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Genetics of Salt-Sensitive Hypertension

Hironobu Sanada,

Division of Health Science Research, Fukushima Welfare Federation of Agricultural Cooperatives, Fukushima, Japan

John E. Jones, and

Department of Pediatrics, George Washington University School of Medicine and Health Sciences, 2300 I Street, NW, Washington, DC 20037, USA. Center for Molecular Physiology Research, Children's National Medical Center, 111 Michigan Avenue, NW, Washington, DC 20010, USA

Pedro A. Jose

Department of Pediatrics, George Washington University School of Medicine and Health Sciences, 2300 I Street, NW, Washington, DC 20037, USA. Center for Molecular Physiology Research, Children's National Medical Center, 111 Michigan Avenue, NW, Washington, DC 20010, USA

Hironobu Sanada: sndmak2006@yahoo.co.jp; Pedro A. Jose: PJose@cnmc.org

Abstract

The assessment of salt sensitivity of blood pressure is difficult because of the lack of universal consensus on definition. Regardless of the variability in the definition of salt sensitivity, increased salt intake, independent of the actual level of blood pressure, is also a risk factor for cardiovascular morbidity and mortality and kidney disease. A modest reduction in salt intake results in an immediate decrease in blood pressure, with long-term beneficial consequences. However, some have suggested that dietary sodium restriction may not be beneficial to everyone. Thus, there is a need to distinguish salt-sensitive from salt-resistant individuals, but it has been difficult to do so with phenotypic studies. Therefore, there is a need to determine the genes that are involved in salt sensitivity. This review focuses on genes associated with salt sensitivity, with emphasis on the variants associated with salt sensitivity in humans that are not due to monogenic causes. Special emphasis is given to gene variants associated with salt sensitivity whose protein products interfere with cell function and increase blood pressure in transgenic mice.

Keywords

Blood pressure; Salt sensitivity; Sodium; Genes; Cardiovascular disease; Kidney disease; Low-salt diet; Proteins; Renin-angiotensin system; Renal sodium transport

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Correspondence to: Pedro A. Jose, PJose@cnmc.org.

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Introduction

High sodium intake, independent of blood pressure, is associated with increased cardiovascular risk [1, 2••]. Mortality and morbidity are both higher in hypertensive subjects and in salt (NaCl)–sensitive normotensive subjects than in salt-resistant normotensive subjects [1, 2••, 3••]. However, the assessment of salt sensitivity of blood pressure is difficult because of the lack of universal consensus on definition [1, 4–8]. Salt sensitivity has been defined as a change in blood pressure (office measurement) of at least 5% or at least 10% in response to a change in NaCl intake [4]. Salt sensitivity has also been defined as an increase in mean blood pressure (MBP) of 10 mmHg or more after an infusion of 2 l of normal saline over 4 h relative to that measured the morning after 1 day of a low-sodium (10 mmol) diet and administration of a loop diuretic [1]. Another definition of salt sensitivity is an increase in MBP of more than 4 mmHg (24-hour ambulatory blood pressure monitoring) with an increase in NaCl intake [5]. Patients with a salt sensitivity index (difference between MBP in low-salt vs high-salt diets divided by the MBP during the low-salt diet) of 5% or higher have also been considered to be salt-sensitive [6]. However, one method to determine salt sensitivity may not be reproduced by another method [7]. Apparently, the most reliable method requires putting patients on a diet with normal sodium intake for 5 to 7 days, followed by a reduction of sodium intake for 5 to 7 days, and then high sodium dietary intake for 5 to 7 days [7, 8]. Although a shorter 2-week protocol has been suggested, there is only a 0.69 correlation coefficient between blood pressures obtained in shorter protocols [9] and the definitive method of strict dietary regimen [5–8]. The increase in blood pressure in response to an increase in sodium in the diet depends on the amount of sodium intake [10], sodium as halide salts [11], and ethnicity [11]. Sodium bicarbonate and other nonchloride sodium salts may not elevate blood pressure in most ethnic groups, but in severely salt-sensitive blacks, sodium bicarbonate can increase blood pressure [11]. The differential effect of chloride and non-chloride sodium salts may be related also to deficiencies of other ions (e.g., potassium, calcium, magnesium).

Regardless of the variability in the definition of salt sensitivity, increased salt intake, independent of the actual level of blood pressure, is also a risk factor for cardiovascular morbidity and mortality and kidney disease [1, 2••, 3••]. Increased salt intake may increase calcium excretion and loss of hip bone density [3••]. Excessive sodium intake induces hypertrophy of vascular smooth muscles, independent of blood pressure, increases NADPH oxidase activity and oxidative stress, and reduces the availability and production of nitric oxide [12, 13]. High salt intake also activates angiotensin II signaling in blood vessels, kidney, and brain [14]. A high-sodium diet also decreases aortic hyaluronan content and large artery compliance that is independent of blood pressure. Endothelial cell stiffness was unaffected by acute changes in sodium concentration below 135 mM but rose steeply between 135 and 145 mM [13]. There is also an association between asthma and high salt intake and between obesity and high salt intake [3••]. Indeed, the morbidity and mortality in salt-sensitive normotensive subjects is the same as in hypertensive subjects [1, 2••]. Increased sodium intake also contributes to resistance to antihypertensive therapy [15•].

The magnitude of the problem of salt sensitivity can be best illustrated by the fact that about 118 million Americans are afflicted with hypertension and/or salt sensitivity; 50 to 60

million individuals at least 18 years of age are hypertensive and 58 million are salt-sensitive; 26 million are both salt-sensitive and hypertensive [1]. A modest reduction in salt intake in children and adolescents results in an immediate decrease in blood pressure, with long-term beneficial consequences [3•, 16•, 17, 18]. However, some studies have suggested that dietary sodium restriction may not be beneficial to everyone [19]. Although the concern regarding the ability of a low-sodium diet to alter lipid metabolism has not been borne out [20], salt depletion may promote insulin resistance and activation of the renin-angiotensin system (RAS) and the sympathetic nervous system [21]. In addition, salt restriction has been reported to decrease cognitive function in salt-sensitive rats [22]. Thus, there is a need to distinguish salt-sensitive from salt-resistant subjects. This has been difficult to achieve with phenotypic studies [23]. Therefore, there is a need to determine the genes that are involved in salt sensitivity.

This review focuses on genes associated with salt sensitivity, with emphasis on variants associated with salt sensitivity in humans that are not due to monogenic causes; the latter were reviewed recently [24]. The gene mutations in the aldosterone synthase/11 β -hydroxysteroid dehydrogenase, mineralocorticoid receptor, and β and γ subunits of the epithelial sodium channel (ENaC) that cause monogenic hypertension are rare, accounting for less than 1% of the prevalence of essential hypertension, and could not explain the high incidence of salt sensitivity, especially in normotensive humans.

Salt sensitivity may result in an increase in blood pressure that is already in the hypertensive range or in blood pressure that is normal on a low-salt diet but is increased by a “normal” or high-salt diet and may reach hypertensive levels. Salt sensitivity has also been claimed to interfere with the normal circadian rhythm of blood pressure [25•]. A normal dip in nocturnal blood pressure—a 10% fall in nocturnal blood pressure relative to diurnal blood pressure—is important because a failure of the normal night-time dip in blood pressure is associated with an increase in cardiovascular morbidity and mortality [25•, 26].

The kidney is critical to the overall fluid and electrolyte balance and the long-term regulation of blood pressure. Renal cross-transplantation experiments have confirmed the importance of the kidney in the regulation of blood pressure [27, 28•]. Therefore, the pathogenesis of salt sensitivity must involve a derangement in renal NaCl handling: an inability to decrease sodium transport and increase sodium excretion in the face of an increase in NaCl load.

Inhibition of distal sodium transport in individuals who are salt-sensitive restores the normal circadian rhythm in those not exhibiting a normal dip in nocturnal blood pressure (nondippers) without affecting the circadian rhythm of dippers [29]. Thus, increased sodium transport in the distal nephron is probably important in the pathogenesis of salt sensitivity. Indeed, increased activity of sodium transporters, as in monogenic causes of hypertension, is associated with salt sensitivity [24, 30], but does not preclude increased reabsorption at the proximal tubule if distal tubular compensatory mechanisms (e.g., tubulo-glomerular feedback) are also impaired [31].

The increased NaCl transport in salt sensitivity is probably caused by a continued increase in renal tubular sodium transport or a failure to decrease renal tubular sodium transport in the face of increased sodium load. The latter is probably the mechanism in instances in which basal blood pressure is normal but increases with a salt load, resulting in a failure of pressure natriuresis to increase sodium excretion to return blood pressure to normal [32, 33]. Mechanisms that sense sodium or osmolality in organ-specific (kidney and central nervous system) extracellular fluid interface, which normally prevent an increase in blood pressure, may also be involved [34, 35]. Any increase in extracellular fluid volume would result in the activation of compensatory mechanisms, including increased production of endogenous ouabain and/or ouabain-like substances, to decrease renal sodium transport by inhibition of $\text{Na}^+\text{K}^+\text{ATPase}$ [36•]. Inhibition of $\text{Na}^+\text{K}^+\text{ATPase}$ in vascular smooth muscle cells can then lead to an increase in blood pressure, facilitating the pressure-natriuresis process [32, 33]. A failure of the normal pressure-natriuresis mechanisms would result in persistent elevation in extracellular fluid, which could activate the central nervous system; the resulting increase in sympathetic nerve activity [14] would also increase vascular smooth muscle contraction and sodium transport.

Subtle renal injury has been proposed to cause salt-sensitive hypertension [37], but this mechanism cannot explain the increase in blood pressure following an increase in NaCl intake in normotensive humans with normal renal function [1, 2•, 3•, 25•] and also fails to take into account the differential effect of anion with sodium in the development of salt sensitivity with or without hypertension [11], as well as the importance of the increase in renal tubular sodium transport with salt sensitivity. What would instigate an increase in renal tubular sodium transport or an increase in peripheral vascular resistance in absence of renal injury? It is proposed that genetics plays a role in this regard. This review updates the comprehensive reviews of the genetics of salt sensitivity by Beeks et al. [38] in 2004 and Strazzullo and Galletti [24] in 2007.

Genes Expressing Proteins that Increase Renal Sodium Transport or Vascular Smooth-Cell Reactivity

Genes of the Renin-Angiotensin System

The role of the RAS in salt sensitivity has been reviewed comprehensively by Beeks et al. [38]. The RAS is the most important regulator of renal sodium transport and the major system involved in the increase in renal sodium transport, especially under conditions of sodium deficit [39]. There are also components of the RAS that decrease sodium transport, including angiotensin-(1–7) via the *mas* receptor, angiotensin III, and the angiotensin type 2 receptor [40–42].

Angiotensin-Converting Enzyme

At least eight studies have examined the association between angiotensin-converting enzyme (ACE) and salt sensitivity. Six studies in several ethnic groups found no association [24, 38, 43–46]. Two found an association between salt sensitivity and *ACE* I/D and DD (Japanese, American), and one found an association between salt sensitivity and *ACE* II and ID (Spaniards) [24, 38, 45]. The fact that *ACE* I/D (*ACE*, INS/DEL [rs4340]) has been

reported to be associated with many physical and mental illnesses makes it unlikely that *ACE* I/D, by itself, can be the genetic cause of salt sensitivity.

Angiotensinogen

There have been seven studies on the association between salt sensitivity and angiotensinogen (*AGT*) gene variants [24, 38, 45, 46]. Six have found no association between salt sensitivity and M235T (rs699), one found an association between MM and salt-sensitive hypertension, and one found that blood pressure reduction with a decrease in NaCl intake is associated with *AGT* TT and *AGT* MT [24, 38]. One study reported an association between a decrease in blood pressure with a decrease in sodium intake with *AGT*-6GG, which is probably in linkage disequilibrium with *AGT* M235T [24, 38].

Angiotensin Type 1 Receptor

Angiotensin II, via the angiotensin type 1 receptor (AT_1R), is responsible for more than 50% of the sodium reabsorbed by the kidney in the basal state [39]. Deletion of the *AT_{1A}R* gene selectively in mice increases basal sodium excretion and decreases basal blood pressure [27]. Interestingly, increasing the NaCl intake of $AT_{1A}^{-/-}$ mice increased sodium excretion but also blood pressure [47]. The salt sensitivity of the blood pressure of $AT_{1A}^{-/-}$ mice could be taken to indicate that genes other than *AT_{1A}R* are important in salt sensitivity. *AGTR1* A1166C (rs5186) was not associated with salt sensitivity in two studies [24, 38], but one study found an association of intronic polymorphism rs4524238 alleles G/A and A/A and salt sensitivity in a Chinese population [48].

Genes Related to Aldosterone and Other Mineralocorticoids

Aldosterone Synthase—If a gene were to be involved in salt sensitivity, a good candidate would be any gene involved in distal sodium transport, such as aldosterone. However, mineralocorticoid receptors are also expressed in the proximal tubule [49]. The aldosterone synthase gene variant, *CYP11B2* T-344C (rs179998), was not associated with salt sensitivity in five studies [24, 38, 45]. In addition, the reported association of *CYP11B2* IC (intron 2 conversion) in one study was not confirmed in another study using a similar population [24, 38]. The conclusion that one may draw from these studies is that although the RAS-aldosterone system may be important in the pathogenesis of hypertension, it is probably not a primary cause of salt-sensitive hypertension and, more specifically, of salt sensitivity.

Serum/Glucocorticoid Regulated Kinase 1—Serum/glucocorticoid regulated kinase 1 (*SGK1*) is an aldosterone- and insulin-dependent positive regulator of ENaC activity and density at the plasma membrane. *SGK1* intron 6 CC has been associated with increased blood pressure and *SGK* exon8 TT (Asp240/Asp) has been associated with decreased blood pressure. In a more extensive study, however, *SGK1* mutations in exons 4 through 8 were not found to be associated with hypertension. Although these reports did not investigate the association of these *SGK1* polymorphisms with salt sensitivity, it was suggested that the low prevalence of these *SGK1* variants (16%) argues against the importance of SGK1 variants in the pathogenesis of essential hypertension or salt sensitivity [50]. However, new preliminary studies from the International Hypertensive Pathotype group suggest that major allele

carriers of rs2758151 (C/T) and rs9402571 (T/G) have salt sensitivity [51]; these gene variants have 28% and 18% minor allele frequency, respectively.

11-B-Hydroxysteroid Dehydrogenase—Mineralocorticoid activity may be increased with decreased activity of 11- β -hydroxysteroid dehydrogenase (*HSD11B2*), which inactivates 11-hydroxy steroids in the kidney, thereby protecting the nonselective mineralocorticoid receptor from occupation by glucocorticoids. Three polymorphisms have been studied: G-534A (rs45483293, one negative and one positive association) and a positive association between CA-repeat polymorphisms in intron 1 or G-209A (rs45598932) and salt sensitivity [38, 52].

Cytochrome P450 3A—Members of the cytochrome P (CYP) 450 3A subfamily are involved in the metabolism of environmental carcinogens, many drugs, and endogenous substrates, including steroids, converting circulating cortisol to 6- β -hydroxycortisol and corticosterone to 6- β -corticosterone. These metabolites increase renal sodium transport [53]. *CYP3A5* is of particular interest because it is expressed in the kidney; *CYP3A5**1 expresses the wild-type protein while the *CYP3A5**3 allele (A6986G, rs776746) reduces *CYP3A5* protein expression. In a population of East African descent, *CYP3A5**1, by itself, or by interacting with ATP-binding cassette, subfamily B, member 1 (*ABCB1*), also known as the multidrug resistance 1 gene, increases post-renal proximal tubular sodium reabsorption [54]. In a Japanese population, however, blood pressure was associated with the level of salt intake in *CYP3A5* *3/*3 but not *CYP3A5* *1/*1 [55].

Genes of the Sympathetic Nervous System

Increased sympathetic activity has been demonstrated in salt-sensitive hypertension [6, 14, 56, 57]; salt-sensitive men have increased noradrenergic receptor sensitivity and circulating cortisol levels [57]. Common variants of the tyrosine hydroxylase (*TH*) gene, especially C-824T (rs10770141), predict catecholamine secretion, stress-induced increase in blood pressure, and hypertension [58]. It has also been suggested that increased sympathetic activity may subsequently cause the vascular injury leading to salt sensitivity in older individuals [37]. We recently reported that in lean patients with essential hypertension, salt sensitivity of blood pressure is associated with sympathetic overactivation and reduced suppression of the RAS [6]. Although polymorphisms of the α -adrenergic receptors have not been associated with salt sensitivity, a β 2-adrenergic receptor diplotype, 46AA/79CC, has been reported to be associated with salt-sensitive hypertension [59]. In addition, polymorphisms of *TH*, by itself or via interaction with variants of *ADRB2*, *CYP11B*, and *GRK4*, are associated with hypertension [58, 60]. The interaction with *GRK4* 486V (rs1801058) is of interest because *GRK4* 486V has been reported to be associated with salt sensitivity [61] (although salt sensitivity was not taken into consideration in the report of Gu et al.) [60]. Sympathetic function has also been reported to be increased in human carriers of melanocortin-4 receptor gene mutations [62, 63]. Because melanocortin-4-deficient mice are neither hypertensive nor salt-sensitive despite being obese, hyperinsulinemic, and hyperleptinemic, it has been suggested that a functional melanocortin-4 may be necessary for the hypertensive phenotype to be expressed [64].

Amiloride-Sensitive Epithelial Sodium Channel

Rare mutations in the β and γ subunits of the amiloride-sensitive ENaC cause severe hereditary hypertension associated with hyperkalemia (Liddle syndrome) [24, 30]. There are no studies on the association of common ENaC gene variants and salt sensitivity. However, variants of neural precursor cell expressed developmentally down-regulated 4-like (*NEDD4L* rs4149601, A/G) GG genotype, together with the C-allele of *NEDD4L* (rs2288774, C/T), a regulator of ENaC, have been associated with salt sensitivity [65, 66]. However, sodium balance is not impaired in mice with renal collecting duct-specific gene inactivation of α ENaC [67].

β -3 Subunit of G-Protein

A recent meta-analysis of genome-wide gene expression of differences in onset and maintenance of hypertension reported that one of the genes that may be relevant to the onset of hypertension is the β -3 subunit of G-protein (*GNB3*). A meta-analysis of association studies of *GNB3* C825T (rs5443) also showed a small but significant increase in the risk of essential hypertension [68]. *GNB3* C825T does not affect the amino acid sequence, but the T allele is in almost complete linkage disequilibrium with other polymorphisms within the *GNB3* gene. The mechanism by which *GNB3* C825T or the “T haplotype” increases renal sodium transport remains to be determined. *GNB3* variant has been reported to increase activity of sodium hydrogen exchanger type 1 (NHE1). However, because NHE1 is expressed in the basolateral membrane of renal tubules, an increase in activity of NHE1 by increasing intracellular sodium would actually decrease renal sodium reabsorption. Five studies did not find an association between *GNB3* C825T and salt sensitivity [24, 38, 45, 69, 70]; one study showed that this gene variant was associated with a positive response to a diuretic [71]. Intronic *GNB3* (rs2301339), which is in perfect linkage disequilibrium with *GNB3* C825T, was not associated with an increase in systolic blood pressure and salt sensitivity [72], but this report found that carriers of at least one copy of the A allele in the non-coding 5' region of *GNB3* (rs1129649) had a decreased blood pressure response to a low-salt diet.

Renal Chloride Channels

Two members of the renal chloride channels (*CLC*) gene family are predominantly expressed in the kidney (*CLCNK*); the *CLCNKA* gene is expressed in the thin ascending limb of Henle, whereas the *CLCNKB* gene is expressed in the distal convoluted and connecting tubules and the cortical collecting ducts. Four single nucleotide polymorphisms (SNPs) of *CLCNKA* (5' of *CLCNKA*, rs848307; rs1739843; non-coding intron, rs1010069; and missense, Thr447Ala, rs1805152) were reported to be associated with salt-sensitive hypertension [73].

Genes Expressing Proteins that Normally Do Not Decrease Renal Sodium Transport

Adducin

Adducins are cytoskeletal proteins that regulate the membrane organization of spectrin-actin. Na^+K^+ -ATPase is responsible for the primary active transport of sodium in renal tubular epithelial cells. The increase in the excretion of sodium following an increase in sodium intake is secondary to the inhibition of the activity of Na^+K^+ -ATPase, which is mediated, in part, by internalization of its subunits involving the actin-microtubule cytoskeleton. Salt sensitivity has been ascribed, in part, to a failure of natriuretic hormones, including renal dopamine, to decrease Na^+K^+ -ATPase activity in renal proximal tubule cells of salt-sensitive rats [74, 75]. Wild-type α -adducin expressed in opossum kidney (OK) or Madin-Darby canine kidney (MDCK) cells minimally increases Na^+K^+ -ATPase activity. In contrast, rat α adducin (*Add1*) *F316Y* or human α -adducin (*ADD1*) *G460W* (rs4961)/S58C (rs4963) transfected into OK or MDCK cells increases Na^+K^+ -ATPase activity by about 25% [75, 76]. These polymorphisms cause an increase in proximal tubule reabsorption in hypertension, the frequency of which varies: 8% in African Americans, 15% to 20% in whites, and 50% in Japanese. There are many studies on the association of *ADD1 G460W* and salt sensitivity. The authors of a recent meta-analysis involving 454 salt-sensitive and 366 non-salt-sensitive participants concluded that the association between *ADD1 G460W* and salt sensitivity is statistically significant in Asian but not Caucasian populations; the difference may be related to the greater frequency of *ADD1 G460W* in Asians than in Caucasians [77]. This meta-analysis did not include a recent study in 1,906 Han Chinese that showed no association between *ADD1 G460W* and salt sensitivity but found an association with a rare adducin intron variant (rs17833172), at least in a Han Chinese population [72]. Other studies have also indicated that there may be an interaction between *ADD1 G460W* and high circulating ouabain levels [78], female gender, and high body mass index [79]. Human carriers of *ADD1 460W*, *WNK1* GG, and *NEDD4L* GG need a greater increase in systolic blood pressure to excrete the same amount of sodium relative to the carriers of *ADD1 G460*, *WNK1* AA, and *NEDD4L* AA [66]. The interaction among *ADD1 460WW*, *ACE* DD, and *CYP11B2-344CC* may also contribute to the risk of salt-sensitive hypertension [80]. Homozygosity for the A allele of a variant of *ADD1* (rs 17833172) was associated with an increase in blood pressure with a high-salt diet [72]. The increase in Na^+K^+ -ATPase activity caused by *ADD1 460W* needs a functional salt-inducible kinase 1 [81].

There is also a report of increase an association of blood pressure, decreased sodium excretion, and β -adducin (*ADD2*) *C1797T* (Ser599Ser, rs4984) [82].

Genes Expressing Proteins that Normally Decrease Renal Sodium Transport

Adrenomedullin

Adrenomedullin (ADM) and ADM2/intermedin are widely distributed in the body, including blood vessels and the kidney. Whereas ADM is expressed in renal glomeruli, cortical distal

tubules, and medullary collecting ducts, ADM2/intermedin is expressed in the proximal and distal tubule, thick ascending limb, and collecting ducts. ADM and ADM2 or intermedin can reduce blood pressure and increase sodium excretion, in part through an increase in renal nitric oxide synthase activity [83, 84]. An *ADM* polymorphism (-1984G), which results in the appearance of a binding site for the glucocorticoid receptor, is associated with lower sodium excretion but a lower systolic blood pressure [85].

Dopamine, Dopamine Receptors, and GRK4

Dopamine produced in the kidney (mainly by proximal tubules) acts in an autocrine/paracrine manner to regulate renal ion transport [31, 86, 87]. In mammals, the effects of dopamine are exerted via two families of receptors belonging to the superfamily of G protein-coupled receptors: D₁-like receptors, comprised of D₁R and D₅R; and D₂-like receptors, comprised of D₂R, D₃R, and D₄R. During conditions of mild volume and sodium excess, dopamine in the kidney is responsible for more than 50% to 60% of sodium excretion [31, 86, 87], either by itself or via a synergistic interaction with other natriuretic factors such as ANP/ANPA [88], eicosanoids [89, 90], endothelin/ETBR [91], insulin [92], nitric oxide [93], prolactin [94], urodilatin [88], angiotensin III/AT₂R [41], and inhibition of renin, AT₁R [87, 95, 96], and aldosterone [89]. The inhibition of renal transport of sodium and other ions occurs in multiple segments of the nephron, including proximal and distal convoluted tubule, thick ascending limb of Henle, and cortical collecting ducts [31, 74, 75, 86, 87, 95, 96, 97, 98, 99]. During conditions of volume deficit, the natriuretic effect of dopamine is no longer apparent. It could actually increase renal sodium reabsorption via D₂-like receptors [31, 100] and an increase in renin [87] when COX2 activity is suppressed [89]. Indeed, depending on the genetic background [87, 101–103], knockout of all the dopamine-receptor gene subtypes in mice causes hypertension that can be aggravated by an increase in NaCl intake in D₂^{-/-}, D₃^{-/-}, D₄^{-/-}, and D₅^{-/-} mice; salt sensitivity of D₁^{-/-} mice has not been tested.

Salt sensitivity in some humans with essential hypertension and type 1 diabetes has been associated with a decrease in renal dopamine production in response to a salt load [104–106]. In humans with essential hypertension, inhibition of renal proximal (but not distal) sodium transport by D₁-like receptor agonists is impaired [99]. The intravenous infusion of dopamine and agonists to test their effects on renal sodium handling may not decipher any dopaminergic defect in hypertension because the drugs may reach nephron segments that are “normally” capable of responding to such stimulation [98]. For example, the response of the distal nephron to D₁-like receptor (probably D₅R) stimulation is preserved in Dahl salt-sensitive rats [87].

Chronic D₁-like receptor blockade in rodents and humans increases blood pressure [87, 107], and renal D₁R expression may be decreased in some genetically hypertensive rats [108]. The ability of dopamine to increase sodium excretion is impaired in humans with essential hypertension, which has been related to polymorphisms in the promoter region of the D₁R gene (*DRD1*) G-94A (rs5326) [109]. Whether or not this polymorphism in the promoter region of *DRD1* is associated with salt-sensitive hypertension remains to be determined. Nevertheless, even when renal *DRD1* expression is normal, the inhibitory effect

of dopamine and D₁-like receptor agonists on sodium transport is still impaired in hypertension [86, 87, 97•, 99, 110]. There are some rare nonfunctional SNPs in the coding regions of some of the dopamine receptors, but they have not been associated with salt-sensitive hypertension [111]. We and others have reported that the decreased function of dopamine receptors in hypertension—specifically D₁R and D₃R—may be related to a state of constitutive desensitization [87, 97•].

The normal recycling of D₁R and D₃R involves G protein–coupled receptor kinases (e.g., GRK4), and other proteins, including sorting nexins [97•]. Heterologously or endogenously expressed activating variants of *GRK4*, including GRK4 R65L (rs296036), A142V (rs1024323), and A486V (rs1801058), impair D₁R and D₃R function [97•], [112]. Transgenic mice expressing human wild-type *GRK4* are normotensive and salt-resistant, whereas those expressing *GRK4* 142V are hypertensive and salt-resistant [97•]. Transgenic mice expressing human *GRK4* 486V are normotensive on a normal-salt diet and become hypertensive on a high-salt diet, dependent upon the genetic background [97•]. Transgenic mice expressing human *GRK4* 65L are normotensive on both normal and high salt intake. This finding may be related to the fact that *GRK4* needs to interact with other variants of *GRK4* or variants of other genes that regulate blood pressure (see below) to express a hypertensive phenotype [97•].

Several studies in different ethnic groups have shown that *GRK4* gene variants are associated with human essential hypertension [61, 97•, 113–116]. Mental stress increases blood pressure and decreases sodium excretion in African American adolescent males carrying *GRK4* 65L [116]. Salt-sensitive hypertensive Japanese patients carrying at least three *GRK4* gene variants have an impaired natriuretic response to a dopaminergic drug, and salt-sensitive hypertension can be correctly predicted in 94% [114]. In Ghanaians, multilocus genotype combinations of *ACE* I/D and *GRK4* 65L had an estimated predictive accuracy for hypertension of 70%, confirming an earlier study [113]. A meta-analysis revealed a significant association of *GRK4* 486V with hypertension, with an odds ratio of 1.5 (95% CI, 1.2–1.9) [117]. One study, however, did not find an association of *GRK4* 486V with diastolic blood pressure in the top 5% of subjects with white European ancestry; the association of *GRK4* gene variants with hypertension was not tested [118]. Another study did not find an association between *GRK4* 142V and hypertension but did find an association between variants of the promoter region of *DRD1* and hypertension [109]. The discordance between this report in European Caucasians [109] and other reports involving other populations may be a result of the influence of genetic background in the phenotypic expression of the quantitative trait of essential hypertension. Ethnicity may also explain some of the discordances. *GRK4* 486V is more frequent in Asians (47%) than in Caucasians (40%), Hispanics (28%), or African Americans (19%). In contrast, *GRK4* 65L and *GRK4* 142V are more frequent in African Americans (47% and 45%, respectively) than in the other ethnic groups: Caucasians (35% and 40%), Hispanics (25% and 29%), and Asians (7% and 20%) [119]. Recent genome-wide association studies (GWAS) and a meta-analysis [68] of genes related to essential hypertension did not identify *GRK4* as associated with hypertension, probably because salt sensitivity and gene-gene interaction were not taken into account [61, 114]. Previous studies have shown that it is critical to assess the association of

GRK4 with hypertension in conjunction with other *GRK4* SNPs [114] and genes (e.g., *ACE* I/D with *GRK4* 65L [113], *ADRB2*, *TH*, and *GRK4* 486V [60]). *GRK4* A142V and *GRK4* A486V are also not included in the Affymetrix or Illumina platforms, respectively, which were used in the GWAS reports [97•].

Endothelial Nitric Oxide Synthase

Of the several polymorphisms of endothelial nitric oxide synthase (eNOS), T-786C (rs2070744), G894T (Glu298Asp, rs1799983) [120], and the 27-bp tandem repeats in intron 4 b/b [121] have been associated with essential hypertension. A meta-analysis of 53 studies showed that the effect of eNOS G894T SNP may be dependent on total cholesterol status; no association between hypertension and eNOS T-786TC was found [122]. However, two studies found an association between eNOS-786TC and CC and hypertension with an increase in salt intake [123, 124]. Several other mechanisms have been proposed to be involved in salt sensitivity, involving reactive oxygen species and immunity and nitric oxide. Thus, the mononuclear phagocyte system interacting with nitric oxide may act to control interstitial/lymph volume serving as a buffer for salt-sensitive hypertension [125, 126].

Eicosanoids

20-hydroxyeicosatetraenoic acid (20-HETE) and epoxyeico-satrienoic acids, which result from the metabolism of endogenous arachidonic acid by CYP4A and CYP2C, respectively, have been shown to be important in regulating blood pressure. 20-HETE increases blood pressure by vasoconstriction but can also decrease blood pressure by decreasing renal sodium transport, especially at the proximal tubule and thick ascending limb of Henle [127]. The impaired natriuresis of salt-sensitive hypertensives has been shown to involve an altered 20-HETE response to furosemide [128]. The hypertension of *Cyp4a14*-deficient mice is apparently a 20-HETE-mediated hemodynamic phenomenon, whereas the hypertension of *Cyp4a10*-deficient mice is salt-sensitive and related to an action on ENaC [129]. Several studies support the role of *Cyp4a* in salt sensitivity in rats [130], but the association between *CYP4A* or *CYP2C* variants in salt-sensitive hypertension in humans remains to be determined.

Endothelin

The endothelin (ET) system comprises three vasoactive isopeptides (ET-1, ET-2, and ET-3), which exert their effects via the ET_A and ET_B receptor (ET_AR, ET_BR). ET_AR and ET_BR in vascular smooth muscle cells mediate vasoconstriction, and ET_BR in endothelial cells mediate vasodilatation that may be related to nitric oxide production [131]. Endothelin may also increase oxidative stress in Dahl salt-sensitive prehypertensive rats. ET_BR in the kidney decreases sodium transport and deletion of *Etbr* in rats is associated with salt-sensitive hypertension [132]. In rats, the administration of an ET_AR antagonist prevents an increase in blood pressure induced by angiotensin II and a high-salt diet, whereas an ET_BR antagonist exacerbates this effect [133••]. These studies indicate the importance of ET_AR in the pathogenesis of this animal model of hypertension and show that ET_BR may be protective. *ETBR* 1065AA+GA (rs5351) has been reported to be more frequent in salt-resistant

hypertensives, whereas *ETBR* 1065GG and *ACE* DD/ID are more frequent in salt-sensitive hypertensives [24, 38].

Kallikrein-Kinin System

Oral kallikrein administration has been reported to decrease blood pressure levels only in salt-sensitive hypertensive patients [134]. Recombinant adeno-associated viral-mediated human kallikrein gene therapy prevents hypertension induced by a high-salt diet without affecting basal blood pressure [135, 136]. Deletion of the bradykinin B₂ receptor gene (*Bdkrb2*) in mice produces salt-sensitive hypertension [137]. It remains to be determined whether polymorphisms of genes of the kallikrein-kinin system are associated with human salt-sensitive hypertension.

Natriuretic Peptide Precursor A/B

Common genetic variants at the natriuretic peptide precursor A/natriuretic peptide precursor B (*NPPA-NPPB*) locus found to be associated with circulating natriuretic peptide concentrations contribute to interindividual variations in blood pressure and hypertension [138]. An atrial natriuretic peptide (*ANP*) gene promoter variant is associated with increased susceptibility to early development of hypertension in humans [139]. The *ANP* Hpa II polymorphism was not found to be associated with salt sensitivity [140].

Conclusions

Several criteria have been suggested to link genes to complex diseases, including hypertension and salt sensitivity; these include gene chromosomal locus linkage and gene variant association [141, 142]. Another criterion is circumstantial evidence of the involvement of gene variants—in this instance, hypertension and salt sensitivity. *ADD1* polymorphisms have been shown to increase renal tubular Na⁺K⁺-ATPase activity [75, 76, 81], and the *HSD11B2* G-209A (rs45598932) variant reduces promoter activity, in keeping with the reduced activity in high blood pressure [52]. The in vitro effects of *GRK4* polymorphisms are also in keeping with a decrease in D₁R function in renal proximal tubules in essential hypertension [97•, 110, 112, 117]. According to Glazier et al. [141], the most conclusive evidence that gene variants cause complex disease is the demonstration that replacement of the variant nucleotide results in switching one phenotype for another. A polymorphism of *Add1*, *F316Y*, has been found in the Milan hypertensive rat, which is also salt-sensitive [75], but this polymorphism has not been shown to cause hypertension in transgenic mice. As stated above, transgenic mice expressing wild-type human *GRK4* γ are normotensive and salt-resistant [97•, 110, 117]. In contrast, with the appropriate genetic background, transgenic mice expressing human *GRK4* γ 486V are normotensive on a normal-salt diet but become hypertensive on a high-salt diet. It remains to be determined whether variants of other genes that are associated with salt sensitivity can cause salt sensitivity in transgenic mice.

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