Quantitative trait locus mapping of human blood pressure to a genetic region at or near the lipoprotein lipase gene locus on chromosome 8p22. J Clin Invest 1996; 97: 2111-8.

39. Frossard PM, Lestringant GG. Association between a dimorphic site on chromosome 12 and clinical diagnosis of hypertension in three independent populations. Clin Genet 1995; 48: 284-7.
40. Julier C, Delepine M, Keavney B, et al. Genetic susceptibility for human familial essential hypertension in a region of homology with blood pressure linkage on rat chromosome 10. Hum Mol Genet 1997; 6: 2077-85.
41. Schaadt O, Sorensen H, Krogsgaard AR. Association between the C3F-gene and essential hypertension. Clin Sci 1981; 61: 363S-365S.
42. Miyamoto Y, Saito Y, Kajiyama N, et al. Endothelial nitric oxide synthase gene is positively associated with essential hypertension. Hypertension 1998; 32: 3-8.
43. Iwai N, Ohmichi N, Hanai K, Nakamura Y, Kinoshita M. Human SA gene locus as a candidate locus for essential hypertension. Hypertension 1994; 23: 375-80.
44. Siffert W, Rosskopf D, Siffert G, et al. Association of a human G-protein $beta_3$ subunit variant with hypertension. Nat Genet 1998; 18: 45-8.
45. Nakayama T, Soma M, Kanmatsuse K. Organization of the human prostacyclin synthase gene and association analysis of a novel CA repeat in essential hypertension. Adv Exp Med Biol 1997; 433: 127-30.
46. Weinberger MH, Miller JZ, Fineberg NS, Luft FC, Grim CE, Christian JC. Association of haptoglobin with sodium sensitivity and resistance of blood pressure. Hypertension 1987; 10: 443-6.
47. Cowley AWJ. Genetic and non-genetic determinants of salt sensitivity and blood pressure. Am J Clin Nutr 1997; 65: 587S-593S.
48. Guyton AC. The surprising kidney-fluid mechanism for pressure control: its infinite gain! Hypertension 1990; 16: 725-30.