Mutations in the Na-Cl Cotransporter Reduce Blood Pressure in Humans

Dinna N. Cruz, David B. Simon, Carol Nelson-Williams, Anita Farhi, Karin Finberg, Laura Burleson, John R. Gill, Richard P. Lifton

Abstract—The relationship between salt homeostasis and blood pressure has remained difficult to establish from epidemiological studies of the general population. Recently, mendelian forms of hypertension have demonstrated that mutations that increase renal salt balance lead to higher blood pressure, suggesting that mutations that decrease the net salt balance might have the converse effect. Gitelman’s syndrome, caused by loss of function mutations in the Na-Cl cotransporter of the distal convoluted tubule (NCCT), features inherited hypokalemic alkalosis with so-called “normal” blood pressure. We hypothesized that the mild salt wasting of Gitelman’s syndrome results in reduced blood pressure and protection from hypertension. We have formally addressed this question through the study of 199 members of a large Amish kindred with Gitelman’s syndrome. Through genetic testing, family members were identified as inheriting 0 (n=60), 1 (n=113), or 2 (n=26) mutations in NCCT, permitting an unbiased assessment of the clinical consequences of inheriting these mutations by comparison of the phenotypes of relatives with contrasting genotypes. The results demonstrate high penetrance of hypokalemic alkalosis, hypomagnesemia, and hypocalciuria in patients inheriting 2 mutant NCCT alleles. In addition, the NCCT genotype was a significant predictor of blood pressure, with homozygous mutant family members having significantly lower age- and gender-adjusted systolic and diastolic blood pressures than those of their wild-type relatives. Moreover, both homozygote and heterozygote subjects had significantly higher 24-hour urinary Na⁺ than did wild-type subjects, reflecting a self-selected higher salt intake. Finally, heterozygous children, but not adults, had significantly lower blood pressures than those of the wild-type relatives. These findings provide formal demonstration that inherited mutations that impair renal salt handling lower blood pressure in humans. (Hypertension. 2001;37:1458-1464.)

Key Words: blood pressure ■ sodium, dietary ■ hypokalemia ■ human ■ diuretics ■ genetics

Despite decades of investigation, determination of the role of salt in blood pressure variation in humans has proved difficult. Observational studies in large populations have often relied on recollections or a small number of measurements of salt intake as a surrogate of long-term dietary habits; interventional studies have typically studied small cohorts for short duration, making their interpretation difficult.¹ As a result, advocating reduction in dietary salt in the general population has been controversial.¹ One fundamental question in this debate has remained paramount: does alteration in net salt balance alter blood pressure in humans?

Studies of rare inherited forms of hypertension have begun to provide insight into this issue. In recent years, the molecular basis of glucocorticoid-remediable aldosteronism, Liddle’s syndrome, and the syndrome of apparent mineralocorticoid excess have been defined.² All result from mutations that lead to increased renal reabsorption of salt by the epithelial Na⁺ channel of the distal nephron. This initiates a rise in blood pressure by the expansion of plasma volume and the consequent increased cardiac output. The cosegregation of hypertension with these mutations has demonstrated a causal link between them.²

These observations raise the question of whether mutations that diminish renal salt reabsorption have the opposite effect, ie, lowering blood pressure. Patients with Bartter’s and Gitelman’s syndromes have salt wasting with hypokalemic alkalosis but, in contrast to the above disorders, remain free of hypertension, with so-called normal blood pressure.³⁻⁵ These observations raise the question of whether the normal blood pressure in these syndromes actually reflects diminished blood pressure resulting from reduced salt balance. Studies to test this possibility have been difficult to perform for several reasons: these disorders are rare autosomal recessive traits, making the investigation of many individuals under a uniform protocol problematic; second, there has been marked clinical variation among patients with hypokalemic alkalosis, raising the question of how to define distinct disease entities within this group. Third, for rare disorders with affected subjects of

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1458
diverse ethnic and geographic backgrounds, identifying appropriate control populations for comparison has proved difficult. This situation has changed with the recent demonstration of the molecular basis of Gitelman’s and Bartter’s syndromes. Bartter’s syndrome is caused by mutation in any of 3 genes involved in salt reabsorption in the thick ascending limb of Henle.\(^6,7\) These patients are typically diagnosed in the neonatal period with severe intravascular volume depletion. In contrast, Gitelman’s syndrome is caused by loss of function mutations in the Na–Cl cotransporter of the distal convoluted tubule (NCCT); a wide range of mutations causing disease have been identified.\(^6,7\) Patients with Gitelman’s syndrome typically have a more benign clinical course, presenting with neuromuscular signs and symptoms in adolescence or adulthood; clinical signs of volume depletion are typically not apparent.\(^3,4\) In both disorders, the renal salt wasting activates the renin-angiotensin system, increasing Na\(^+\) reabsorption via the epithelial Na\(^+\) channel in the distal nephron. This provides the electrical gradient for increased secretion of K\(^+\) and H\(^+\), accounting for the hypokalemic alkalosis seen in affected patients. In addition, patients with Gitelman’s syndrome typically have hypomagnesemia and hypocalciuria, in contrast to the normal serum Mg\(^{2+}\) levels and hypercalciuria typically seen in Bartter’s syndrome.\(^3,4,6,7\) It is important to point out that these effects of NCCT mutations have been identified only in patients presenting with these biochemical abnormalities, leaving open the possibility of ascertainment bias. Thus, although all patients with these clinical features of Gitelman’s syndrome appear to have NCCT mutations, it has not been possible until now to determine the penetrance of the various clinical features resulting from NCCT mutations.

We have identified an Amish kindred with Gitelman’s syndrome spanning 10 generations with many consanguinous loops; the ancestry of this kindred can be traced to a common pair of founders in the 18th century. Identification of the mutations underlying the disease in this kindred affords the opportunity to unambiguously follow the inheritance of mutant NCCT alleles and to then determine the impact of these alleles on biochemical features and blood pressure. This within-family study design provides an ideal control population, substantially eliminating the effects of differences in genetic backgrounds of cases and controls and permitting the assessment of clinical features free of ascertainment bias.

**Methods**

**Family Studies and Clinical Investigation**

The study population consisted of 199 members of a single Amish kindred ascertained through an index case, a 45-year-old white male who was diagnosed with Gitelman’s syndrome at age 30, when he presented with complaints of muscular weakness. His laboratory values at presentation revealed the following: serum K\(^+\) 2.5 mmol/L, Mg\(^{2+}\) 1.3 mg/dL (0.53 mmol/L), bicarbonate 32 mmol/L, and urine Ca\(^{2+}\)/creatinine ratio 0.192 mmol/mmol. In the absence of thiazide diuretics, these clinical features are now recognized to be diagnostic of Gitelman’s syndrome. The extended kindred of the index case was investigated. Most members lived in Pennsylvania Dutch country and had similar lifestyles. The research protocol was approved by the Yale Human Investigation Committee, and all subjects provided written informed consent.

Blood pressure was measured in a standardized fashion. All blood pressures were measured by a single physician (D.N.C.). Three oscillometric blood pressure readings were measured at 5-minute intervals, by using the left arm of the patient, who was seated. The first reading was discarded, and the average of the second and third readings was used in data analysis. Hypertension was defined as a blood pressure >140/90 or the use of antihypertensive medications. Valid measurements were obtained in 194 subjects. Three young children could not cooperate for valid measurement. Two additional patients were excluded from analysis: 1 patient for chronic steroid use for multiple sclerosis and 1 patient for diltiazem use for cardiac dysrhythmia. Twenty-nine months after the initial blood pressure recordings, measurements were repeated in 63 subjects by the same methods. The repeated blood pressures, measured in a blinded fashion, showed a highly significant correlation with the initial readings \(R=0.491\) and \(P<0.001\) for systolic blood pressure, \(R=0.459\) and \(P<0.001\) for diastolic blood pressure.

Biochemical measurements were all performed in the same laboratory by using standard procedures with subjects consuming their typical ad libitum diets. Serum K\(^+\) and Mg\(^{2+}\) levels were determined in all subjects. Measurements of serum bicarbonate (HCO\(_3\)) levels were performed in a subset of the subjects \((n=39)\). In a subset of patients, 24-hour urinary Na\(^+\), urinary K\(^+\), and urinary Ca\(^{2+}\) levels were also measured \((n=87, 87,\) and 125, respectively). These values are expressed as the millimolar ratios of urine electrolytes/creatinine (ie, urine Na\(^+\)/creatinine, K\(^+\)/creatinine, and Ca\(^{2+}\)/creatinine).

**Mutation Identification and Genetic Testing**

Genomic DNA was prepared from venous blood samples by standard procedures.\(^8\) Mutations were sought by single-strand conformational polymorphism of the NCCT gene as previously described.\(^7\) Identified variants were subjected to DNA sequencing according to standard procedures.

The missense mutation identified in this kindred was genotyped in family members by polymerase chain reaction (PCR), followed by single-strand conformational polymorphism in kindred members. The deletion identified in this kindred was genotyped in family members by PCR. Deletion homozygotes were identified by the absence of NCCT PCR products, whereas exons from other genes in the same PCR reaction were successfully amplified, providing a positive control. These results were confirmed by Southern blotting, hybridizing probes from the deleted NCCT exons to genomic DNA of kindred members. Heterozygous carriers of the NCCT exon-1 to -7 deletion were identified by quantitative comparison of PCR amplification of exons 1 to 7 in family members with obligate heterozygotes and in normal control subjects. Inheritance of specific mutations was further confirmed by genotyping polymorphic markers tightly linked to NCCT. Importantly, all genotypic assignments were performed by individuals blinded to clinical data.

**Statistical Analysis**

The data are presented as mean±SEM. The primary analysis compared the clinical characteristics of the 3 genotype groups by use of ANOVA for continuous variables (age, serum K\(^+\), Mg\(^{2+}\), HCO\(_3\)\(^-\), and urinary Ca\(^{2+}\)/creatinine) and \(\chi^2\) for categorical variables (gender and the presence of hypertension), with a 2-tailed probability value. Comparison of continuous variables between any 2 groups was performed by use of the Student \(t\) test. Univariate linear regression analysis (Pearson correlation) was used to examine the relationship between serum K\(^+\), Mg\(^{2+}\), HCO\(_3\)\(^-\), and urinary Ca\(^{2+}\)/creatinine among affected patients. This was also used to examine the correlation between repeated blood pressure measurements (see above). Systolic and diastolic blood pressure was analyzed for the effect of genotype by using forward stepwise regression, with age and gender considered a priori as covariates. Calculations were performed by using SPSS 6.1 for Macintosh (SPSS Inc). A value of \(P<0.05\) was considered statistically significant.
first base of codon 642 from G to C, altering the wild-type (WT) arginine (R) to glycine (G). C, Deletion of exons 1 to 7 of the gene in these individuals was confirmed by Southern blotting. An autoradiogram of a Southern blot of genomic DNA of selected members of kindred K140 is shown. Genomic DNA was digested with restriction enzyme BglII, fractionated by electrophoresis on 0.7% agarose gel, denatured, and transferred to nylon membrane. 32-P-labeled NCCT probes corresponding to exons 1 to 7 of the NCCT cDNA were hybridized to the filter as described in Methods. In contrast to normal controls, who show hybridization to fragments of 4.0 and 2.0 kb, 3 kindred members shown have complete deletion of these sequences.

**Results**

Mutations Causing Gitelman’s Syndrome in K140

Two different NCCT mutations were identified in K140 (Figure 1). One mutation introduced a single base substitution (CGC→GGC) in codon 642; this mutation substitutes glycine for the normal arginine in the cytoplasmic C-terminus of the encoded protein. This arginine residue lies in a 14–amino acid segment that is completely conserved among flounder, rat, and human NCCTs, and the observed substitution is nonconservative, eliminating a positive charge. This mutation is not a simple polymorphism in the population, inasmuch as it was absent among 160 control chromosomes studied. From these observations, as well as the cosegregation of this mutation with the biochemical features of Gitelman’s syndrome (see below), we infer that this mutation leads to loss of NCCT function. The other allele in the index case contains a deletion that eliminates exons 1 to 7 of the gene. Seventeen individuals in the kindred were found to be homozygous for this deletion by PCR, and the absence of this segment of the gene in these individuals was confirmed by Southern blotting (Figure 1). Because this deletion removes the start codon as well as the first 5 transmembrane domains of the encoded protein, this mutation is also inferred to result in a loss of function of NCCT. Nine individuals were compound heterozygotes with 1 copy of the deletion and 1 copy of the missense mutation. There were no significant phenotypic differences between the 2 classes of individuals homozygous for defective NCCT alleles. No other mutations in NCCT were identified in this kindred.

Genotypes in the Extended Kindred

The identification of these 2 mutations and marker haplotypes segregating with them permitted unambiguous assessment of the inheritance of these mutations through the extended kindred as described in Methods. In sum, 199 members of this kindred were studied. All members were classified as inheriting 0, 1, or 2 copies of NCCT mutations (Figure 2). This analysis revealed that 26 members had inherited 2 defective copies of the gene (referred to as genotypically affected subjects), 113 had inherited 1 defective copy (heterozygotes), and 60 had inherited neither mutation (homozygous wild types).

Among the 26 genotypically affected patients, there were 14 males and 12 females; among the heterozygous subjects, 52 males and 61 females; and among the wild-type subjects, 25 males and 35 females. The gender ratio of affected subjects was not significantly different from the expected 1/1 ratio, and the gender ratios among the 3 groups were not significantly different. Individuals inheriting 2 mutant alleles were older (mean age, 47.3 years) than their heterozygous and wild-type relatives (31.8 and 36.2 years, respectively; \(P=0.003\)), attributable to pedigree structure (Figure 2).

Biochemical Features of Members of K140

Heretofore, identification of patients with Gitelman’s syndrome has relied on the identification of abnormal serum chemistries, potentially introducing ascertainment bias in assessment of the severity of disease; ie, previously, one would not have been able to identify patients inheriting these
mutations who had no biochemical abnormalities. Consequently, identification of 25 genotypically affected family members based solely on their relationship to the index case permits an unbiased assessment of the effect of inheritance of these mutations on clinical and biochemical parameters. Moreover, tracing the inheritance of mutations through the family for the first time permits unambiguous genotypic distinction of heterozygous from wild-type homozygous individuals. The laboratory values in patients of different genotypic classes are shown in Figure 3. Individuals inheriting 2 defective copies of NCCT all had significant hypokalemia, (mean K⁺ 2.8 mmol/L, range 1.9 to 3.4 mmol/L), whereas the means of both the homozygous wild-type and heterozygous individuals were 4.3 mmol/L, with no individual <3.5 mmol/L (P<0.0001, Figure 3A). Similarly, the mean serum bicarbonate levels were also significantly higher than those of the homozygous wild-type and heterozygous individuals (Figure 3C).

In addition to these effects on K⁺ and bicarbonate, significant effects were also seen on Mg²⁺ and Ca²⁺ handling. Serum Mg²⁺ was markedly diminished among genotypically affected subjects, with a mean of 1.1 mg/dL (0.45 mmol/L, range 0.6 to 1.8 mg/dL or 0.25 to 0.74 mmol/L) compared with 1.9 mg/dL (0.78 mmol/L) in unaffected relatives (P<0.0001, Figure 3B). Patients with Gitelman’s syndrome have been noted to have diminished urinary Ca²⁺/creatinine ratio (0.14 versus 0.15 mmol/mmol). Among the affected patients, there were no significant correlations among these 4 laboratory values.

Effects of Mutations on Blood Pressure

None of the 26 genotypically affected subjects had a diagnosis of hypertension, none was being treated with antihypertensive medication, and none had a blood pressure >140/90 mm Hg. The mean blood pressure in this group was 109/68 mm Hg for adult males and 113/66 mm Hg for adult females.

The quantitative impact of Gitelman’s mutations on blood pressure was analyzed by multiple linear regression, comparing blood pressures of relatives of contrasting NCCT geno-
types. NCCT genotype, age, and gender were all significant predictors of diastolic and systolic blood pressure (Table). The effect of genotype on diastolic blood pressure was highly significant ($P = 0.002$), with genotypically affected individuals having age- and gender-adjusted diastolic blood pressures 7.0 and 8.6 mm Hg lower than those of their heterozygous and wild-type relatives, respectively (Figure 4). The effect of genotype on systolic blood pressure was also significant and quantitatively similar (Table, $P = 0.038$).

**Effects in Heterozygous Individuals**

We compared the phenotypes of heterozygous individuals with those of their wild-type relatives. There were no statistically significant differences in the heterozygous and the homozygous wild-type subjects in terms of serum $K^+$, $Mg^{2+}$, bicarbonate, and urinary $Ca^{2+}$ and $K^+$ excretion (Figure 3). However, 24-hour urinary $Na^+$ excretion was significantly higher in the heterozygous individuals (urinary $Na^+/creatinine$ 20.3 versus 14.4 mmol/mmol, heterozygous versus wild-type individuals, respectively; $P = 0.003$). This observation is consistent with these patients having mild salt wasting. Although analysis of blood pressure for the entire study population did not detect a significant difference in age- and gender-adjusted diastolic blood pressure between heterozygous and wild-type individuals, $P = 0.038$.

**Predictors of BP in Kindred Git140**

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$BP$ indicates blood pressure.

**Figure 3.** Effect of NCCT mutations on laboratory parameters. The mean±SEM values of indicated laboratory parameters are shown for individuals inheriting 0 (+/+), 1 (+/-), or 2 (-/-) mutations in NCCT. Values for serum $Mg^{2+}$ can be converted to mmol/L by multiplying by 0.4114. Cr indicates creatinine. $P$ values for ANOVA among different genotype classes are indicated.

**Figure 4.** Effect of NCCT mutations on blood pressure. The mean±SEM values of age- and gender-adjusted diastolic blood pressures for members of kindred K140 with different NCCT genotypes are shown. $P$ values for ANOVA among different genotype classes are indicated. Individuals who have inherited 2 defective copies of NCCT have blood pressure that is significantly lower than that of their wild-type relatives.
gous and homozygous wild-type individuals, the higher urinary Na⁺ excretion in the heterozygous group suggests that the heterozygous individuals have self-selected a higher Na⁺ intake to compensate for a mild salt-wasting defect.

Because young individuals may have less opportunity to self-select their salt intake and may therefore have less ability to compensate for a mild defect, we tested the genotypic effect on blood pressure in children (aged <18 years). Young heterozygous individuals (n = 29) had mean age and gender-adjusted diastolic blood pressure 8.7 mm Hg lower than that of homozygous wild-type relatives (n = 11; P = 0.004). Although there were only 2 genotypically affected children in the kindred, their mean diastolic blood pressure was 12.9 mm Hg lower than that of homozygous wild-type individuals, consistent with a stepwise effect of mutant gene dose on blood pressure in children. Together, these results provide evidence of a significant effect of the heterozygous genotype on salt homeostasis and blood pressure.

**Discussion**

Gitelman’s syndrome is caused by a wide variety of loss of function mutations in NCCT, the Na-Cl cotransporter of the distal convoluted tubule (DCT). The results of the present study of a very large extended kindred indicate effects of homozygous and heterozygous mutations in the thiazide-sensitive Na-Cl cotransporter on electrolyte homeostasis and blood pressure.

Prior studies of this syndrome have largely relied on the identification of cases via abnormalities in electrolytes, potentially introducing ascertainment bias. Identification of 25 patients with 2 inherited NCCT mutations based solely on their relationship to an index case and the finding that all of these subjects have hypokalemia, metabolic alkalosis, hypomagnesemia, and hypocaliuria demonstrate the complete penetrance of these features among such individuals. Moreover, the cosegregation of this constellation of biochemical abnormalities with mutant NCCT alleles across this extended kindred constitutes proof that the observed hypomagnesemia and hypocaliuria, findings of uncertain etiology from known physiology, are in fact attributable to inheritance at the NCCT locus, underscoring the relationship between salt reabsorption in the DCT and renal Mg²⁺ and Ca²⁺ homeostasis.

The effects of Mg²⁺ homeostasis are particularly striking. Renal Mg²⁺ reabsorption has been believed to be mediated largely through paracellular conductance in the thick ascending limb of Henle, with only a small fraction of reabsorption occurring in the DCT. It is consequently surprising that a defect in salt reabsorption in the DCT should result in hypomagnesemia. This observation raises the possibility that the DCT normally mediates the final fine tuning of Mg²⁺ homeostasis, analogous to the role played by the epithelial Na⁺ channel for salt homeostasis in the distal nephron. The mechanism underlying this defect is uncertain. Similarly, hypocaliuria is a consistent finding among patients with these mutations, indicating a consistent influence of salt handling in the DCT on renal Ca²⁺ homeostasis.

The results of investigation of this kindred provide formal demonstration that the homozygous state for Gitelman’s syndrome lowers blood pressure in humans. The salt wasting of Gitelman’s syndrome is relatively mild. Nonetheless, these individuals have blood pressure lower than that of their unaffected relatives. This reduction in blood pressure is highly significant and is seen in both genders. Moreover, because these subjects have self-selected a markedly higher salt diet, it is likely that their blood pressures would be even lower without this adaptation. Although thiazide diuretics have long been recognized to have blood pressure–lowering effects, the present study indicates that loss of a single target, the gene product of NCCT, is sufficient to account for the blood pressure–lowering effects of these agents. Moreover, these findings indicate some of the inherent limits in the use of antagonists of the NCCT gene product. For example, complete inhibition of this target can be predicted to almost invariably lead to hypomagnesemia. Therefore, these observations predict both the utility and the limits in the use of antagonists of this target.

These findings are unlikely to be unique to the kindred studied. We have investigated a cohort of 70 unrelated adult patients with Gitelman’s syndrome in whom 2 mutant NCCT alleles have been identified. In this group, 83% of subjects had blood pressures that fell below the median diastolic blood pressure of the National Health and Nutrition Examination Survey (NHANES) participants of comparable age and gender (D.N. Cruz and R.P. Lifton, unpublished data, 2000), supporting the general effect of NCCT mutations in lowering blood pressure.

Previous studies have demonstrated that mutations that increase renal salt reabsorption increase blood pressure. The present observations formally demonstrate the opposite side of this equation, namely, that mutations that reduce renal salt reabsorption reduce blood pressure. These findings together demonstrate a strong and consistent effect of salt balance on blood pressure in humans that operates in both directions, demonstrating that alteration in salt balance represents a final common pathway for altering blood pressure in humans.

In addition, the present studies demonstrate a significant effect of the heterozygous state, with significantly increased dietary salt intake and, in younger individuals, lower blood pressure. This is of relevance because ≈1% of the population is likely to be heterozygous for mutations in this gene. These observations raise the question of whether the heterozygous state might underlie additional phenotypes. For example, diuretic-induced hypokalemia is a relatively common complication of loop diuretics; it is possible that NCCT heterozygous individuals may be more susceptible to this complication.

With regard to observational studies of the relationship between salt and blood pressure, it is worth noting that although primary salt wasting leads to lower blood pressure in Gitelman’s syndrome, in these patients there is actually an inverse relationship between dietary salt and blood pressure that is due to compensatory self selection of a high salt diet. Complexities such as these underscore the difficulties in interpreting observational studies of the salt–blood pressure relationship that do not investigate the underlying physiology of individual subjects. These observations raise the question of whether identification of individuals with very high salt
intake but very low blood pressure might identify other subsets of patients with impaired renal salt reabsorption. The demonstration of a consistent relationship between altered renal salt handling and blood pressure variation in humans identifies one of the final common pathways for altered blood pressure. These findings are beginning to put a molecular face on the physiological studies of Guyton,22 who demonstrated the requirement for an active role of the kidney in the development of hypertension. These observations in rare mendelian disorders raise the possibility that common variants in genes that mediate or regulate salt homeostasis in humans might underlie blood pressure variation in the general population. Moreover, they identify targets for the development of improved antihypertensive agents that may more closely address the abnormal physiology contributing to disease pathogenesis.

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References

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