Genetic and nongenetic determinants of salt sensitivity and blood pressure$^{1,2}$

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**ABSTRACT** Salt sensitivity is characterized by an alteration of kidney function that necessitates higher arterial pressure to excrete a given amount of sodium and is expressed as a reduction in the slope of the pressure-natriuresis relation. Excess renal exposure to catecholamines, angiotensin II, aldosterone, and other mineralocorticoids all reduce the sensitivity of the pressure-natriuretic relation and lead to salt sensitivity. Inhibition of these pathways has opposite effects, as do excess circulating atrial natriuretic peptide and overactivity of various intrarenal paracrine systems, including vasodilator and natriuretic products of arachidonic acid metabolism, such as prostaglandin E$_2$ and kinins. Salt sensitivity can also be inherited and ongoing studies are attempting to identify the genes that contribute to this trait. Abnormalities of renal function of Dahl salt-sensitive rats appear to precede the hypertension resulting from high salt intake. Although polymorphic differences have been identified between the Dahl salt-sensitive rat and normotensive rats, the specific genes contributing to the salt sensitivity have not yet been determined. *Am J Clin Nutr* 1997;65(suppl):587S-93S.

**KEY WORDS** Salt sensitivity, hypertension, kidney, genes

**INTRODUCTION**

Much has been learned about the mechanisms responsible for the relation between salt intake and arterial blood pressure, and before discussing the determinants of salt-sensitive hypertension, it is appropriate to briefly review these mechanisms. I introduce this subject with an early study published by Strauss et al (1) in 1958 in which the daily relation between sodium intake and renal excretion was determined in humans subjected to a step increase of salt intake from 10 to 150 mmol/d. In this study, 5 d were required before the rate of sodium excretion became equal to the rate of sodium intake (ie, until sodium balance was achieved) (Figure 1). In this and other studies, it was shown that the amount of sodium and water retained with such an increase of sodium intake leads to a body weight increase of nearly 1 kg (2). These data present the focus of this conference: what mechanisms allow us to achieve sodium and water balance after a step increase of sodium intake, and how do alterations of these mechanisms lead to salt sensitivity?

Some people can effectively excrete increasing amounts of salt without an increase in arterial blood pressure and others cannot. The challenge is to distinguish those who can (salt insensitive) from those who cannot (salt sensitive). In animals this can be readily determined experimentally, but such measurements in the general human population are neither technically nor economically feasible. Much of the work that has been carried out in this area has been directed at finding simple biological markers that can predict salt sensitivity.

**MECHANISMS OF SODIUM HOMEOSTASIS**

Many known physiologic mechanisms allow us to respond to increased salt intake (Figure 2) (3). An increase in salt intake results in a reduction in the activity of the renin-angiotensin-aldosterone system (salt-retaining hormones) and an increase in the release of atrial natriuretic peptides (salt-losing hormones). Each of these systems interacts in turn with other paracrine systems within the kidney, such as the kallikrein-kinin system and prostaglandins, which either enhance or buffer the responses. In addition, an increase in salt intake results in a reduction in the sympathetic nerve activity to the kidneys. The net effect of these responses is an increased daily excretion of sodium.

Physical factors such as plasma colloid oncotic pressure (COP) and renal arterial blood pressure have an important influence on sodium excretion. Dilution of plasma proteins reduces COP within the renal capillaries, which increases glomerular filtration and reduces tubular reabsorption of sodium and water. However, the most important physical factor related to the long-term achievement of sodium and water balance is the arterial blood pressure in the kidneys. We have long known that an increase in arterial blood pressure to the kidney results in an increased excretion of sodium and water, a phenomenon known as pressure natriuresis (diuresis). The kidney’s response to changes of arterial pressure defines the salt sensitivity of individuals.

Normally, an increase of daily sodium intake is excreted and a minimal rise of blood pressure results (4). The relation between arterial pressure and sodium and water excretion as daily sodium intake is increased is illustrated in Figure 3. After 3–4 d, when a steady state has been achieved, the daily sodium and water intake must equal the urine flow and sodium excretion (minus extrarenal sources of loss). When this steady state relation is plotted, as seen in Figure 3, it is normally observed

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that mean arterial pressure changes little despite sodium intake ranging from one-half normal (point C) to six times normal (point B). Thus, "salt sensitivity" is defined by the observed changes of arterial pressure as daily salt intake is changed, which has been called by Guyton (4) the "chronic pressure-natriuresis relationship." All the mammals that we and others have studied (dogs, rabbits, and rats) exhibit this response (3). Weinberger et al (5) showed that the same is true in normal human subjects by strapping bags of saline on the subjects' backs to enable achievement of a daily sodium intake of nearly 1500 mmol/d by intravenous infusion. Arterial blood pressure appears generally to be insensitive to salt, at least for several weeks. The effects of a high salt intake in humans over months (or longer) remains to be determined in a well-controlled prospective study.

**EXPERIMENTALLY INDUCED SALT SENSITIVITY**

Under certain conditions, arterial pressures rise significantly as salt intake is slowly increased (salt sensitivity). One of the most commonly studied animal models of salt-sensitive hypertension is illustrated in Figure 4 (6). In this model, from two-thirds to seven-eighths of the total renal mass is surgically removed. This reduction tends to cause the animals to be uremic but with a low-to-normal–salt diet they are still not hypertensive. When sodium intake is increased to two to three times normal, arterial pressure rises to hypertensive levels.

In this model, salt sensitivity is related to the compromised excretory function of the kidneys. Apparently the only way for renal excretion to rise as high as salt intake is with increased arterial blood pressure and increased excretion via the mechanism of pressure natriuresis and diuresis. This experimental model of salt-sensitive hypertension has been studied in great detail in rats and dogs, and much has been learned about the responses that occur when the kidney has a reduced capacity to excrete a salt and water load. Sodium and water retention initially expand blood volume and lead to elevation of cardiac output (6). This then leads to a gradual increase in total peripheral resistance of the systemic circulation, a phenomenon known as long-term flow autoregulation (7). The rise of total resistance is eventually sustained by structural changes in the heart and systemic vasculature, such as hypertrophy and microvascular rarefaction (the loss of small blood vessels) (8).

**THE KIDNEY AS THE COMMON ELEMENT IN SALT-SENSITIVE FORMS OF HYPERTENSION**

Nearly 30 y ago Guyton and Coleman (9) proposed that if an increase in arterial pressure could produce sustained elevations in urine flow and sodium excretion through the mechanism of pressure diuresis, then the system would have an infinite gain
for the long-term control of arterial pressure by regulating blood volume. Whenever arterial pressure is elevated, pressure natriuresis enhances the excretion of sodium and water until blood volume is reduced sufficiently to return arterial pressure to control values (Figure 5). According to this well-supported hypothesis, hypertension can develop only when something impairs the excretory ability of the kidney and shifts the relation between sodium excretion and arterial pressure toward higher values (3).

Although there is strong evidence that the kidney is the final common pathway in the long-term control of pressure (3), the initial abnormality of the kidney need not be intrinsic to the development of hypertension (10). Circulating hormones such as angiotensin II, aldosterone, atrial natriuretic peptide, renal sympathetic nerve activity, and others represented in Figures 2 and 5 have an important influence on the pressure-natriuresis relation and lead to various forms of hypertension. Therefore, a variety of factors can lead to a reduction of renal excretory function and result in hypertension.

The influence of many of the neural and hormonal control systems on the pressure-natriuresis relation and salt sensitivity has been studied in great detail over the past 20 y. In a series of studies carried out in anesthetized rats in which the amount of circulating hormones to the kidneys was controlled by infusion, the relation between renal perfusion pressure and the excretion of sodium and water was systematically determined under various conditions (11). The effects of changes of renal arterial perfusion pressure on excretion were quantified in response to different hormones and nerve activity. As shown in Figure 6, sodium excretion nearly doubled for every 10-mm Hg rise of arterial pressure in volume-expanded rats. However, in volume-depleted (hydrogenic) rats, this relation was significantly attenuated as represented by the flattened curve. Salt sensitivity can be predicted in this figure under a variety of neural and hormonal states. For example, when going from a low salt intake (where extracellular volume is reduced) to a high salt intake, arterial pressure normally does not change much. Thus, it is possible to excrete higher amounts of salt with a small increase in blood pressure (see the steep broken line connecting the flat curve with the steep curve in the upper graph). This predicts the long-term chronic relation between sodium intake and arterial pressure that was shown in Figure 5 (sometimes referred to as the chronic renal function relation).

From such studies, we showed how changes of various hormones and the renal sympathetic nerves influence the acute pressure-natriuresis relation and thereby predict salt sensitivity to long-term changes in sodium intake. Factors that shift the steepness of this relation downward and to the right are therefore those that result in salt-sensitive forms of hypertension (high aldosterone, high adrenergic hormones, high COP, low prostaglandin E2, low kinins, and low atrial natriuretic factor). These are largely sodium-retaining hormones and paracrine systems that influence tubular reabsorption of filtered sodium.

The chronic pressure-natriuresis relation can also be shifted in the opposite direction. Such observations in acute studies would predict that if the factors that shift the relation upward are sufficiently suppressed (low aldosterone, low adrenergic hormones, and low COP) or if factors that enhance natriuresis (prostaglandin F2, high kinins, and high atrial natriuretic factor) begin to predominate, arterial pressure would be reduced as daily salt intake was increased. These predictions are particularly interesting in that arterial pressure in human subjects (5) and rats (12) is sometimes reduced when salt intake is increased. In normal Sprague-Dawley rats, angiotensin concentrations were reduced from 21 to 7 ng/L as daily salt intake was increased by intravenous infusion (13). This enabled sodium and water to be excreted at a reduced mean arterial pressure, as shown by the decrease of 10 mm Hg. However, when this study was repeated in rats in which the renin-angiotensin system was

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FIGURE 4. Hemodynamic responses to an increase in salt intake from 0.1% to 4% of dietary intake in hypertensive rats with reduced renal mass. Mean arterial pressure (MAP) and the percentage change from control in cardiac index and total peripheral resistance (TPR) are shown during the control period (con) with 0.1% NaCl and at 8 and 96 h and 6 wk with 4% NaCl. *Significantly different from control, P < 0.05. Data are regraphed from results presented in reference 6.

FIGURE 5. Relation between arterial pressure and renal function in normal and hypertensive animals. When arterial pressure is elevated, pressure natriuresis would result in the excretion of sodium and water until blood volume is decreased enough to return arterial pressure to control values. The relation between sodium excretion and arterial pressure is blunted or shifted to a higher pressure in every hereditary and experimental model of hypertension studied. ALI, angiotensin II; ALDO, aldosterone; Dahl S, Dahl salt-sensitive rats; DOCA, deoxycorticosterone acetate; MAP, mean arterial pressure; RRM, reduced renal mass; SHR, spontaneously hypertensive rats; TGR, transgenic rats. From reference 10.
FIGURE 6. Ability of acute renal function curves to predict chronic renal function curves. ALDO, aldosterone; ANF, atrial natriuretic factor; ANG II, angiotensin II; COP, colloid osmotic pressure; PGE₂, prostaglandin E₂; UNaV, urinary sodium excretion. Reproduced with permission from the American Physiological Society (3).

prevented from decreasing with high salt intake by the continuous intravenous infusion of angiotensin II, the rats became salt sensitive (Figure 7).

A similar decrease in arterial pressure was observed by Ott et al (12); thus, there are mechanisms that enable the balance of salt intake and excretion to be achieved at a lower-than-normal renal perfusion pressure. In the study by Ott et al, mean arterial pressure decreased from 133 to 121 mm Hg as daily sodium intake was increased. In animals such decreases in pressure in response to increased salt intake have been observed only when salt intake is increased from very low amounts (eg, < 0.1% of daily sodium intake). As reflected in Figure 6, such changes are predicted under certain conditions and appear to be determined by the sensitivity of various feedback-control systems, which varies in intensity in individual rats and human subjects.

In summary, studies in experimental animals and humans that have evaluated the relation between salt intake and arterial pressure show that it is possible to observe no change, an increase, or a decrease of arterial blood pressure depending on the responses of the various controllers and their sensitivities in any given animal. Pressure generally will rise only moderately, if at all, with a large increase of sodium intake.

SALT SENSITIVITY IN GENETIC FORMS OF HYPERTENSION

The identification of causal genes for hypertension and, specifically, genes for salt sensitivity in humans is difficult because of genetic heterogeneity and the polygenic inheritance of hypertension. Genetic studies reported in human populations have focused on candidate genes, testing whether a specific chromosomal locus cosegregates with hypertension. Some of the problems associated with genetic research in humans can be obviated by studying the genetics of hypertension in animal models, and it is believed that genes of potential interest found in animals can then be evaluated in humans.

The genetic link to salt and hypertension was one of the early issues addressed by using rats. The inbreeding of rats that developed elevated arterial pressure when placed on a long-term high-salt diet by Dahl et al (14) provided a useful hereditary model of salt sensitivity that can be used to study genetic loci linked to the salt-sensitive nature of hypertension. Studies by Tobian et al (15), Roman (16), and Roman and Kaldunski (17) showed that Dahl salt-sensitive rats (Dahl S rats) demon-
strate a renal deficit in their ability to excrete sodium even at very young ages. Roman and Kaldunski (18) also showed that the pressure-natriuresis relation is reduced in Dahl S rats aged 3–5 wk, even before the development of hypertension with high salt. This appears to be due to enhanced sodium and chloride reabsorption in the thick ascending loop of Henle of the Dahl S rat. As hypertension develops, these animals also rapidly develop severe glomerular sclerosis, which further shifts the relation between sodium excretion and arterial pressure to higher pressures and prevents arterial pressure from being lowered in these animals even when they are returned to a low-salt diet (17).

It is especially interesting that these characteristics are remarkably similar to the phenotypic traits of hypertensive African Americans (19–21). The rats are salt sensitive (22), insulin resistant (23), and hyperlipidemic (24) and exhibit a low-renin form of hypertension that is refractory to treatment with angiotensin-converting enzyme inhibitors and is effectively treated with diuretics (22, 25, 26). The rats also develop severe progressive hypertensive glomerulosclerosis that leads to end-stage renal disease. For this reason, genetic insights and findings obtained from studies of Dahl S rats may be especially relevant to the understanding and treatment of hypertension in African Americans.

Genetic and physical mapping of the genome coupled with functional studies of quantitative trait loci identified in hereditary models of hypertension can be used to identify candidate loci to be studied in humans. Animal models are advantageous in that inbreeding can be used to establish homogenous populations, large numbers of progeny can be generated, and extensive invasive phenotyping and mechanistic studies not possible in humans can be performed. Total genomic scans, which consist of genotyping with many polymorphic genetic markers and seeing if any of these markers cosegregate with blood pressure, are now becoming possible as the number of genetic markers in rats has increased (27). This approach offers the possibility of locating unknown genes responsible for hypertension. Until this time, however, only single candidate genes have been examined to determine whether the regions of interest cosegregate with salt sensitivity and hypertension.

Cosegregation of salt sensitivity with a candidate gene is not proof of cause and effect. A phenotypic difference related to the expression of the gene of interest or the function of the gene product in the parental strains that influences arterial pressure must be confirmed. The only genetic marker in Dahl rats for which cosegregation with hypertension and a phenotypic difference in expression of the protein has been established is 11β-steroid hydroxylase (28). However, the Dahl salt-resistant rat (Dahl R rat) carries a mutation in the primary structure of this enzyme (29). This mutation reduces the ability of Dahl R rats to produce the mineralocorticoid 18-hydroxysteroidcortico-

| TABLE 1 |
|---------------------|---------------------|---------------------|
| Cross               | Hypertensive loci    | Phenotype (reference) |
| SHRSP-H × WKY-H     | Chr 10 (ACE), Chr 18 | SBP after salt (30)  |
| SHRSP-H × WKY-H     | Chr 10 (ACE), X Chr  | SBP after salt (31)  |
| SHRSP-I × WKY-I     | Chr 1 (Sα), Chr 10  | SBP after salt (32)  |
| SHR × WKY           | Chr 1 (Sα), SBP     | SBP after salt (33)  |
| SHR × WKY           | Chr 2 (?), SBP      | SBP after salt (34)  |
| SHR × WKY           | Chr 4 (NPY)         | SBP, DBP, MAP (36)   |
| SHR × WKY           | Y Chr (?), SBP      | SBP (37, 38)         |
| SHR × WKY           | Chr 13 (renin), SBP | SBP, DRP (39)        |
| SHR × DRY           | Chr 10 (NGF), MAP   | (40)                 |
| R1(SHR × BN)        | Chr 20 (HSP70), SBP | (41)                 |
| R1(SHR × BN)        | Chr 12 (HSP27), SBP | (42)                 |
| R1(SHR × BN)        | Chr 13 (Renin), SBP | (43)                 |
| R1(SHR × BN)        | Chr 1 (Kalikrein),  | SBP (44)             |
| S × R outbred       | Chr 7 (11β-steroid  | SBP after salt (28)  |
| SS/JR × JR/JR       | Chr 13 (Renin), SBP | SBP after salt (45)  |
| SS/JR × MNS         | Chr 2 (GCA), Chr 10 | SBP after salt (46)  |
| SS/JR × WKY         | Chr 2 (GCA), SBP    | SBP after salt (47)  |
| SS/JR × Lew         | Chr 5 (ET2), Chr 17 | SBP after salt (48)  |
| SS/JR × Lew         | Chr 1 (SA), SBP     | SBP after salt (49)  |
| GH × BN             | Chr 2 (GCA), SBP    | (50)                 |
| LH × LL             | Chr 2 (?), PP       | (50)                 |
| LH × II             | Chr 13 (Renin), DBP | (50)                 |

7 Chr, chromosome; ACE, angiotensin-converting enzyme; SBP, systolic blood pressure; DBP, diastolic blood pressure; BP, blood pressure; MAP, mean arterial pressure; HSP, heat shock protein.

process of determining the causal genes for hypertension, the blood pressure regulatory pathway is complex and contains many potential sites that, if disrupted, could result in high blood pressure. There is currently some confusion in data interpretation because different crossovers between normal and hypertensive strains using one or both of the same strains often do not reveal the same quantitative trait loci cosegregating with blood pressure. This is because these techniques of genetic dissection can identify only genetic differences (polymorphisms) between the parental strains used in a particular cross. One cannot tell if other genes in common between two strains are also critical to the development of hypertension. Future work will require the development of more informative genetic crosses, more extensive and careful phenotyping, and the use of additional informative markers on the rat genome.

In summary, animal models that are salt sensitive have at least one fundamental characteristic in common, that is, an abnormality in the ability to excrete sodium at any given arterial pressure. Studies using secondary experimental forms of salt-sensitive hypertension showed that this abnormality can result from numerous hormonal and neural pathways that regulate the renal filtration and tubular reabsorption of sodium. Furthermore, in various hereditary forms of hypertension there are many differences in the production of intrarenal paracrine factors and the end-organ responsiveness to these factors that can alter renal function. The genetic differences responsible for
the various responses are not known and will have to be laboriously identified and characterized if we are to more fully understand the genetic basis of salt sensitivity.

REFERENCES


