Annu. Rev. Nutr. 2006. 26:343–65
doi: 10.1146/annurev.nutr.26.061505.111316

First published online as a Review in Advance on February 28, 2006

SALT HANDLING AND HYPERTENSION

Kevin M. O'Shaughnessy[1] and Fiona E. Karet[2,3]
[1]Clinical Pharmacology Unit, [2]Department of Medical Genetics, and [3]Division of Renal Medicine, University of Cambridge, Cambridge, United Kingdom;
email: fek1000@cam.ac.uk

Key Words sodium, kidney, animal models, blood pressure, stroke

■ **Abstract** The kidney plays a central role in our ability to maintain an appropriate sodium balance, which is critical for the determination of blood pressure. The kidney's capacity for salt conservation may not be widely appreciated, and in general we consume vastly more salt than we need. Here we consider the socioeconomics of salt consumption, outline current knowledge of renal salt handling at the molecular level, describe some of the disease entities associated with abnormal sodium handling, give an overview of some of the animal models and their relevance to human disease, and examine the evidence that lowering our salt intake can help combat hypertension and cardiovascular disease.

CONTENTS

INTRODUCTION

The worldwide epidemic of hypertension has had a major effect on health spending and therefore has become a frontline item on health agendas. The clinical impact of hypertension is very wide, varying from silent damage to blood vessels, through stroke or myocardial ischemia, to a sometimes-fatal syndrome of severe uncontrolled elevation of blood pressure (malignant hypertension) where acute renal failure, heart failure, and blindness are features.

Salt (sodium chloride) is of central importance to both our physiology and economics, so it is perhaps unsurprising that its consumption is a controversial topic, especially among medical epidemiologists, health policy makers, and lobbyists for the salt industry (85, 86). The modern literature concerning the relationship between salt and blood pressure in humans really begins in the 1960s with the work of Lewis Dahl. He correlated the prevalence of hypertension in five geographically distinct populations with their average daily salt intakes, and proposed that blood pressure rises linearly with salt consumption (26). Some populations display a higher-than-average susceptibility to hypertension, including African Americans and Bahamians, but in general, larger epidemiological studies have confirmed that blood pressure among societies correlates with salt consumption (31).

Experiments as far back as the late 1920s showed that loading hypertensive individuals with sodium bicarbonate did not have the same pressor effect as sodium chloride (8). This observation has been confirmed in more recent studies using citrate or phosphate as the counter-anion (47, 73). Loading with equivalent amounts of sodium salts causes similar degrees of sodium retention, weight gain, and suppression of the hormones renin and aldosterone, but curiously, only sodium chloride causes an expansion of plasma volume and a rise in blood pressure. Why chloride should have this unique property against other sodium salts is not clear, but from a dietary viewpoint, it makes little difference, since the bulk of the sodium we consume is in the form of sodium chloride.

THE SOCIOECONOMICS OF SALT

A low salt intake (<1 g/day) was inevitable for our ancestors, who evolved over several million years in a hot savannah environment remote from the sea. Our genome has almost certainly been shaped by the need to conserve bodily salt at this point in our evolution. Even today, hypertension is unknown in nonindustrialized and isolated tribal populations that have maintained a low-salt diet (<3 g/day). These same populations also lack the age-related rise in blood pressure that is a feature of modern industrialized societies (31). Salt only became an important commodity with the development of agriculture some 10,000 years ago, which produced food surpluses that could be accommodated by salt preservation. Since the Industrial Revolution there has been further intensification of the use of salt as food processing came of age. Recent globalization has meant this trend has spread

widely, so that typical salt intake in industrialized populations now exceeds 10 g/day and has reached as high as 60 g/day in some parts of northern Japan. This should be viewed in the context of a recent World Health Organization (WHO) recommendation that we should have a daily salt intake of no more than 5 g (1).

The economic importance of salt has had a profound impact throughout our history. Greek slave traders bartered with salt (hence "to be worth one's salt") and the Romans paid their legionnaires a *salarium* (hence "salary") to buy salt. But governments were raising revenues from salt long before this: The Chinese emperor Hsia Yu imposed the first recorded salt tax in 2200 BC. Revenues from salt monopolies have brought considerable wealth and shaped, for example, the rise of the Venetian empire. Not surprisingly, wars have been fought over salt, even as recently as the late nineteenth century in the 1877 Texas Salt War.

The burden of salt taxation has also been an important force for political change. Resentment of the French salt tax called the "Gabelle" helped fuel the French Revolution, and opposition to the British Salt Tax in India contributed to Gandhi's creation of a free state. The salt industry is still important economically, with sales exceeding $1.3 billion in 2004 (http://www.saltinstitute.org), equating to a per capita usage in the United States of some 500 g/day. Most of this goes onto highways or into manufacturing, but the importance of the small minority (<5%) that we consume through our diet has increased, thanks to trends in our eating behavior. In the past few decades, this has shifted markedly in favor of energy- and salt-rich snack foods, with parallel changes in the consumption of soft drinks to slake our thirst.

This is the nub of the current problem: Salt consumption is closely wedded to the processed food industry and to its highly lucrative fast food and soft drinks elements in particular. Hence, it is not difficult to see why there has been considerable opposition to revising national salt consumption downward. Although there may be cogent reasons to do this as a public health maneuver, it has huge financial repercussions for some of the most powerful multinational players in the food industry. Their possibly predictable response has been to obfuscate the data and undermine the antisalt lobby. In Europe, there are signs that food manufacturers are beginning to reduce the salt content of processed food, but there is a long way to go to achieve a target salt intake of 5–6 g/day.

MOLECULAR PHYSIOLOGY OF RENAL SALT HANDLING

Although the body has several means of maintaining a normal blood pressure (including neurologic and hormonal responses), the kidney's contribution to regulation of blood pressure by controlling sodium homeostasis is crucial. Prior to the elucidation of the molecular contributors to both renal sodium reabsorption and its linked functions, particularly of potassium and chloride handling, it was clear that the kidney was centrally involved in blood pressure determination. For example, it was demonstrated in the 1980s that transplantation of a kidney from a normotensive

donor into a hypertensive recipient corrects the hypertension, provided that the native kidneys are resected (25).

While it is true that the relationship between sodium homeostasis and final blood pressure is complex and involves intricate interactions with hormones such as dopamine, aldosterone, angiotensin II and ANP, the nephron's handling of filtered sodium is of central importance. As displayed in Figure 1, reabsorption of filtered sodium takes place at various sites along the nephron and involves several different types of transporter. In the context of normal renal function, about 25 moles per day of sodium ions pass across the glomerular filter into the nascent urine. The vast majority of this is reabsorbed. Around 60% of this reabsorption occurs in the proximal tubule, 25% in Henle's loop, 10% in the distal convoluted tubule, and the final 2% to 3% in the collecting duct (Figure 1*a*). This last step confers the tight regulation characteristic of normal renal function, and the result is a normal fractional excretion of sodium of less than 1%. In all segments, the electrogenic drive for sodium conservation is the basolateral activity of the Na-K-ATPase (Figure 1*b*), which is a P-type ATPase consisting of α and β subunits.

Proximal Tubule

The sodium-hydrogen exchanger NHE3 that is responsible for electroneutral apical sodium movement in the proximal tubule (Figure 1*c*) is an ATP-dependent protein with 12 transmembrane domains, a long intracellular C-terminal tail, and two extracellular glycosylation sites (10). It is located on the apical membrane with a fraction residing in subapical vesicles, suggestive of membrane recycling. NHE3 activity is at least partly regulated by interaction with the PDZ protein NHERF1 (91). NHE3 is sensitive to dopamine, and unlike some other renal sodium transporters, it is also found in intestinal epithelial cells. This accounts for the finding that *Nhe3*-null mice are not only hypotensive, hyperkalemic, and acidotic, but also have diarrhea (70). The potassium- and proton-handling abnormalities are due to the overwhelming of more distal nephron segments with the excess sodium and fluid still present in the proximal tubule.

On the basolateral surface, cotransport of sodium and bicarbonate occurs via the sodium-bicarbonate cotransporter NBC1. This is an electrogenic process with an apparent stoichiometry of three bicarbonate ions per sodium ion (67).

Loop of Henle

The electroneutral sodium-potassium-chloride cotransporter (NKCC2), which is expressed apically in the thick ascending limb of Henle's loop (Figure 1*c*), is the target for loop diuretics (e.g., furosemide). NKCC2 function is dependent on the recycling of K^+ ions back into the tubular fluid via ROMK, the inward-rectifier renal outer medullary K channel. ROMK is in turn regulated by the serine-threonine kinase WNK4 in a manner that is independent of its kinase activity (44).

Distal Convoluted Tubule

In the distal convoluted tubule, some 7% to 10% of overall sodium reabsorption takes place electroneutrally through renal tubular Na-Cl cotransporter (NCCT), the sodium chloride cotransporter that is the target of thiazide diuretics (e.g., bendroflumethiazide). NCCT function is regulated by the kinase WNK4, and here the action is kinase dependent (cf. ROMK). It is not known if NCCT is itself the phosphorylation target of WNK4, but the closely related serine/threonine kinase, WNK1, is able to block the action of WNK4, suggesting the WNKs form a regulatory complex with NCCT.

Collecting Duct

Electrogenic sodium channels known as ENaCs (epithelial Na channels) are expressed at the apical surface of collecting duct principal cells and are composed of at least three subunits: α, β, and γ (14). ENaC activity appears to be regulated by variation in the number of channels present at the cell surface. Normally, removal of ENaCs occurs following an interaction between a conserved PY motif in the C-terminal tail of one of its subunits and the E3 ligase Nedd4-2 (79, 81), resulting in ubiquitination, internalization, and proteasome-mediated degradation. Nedd4-2 is phosphorylated via the action of serum and glucocorticoid kinase 1 (SGK1), the function of which is up-regulated by aldosterone (18, 62), making ENaCs aldosterone-sensitive. When Nedd4-2 is phosphorylated, it loses the ability to interact with ENaCs, which results in the observed increase in activity. Pharmacological antagonists of ENaCs are the so-called K-sparing diuretics (e.g., amiloride, which blocks the ion channel) because the ENaC function is obligately coupled to potassium secretion into the urine via ROMK (Figure 1*c*).

HUMAN GENETICS AND RENAL SALT HANDLING: THE SINGLE-GENE DISORDERS

Inheritance undoubtedly contributes to the occurrence of hypertension. Heritability is generally estimated in the range of 30% to ~60%, depending on the population studied (2, 78, 90), and it is generally accepted that in any individual, at least five or six genes contribute to the final arterial pressure level, which reflects a complex network of gene-gene and gene-environment interactions. In some individuals, however, rare single-gene defects can cause marked abnormalities of blood pressure. The genetic causes of almost all of these rare Mendelian forms of hypertension and hypotension have now been discovered, and remarkably, they converge upon a final common pathway: the renal regulation of sodium reabsorption outlined above. Mutations that increase renal sodium reabsorption increase blood pressure, whereas those that decrease renal sodium reabsorption serve to decrease it. This analysis has had a major impact in advancing our understanding

of renal homeostatic mechanisms and reminds us of the importance of salt in determining blood pressure (51).

The following sections outline some of these Mendelian disorders; those serving to lower blood pressure by virtue of renal salt wasting are included.

Liddle Syndrome

In the 1960s, Grant Liddle described a three-generation kindred with autosomal dominant inheritance of early-onset hypertension and low potassium and alkalosis associated with suppressed levels of aldosterone (50). At first suspected to be an adrenal disorder, the renal seat of the hypertension was confirmed when the index patient received a cadaveric renal transplant in 1989, following which her hypertension and biochemical derangements resolved (13).

Liddle syndrome is best treated by a low-salt diet plus the K-sparing diuretics amiloride or triamterene, which suggested a problem with the ENaC. Reduction in salt consumption is an important adjunct to the drug therapy, because sodium competes for drug binding at the channel.

Mutations in either the β- or γ-subunit of the nonvoltage-gated ENaC gene can cause Liddle syndrome (37, 72). Mostly, these mutations result in truncations of the cytoplasmic C-terminal tail of the relevant subunit. These are associated with a gain-of-function in the ENaC, which is consistent with the dominant inheritance pattern.

In the kidney, functional Liddle syndrome mutations all affect the PY motif described above, either point mutations within the motif or frameshifts leading to its truncation, resulting in constitutive ENaC expression and therefore increased sodium reabsorption. Thus, patients with Liddle syndrome behave as if they were consuming and retaining excessive amounts of salt.

Pseudohypoaldosteronism Type 1

Pseudohypoaldosteronism type 1 (PHA1) represents the clinical inverse of Liddle syndrome. It is a rare inherited disorder characterized by renal salt wasting and metabolic acidosis with high potassium levels, despite markedly elevated renin and aldosterone, in the setting of otherwise normal renal and adrenal function (17). This gives a clinical picture of renal resistance to mineralocorticoids. Clinically distinct autosomal recessive and autosomal dominant forms of the disease are recognized. Both generally present in the first weeks of life, with dehydration, sodium wasting leading to low serum sodium, and hyperkalemic metabolic acidosis. In recessive PHA1, patients have severe sodium wasting from the colon, sweat, and salivary glands as well as the kidney. These children have recurrent life-threatening episodes of salt wasting as well as hyperkalemia that is very severe, requiring lifelong sodium supplementation and treatment with potassium-binding resins.

Recessive PHA1 is caused by homozygous loss-of-function mutations in any one of the ENaC subunits (16, 82), leading to a marked reduction of sodium reabsorption in the cortical collecting duct. The linked secretions of potassium and

hydrogen ions in this segment are blocked as well. The ensuing hyperkalemic, volume-depleted state stimulates the renin-angiotensin system, resulting in elevated aldosterone levels and maximal activation of the mineralocorticoid receptor (MR). Due to the absence of a functional ENaC, the MR is unable to stimulate sodium reabsorption, ensuring that sodium wasting and hyperkalemic acidosis persists.

The severity of the clinical course of recessive PHA1 patients highlights the crucial role of ENaCs in sodium homeostasis, even in individuals ingesting a high-salt diet. There is some variability in their prognosis. For patients with homozygous-null mutations, the prognosis is often very poor. Even minor illness can bring on rapid deterioration with hypotension and hyperkalemia; nausea and vomiting often herald and then accelerate the clinical decline.

In the dominant form of PHA1, sodium wasting occurs primarily from the kidney. The reason for this is not clear, but the phenotype is much milder; although children may be quite ill at birth, they generally respond to salt supplementation. They may even be able to discontinue treatment after the first few years of life. Heterozygous loss-of-function mutations in the MR gene cause this form of the disease (45).

Inherited Metabolic Alkaloses: Bartter and Gitelman Syndromes

Bartter and Gitelman syndromes were originally described as variations of a single disease process (7, 33) and together constitute a group of hypokalemic metabolic alkaloses. More recent biochemical and latterly genetic studies have permitted their separation into distinct disorders, with separable phenotypic characteristics. The genetic defects involve either the salt transporters that are targets for diuretics or other transporters that are their essential cellular partners. In both diseases, the mode of inheritance is autosomal recessive. To date, four genes have been implicated in the pathogenesis of Bartter syndrome in different kindreds, whereas all cases of Gitelman syndrome studied, now numbering several hundred, are accounted for by mutations in a single gene. In all these variants, the net effect is renal salt wasting, leading to low blood pressure, reduced serum potassium, and an activated renin-angiotensin system.

Features that differentiate Bartter and Gitelman syndromes are concerned with renal calcium handling and deposition, serum magnesium, and clinical presentation (9). In Bartter syndrome, affected individuals may present in infancy or early childhood with severe volume depletion and failure to thrive. Prematurity and maternal polyhydramnios are common. The metabolic dysfunction is usually accompanied by hypercalciuria with normal serum magnesium and calcium levels. Renal tract calcification is very common and may be present even in neonates. Nephrocalcinosis in infancy suggests type I or II Bartter syndrome. Hyperprostaglandinuria and a therapeutic response to indomethacin are features of type II disease. By contrast, those with type III Bartter syndrome may well be normocalciuric and mildly

hypomagnesemic, and devoid of renal calcium deposition. Type IV patients are deaf.

The biochemical picture in untreated Bartter syndrome is reminiscent of that occasionally seen in otherwise normal people on long-term loop diuretic therapy. The target for loop diuretics being NKCC2, it is perhaps unsurprising in retrospect that defects in the gene encoding NKCC2 cause type I Bartter syndrome (75). Subsequently, two further defective genes that result in loss of NKCC2 function have been identified in different kindreds. These are *ROMK* (type II Bartter syndrome) (76) and *CLCNKB*, which encodes the basolateral chloride channel in the same loop of Henle cells (type III) (74). Most recently, type IV Bartter syndrome has been attributed to loss of function in a novel protein, Barttin, an essential cofactor for CLC-KB function both in the kidney and inner ear, which explains the concomitant deafness (12, 32).

By far, the majority of patients suspected of having Bartter syndrome in fact have the much commoner Gitelman syndrome. The phenotype here is often very much milder and is usually identified in late childhood or even in adulthood. Some affected individuals are asymptomatic, but others may be more severely affected, with growth problems and, not uncommonly, joint problems, tetany, and/or other neuromuscular abnormalities. A survey of presenting symptoms (24) highlights the differences in perception between patients and their physicians; although doctors often consider Gitelman syndrome to be asymptomatic, most patients disagree. Anecdotally, it is reported that affected individuals may note a longstanding preference for salty over sweet foods and snacks. Biochemically, Gitelman syndrome is characterized by hypocalciuria and hypomagnesemia with renal magnesium wasting.

Gitelman syndrome patients display many of the biochemical changes seen in individuals on thiazide diuretics; indeed, the surreptitious abuse of diuretics (or laxatives) remains the commonest differential diagnosis. All cases of Gitelman syndrome are due to loss of function of the thiazide's drug target, NCCT (77) (Figure 1*c*).

The treatment of Bartter and Gitelman syndromes can be difficult because the degree of salt wasting may be severe. Aggressive replacement of salt and K^+ in particular are essential. Some patients respond well to the administration of indomethacin, especially in type II Bartter syndrome. Magnesium supplementation is also usually required in Gitelman syndrome, where very large doses may be needed.

Gordon Syndrome

The clinical inverse of Gitelman syndrome is that bearing Richard Gordon's name (34), also known as pseudohypoaldosteronism type 2. Here, hypertension is associated with chloride-dependent sodium retention, plus elevated serum potassium and acidosis. Despite the clinical indication of overactivity of NCCT, linkage to this gene was formally excluded in favor of at least three other loci (29, 56). Two responsible genes have now been identified, encoding the "with no lysine" (WNK)

kinases WNK1 and WNK4 (93). WNK1 is expressed ubiquitously, and is particularly associated with chloride-transporting epithelia at all sites (20), whereas WNK4 expression is largely limited to the distal nephron. Of particular interest here is recent evidence that disease-causing WNK4 mutations exert their effects by relieving the normal WNK4 inhibition of NCCT expression, leading to transporter overactivity (94, 95). These same mutations actually increase inhibition of ROMK channel activity, which within the collecting duct could explain the hyperkalemia that accompanies the syndrome (44). WNK4 therefore represents an intriguing potential antihypertensive target.

MOVING FROM MOLECULAR GENETICS TO THE POPULATION

Clearly, the majority of hypertensive individuals do not have such severe genetic defects as those outlined above. The single-gene disorders may be rare, but they do highlight an important relationship between salt, the renin-angiotensin-aldosterone axis, and blood pressure. In an extension of the important physiological insights provided by these disorders, the population- or cohort-based genetic studies designed to identify genes implicated in faulty blood pressure regulation currently number several hundreds (see 38, 43). These studies are of two main types: association studies, which usually compare polymorphisms (or occasionally haplotypes) in or near particular candidate genes, and genome-wide linkage analyses, which seek disease-causing genetic loci. Despite enormous efforts to find genes in the wider hypertensive population, the results have often been rather mixed. However, a few genes for which the majority of data from human studies are positive do stand out: *AGT*, encoding angiotensinogen, and that encoding the β-subunit of the ENaC (reviewed in 23). For both of these, there were functional consequences to the genetic findings that suggest a subtle alteration in sodium handling in affected individuals. These results from human genetic and physiologic investigations have gained further credence by supporting information from animal models (see below).

Another gene that has excited interest is that encoding α-adducin. This is in fact a cytoskeletal protein, but it is thought to modulate the activity of the basolateral Na/K-ATPase that plays a key role in electrogenic movement of salt through cells along the nephron (Figure 1) (87). Studies both of sibling pairs and at the population level have supported linkage (reviewed in 58).

A general conclusion, at least, can be drawn from population-based studies reported in the past decade. Rather than supporting a model of a few genes exerting relatively large effects in a hypertensive individual, they point to a model in which there are many genes, each exerting a relatively small effect. Thus, sample sizes for future studies will need to be very much larger (probably 10,000 subjects or more) to have sufficient power to observe these effects. Other reasons for the lack of major progress from many other association-based and genome-wide approaches have been offered. These frequently include criticisms of statistical methodology

or of the subset of individuals selected for study. Hidden stratification within populations is a recurrent concern, which may not be resolved by meta-analysis, since combining genome-wide scans taken from very different populations is just as likely to confound as to enhance the power of this approach (65).

CONTRIBUTIONS FROM ANIMAL STUDIES

Given the enormous background genetic variability of the human species, laboratory animals have been an obvious choice to test hypotheses concerning the relationship between salt and blood pressure, both at the dietary level and more recently by means of genetic manipulation. Gene-targeting experiments in mice have both confirmed the observations of humans with single-gene disorders and extended them. For example, expression of one to four copies of a transgene encoding angiotensinogen results in a gene dose-dependent increase in a mouse's blood pressure (46).

A variety of clinical studies in different species, including rats, baboons, pigs, African green monkeys, and chimpanzees, have all confirmed that there is a positive association between the absolute level of salt consumption and blood pressure (5, 11, 19, 22, 28, 80). Critics of the now classical Dahl strain of salt-sensitive rat (27), however, point to the levels of salt intake required to increase blood pressure as being vastly in excess of the human dietetic range; the Dahl rat was typically given 8% saline to drink. Although this may translate into >20–30 g/day of salt for a rat (well within current human extremes of intake), a study in the chimpanzee showed that this animal's blood pressure could be raised incrementally by elevating salt intake from a baseline of just 0.5 g/day to 5, 10, and 15 g/day (28). As we share 98.4% of our genome with the chimpanzee, this can be viewed as a robust and relevant model for humans.

In addition, in several of these animal studies, a defined period of increased salt intake that produced the predicted blood pressure increases was followed by a second period where salt consumption reverted to lower levels. In each case, the blood pressure fell again.

The Barker hypothesis states that in humans, birth weight and adult blood pressure are reciprocally related (6). This finding has had a considerable impact on how we now view exposure to factors in utero or early in postnatal life, especially the long-term effects on gene expression that may result (30). It is conceivable that our scrutiny of salt intake in adults is partly misplaced, and we should instead be addressing salt intake in infancy and/or early childhood for maximal benefit, particularly since human breast milk contains only 11 mmol/l of sodium, and modern societies tend to wean at a younger age. Animal studies have confirmed, and indeed extended, Barker's findings concerning the materno-fetal origins of blood pressure elevation. In strains of rat with genetically determined blood pressure, the severity of adult hypertension is strongly influenced by the genotype of the mother. Hence, if pups from the spontaneously hypertensive or salt-sensitive Dahl strains are

fostered within two weeks of birth by mothers from normotensive control strains, they have a 20–30 mm Hg lower blood pressure as adults when compared with pups fostered by their biological mothers (21, 59). It is interesting that this effect does not work in reverse; pups from normotensive strains raised by spontaneously hypertensive rat mothers do not show a rise in blood pressure as adults. For a given strain to show this fostering effect, it appears that it must first have genetic sensitivity to dietary salt. Rats from the New Zealand GH strain, which show no increase in body sodium or salt appetite, do show a small transient hypotensive effect of fostering, but blood pressure in the adult GH rat is not affected by its fostering history (49). Thus, it appears that in salt-sensitive rat strains, fostering can modify the programming of the neonatal kidney so that it can excrete more sodium (35).

HUMAN POPULATION AND INTERVENTION STUDIES

The results of human population studies, as alluded to above, have often been conflicting. For example, the 1988 INTERSALT study sponsored by the National Heart, Lung, and Blood Institute, the largest study of its kind, was drawn from 52 centers in 32 countries and contained more than 10,000 individuals (42). Despite its apparent breadth of recruitment, it failed to find any correlation unless four apparent "outliers" with very low salt intakes were included. But without their inclusion, the range of salt intakes across the centers telescoped from 0.12–14 g/day to just 6–14 g/day. With hindsight, the goal of demonstrating a significant dose-response within this narrow range was probably unrealistic. However, this study did report that in populations with a high salt intake, the relation between blood pressure and age was steeper than in populations with a low salt intake: Between the ages of 25 and 55, the slope was approximately 0.9 mm Hg higher for each 10 mmol (0.6 g) difference in salt intake.

A problem with interpopulation-based studies is their openness to ecological confounders, in the sense that the salt content of the diet is not the only difference between so-called low- and high-salt populations. Like spot blood pressure measurements, single measurements of 24-hour sodium excretion are also notoriously variable. This renders studies like INTERSALT susceptible to the statistical effect of dilutional regression bias that may reduce (or inflate) any real association of salt intake and hypertension. Indeed, the final credibility of the INTERSALT study was heavily undermined by attempts to "correct" for this phenomenon to produce much larger estimates of the pressor effect of salt (31).

An alternative to population-based trials is the intervention trial. Dozens of these have been published, though they are often small and have subsequently been combined by meta-analysis. The difficulty with this approach is that many trials are included that have flawed design—they are often unblinded or include treated hypertensives. Nevertheless, the meta-analysis by Law et al. (48), which focused on studies that lasted more than five weeks, reported an average fall in systolic blood pressure of 5 mm Hg resulting from a 50 mmol ($\sim$3 g/day) reduction

in salt intake. This is very close to the figures published in a more recent meta-analysis that again focused on the longer-term intervention trials (Figure 2) (39).

Perhaps the single and most convincing intervention trial to date has been the Dietary Approaches to Stop Hypertension (DASH) study, or more correctly, its substudy, DASH-sodium (68). In this study, 412 individuals were assigned either to a "normal American" diet or to the DASH diet (high in fruit and vegetables and low-fat dairy products) and one of three different levels of salt intake: high, intermediate, and low; approximating 9, 6, or 3 g/day of salt, respectively. Participants were kept on these diets for 30 days, and the blood pressure reductions were as shown in Figure 3. Blood pressure reduction was again in keeping with the values from the meta-analyses above, but the effect of the DASH diet was at least as great. This effect of diet can be explained partly by the well-established interplay of dietary cations. For example, intake of calcium dictated by water hardness is inversely related to cardiovascular mortality, and calciuresis is a feature of salt loading (52, 63). Similarly, potassium supplementation is hypotensive (15), and may even protect against stroke independently of its effect on blood pressure (4). Different levels of dietary folic acid and antioxidant vitamins (C and E) may also be relevant, since they may affect blood pressure through effects on endothelial function and bioavailable nitric oxide levels within the vasculature (66, 89). It is therefore becoming clear that the dietary context in which salt restriction occurs can be as crucial as the restriction itself.

The differences between the population and interventional studies on salt intake can also be partly explained by interindividual variation in susceptibility to the pressor effect of salt loading. This heterogeneity in response to salt was obvious in the original human intervention studies (55) and in the recent salt-loading study in chimpanzees discussed above (28). Salt sensitivity is affected by age, race, and disease state and hence is more common in the elderly, in Afro-Caribbean races, and among type II diabetics. There is a definable genetic influence within families (53). However, there is no universal definition of salt sensitivity, and therefore studies resort to arbitrary cutoffs to define salt "responders" and "nonresponders." This has not perturbed the intense trawls for susceptibility genotypes even within the well-characterized DASH cohort itself (83). Until simple molecular markers like these become available, it will be impossible to identify easily those individuals in the general population who would benefit most from dietary salt restriction.

Using a double-blind placebo-controlled approach, a recent interesting study by MacGregor's group (84) has shown that modest restriction of salt to ~5 g/day (in keeping with WHO recommendations) can reduce blood pressure in black hypertensive subjects. Subjects were randomized to slow sodium tablets or to placebo for four weeks and then crossed over. The switch to placebo reduced urinary sodium excretion from 169 $\pm$ 73 to 89 $\pm$ 52 mmol/24 hours with a corresponding fall in blood pressure of 8/3 mm Hg ($p < 0.01$). This reduction was comparable to that caused by a single antihypertensive agent (57). There was also a small but very significant fall in excretion of urinary protein: 93 $\pm$ 48 mg to

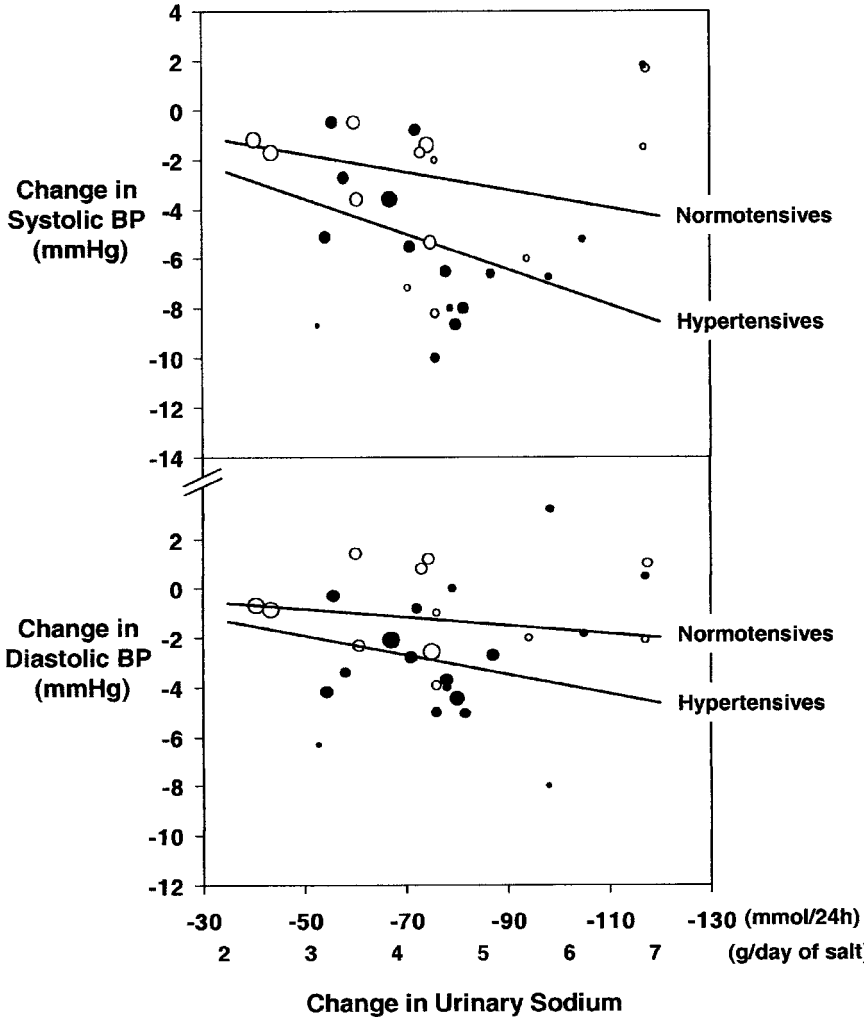

Figure 2 Dose-dependent effect of salt restriction on blood pressure (BP) and 24-hour urinary sodium excretion. This meta-analysis included 17 trials that showed randomized entry and lasted at least four weeks. Open circles, normotensives; solid circles, hypertensives. The size of each circle is proportional to the weight of that trial. The dose-dependent reduction in BP was largest among hypertensive subjects, with predicted falls of 3.6/1.9, 7.1/3.9, and 10.7/5.8 mm Hg (systolic/diastolic) for a 3, 6, and 9 g/day reduction in intake. Reproduced with permission from *Hypertension* (39).

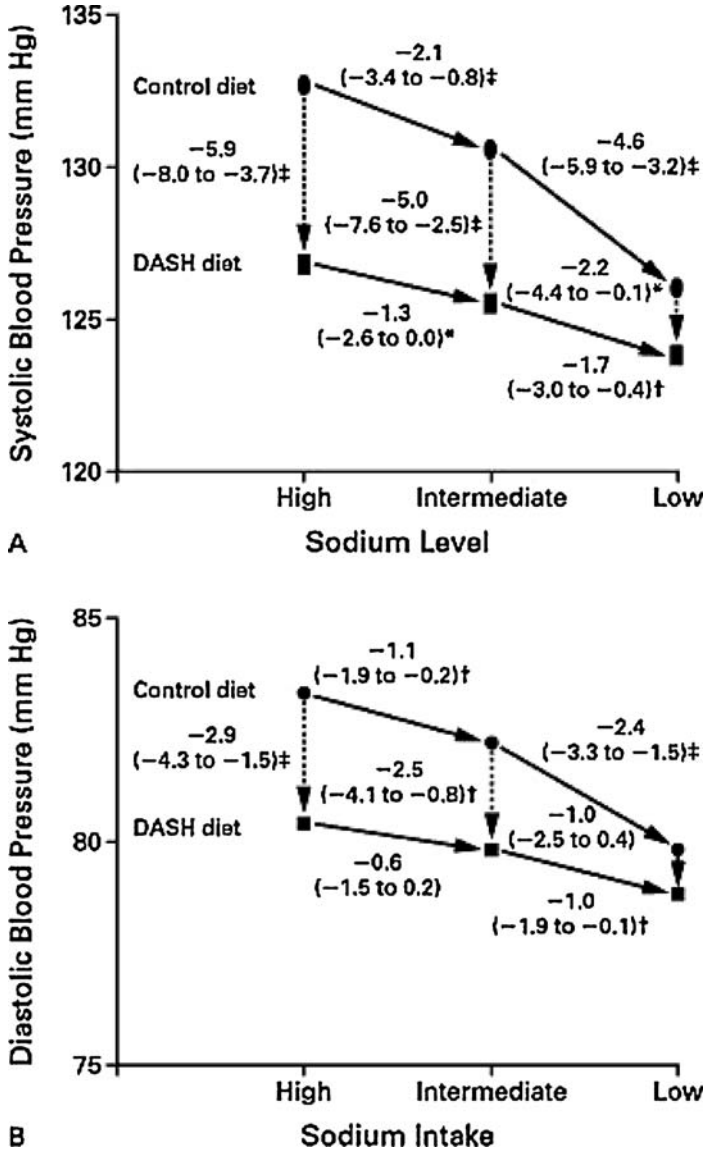

Figure 3 Blood pressure changes during the Dietary Approaches to Stop Hypertension (DASH)-sodium trial. Although arrows are unidirectional, the order in which individuals were assigned a given salt level was random with a crossover design. The numbers next to the lines connecting the data points are the mean changes in blood pressure. The 95% confidence intervals are given in parentheses. Asterisks ($p < 0.05$), daggers ($p < 0.01$), and double daggers ($p < 0.001$) indicate significant differences in blood pressure between groups or between dietary sodium categories. Reproduced with permission from the *New England Journal of Medicine* (68).

75 ± 30 mg per 24 hours ($p < 0.008$). These outcomes are particularly important given the burden of stroke and end-stage renal disease that hypertension causes in black Americans.

PUBLIC HEALTH IMPLICATIONS OF DIETARY SALT RESTRICTION

It is interesting that in 2004, the U.S. Institute of Medicine issued a strong across-the-board recommendation that salt consumption be approximately halved—which may be difficult to achieve in these fast-food days—and also advised a significant increase in potassium intake "to lower blood pressure and blunt the effects of salt," among other benefits (41). But given the consistent body of data linking salt intake and blood pressure, is there actually evidence that salt intake also affects the rates of cardiovascular disease? Perry & Beevers (64) showed originally that across Europe death rates from stroke correlated very significantly with the salt intake recorded in the INTERSALT study (Figure 4). In fact, despite the difference in salt intake being modest across countries (~3 g/day), the benefits were large, with a fourfold difference in the stroke death rate. They showed that the effect of salt intake was independent of BMI, and they observed that it was a stronger correlation than that of stroke and systolic blood pressure. This supports other evidence suggesting that a high salt intake has detrimental effects in addition to simply elevating blood pressure. Increased arterial stiffness and left ventricular mass and platelet aggregability have all been associated independently with salt intake and would be expected to affect cardiovascular risk (36, 69, 96). Analysis of the NHANES I epidemiologic follow-up study also showed that a high salt intake was an independent predictor of cardiovascular disease and all-cause mortality in obese men and women (BMI >27.8 and >27.3 kg/m^2, respectively) (40). A 6 g/day increase in salt intake in this study increased not only the incidence of stroke and CHD, but also their mortality (89% and 61%, respectively). These studies were of course performed retrospectively, but two recent prospective studies have confirmed that salt intake is an independent predictor of cardiovascular death. The first, from Japan, followed up more than 29,000 men and women between 1992 and 1999 and reported that death from ischemic stroke or intracerebral hemorrhage was strongly associated with an individual's tertile of salt intake at entry (61). The second study, from Finland, quantified salt intake with a 24-hour urine collection and found that both the frequency and death rate from coronary artery disease rose with increasing salt intake. A 6 g/day rise in salt intake within the study group increased the frequency of acute coronary events 1.34 fold (1.07–1.68) (88). The authors also noted a significant interaction of obesity and salt intake in determining cardiovascular risk, which emphasizes the same findings from the NHANES I analysis.

It is possible to estimate the impact of a reduced salt intake on cardiovascular disease based on the expected fall in blood pressure, although the relation of

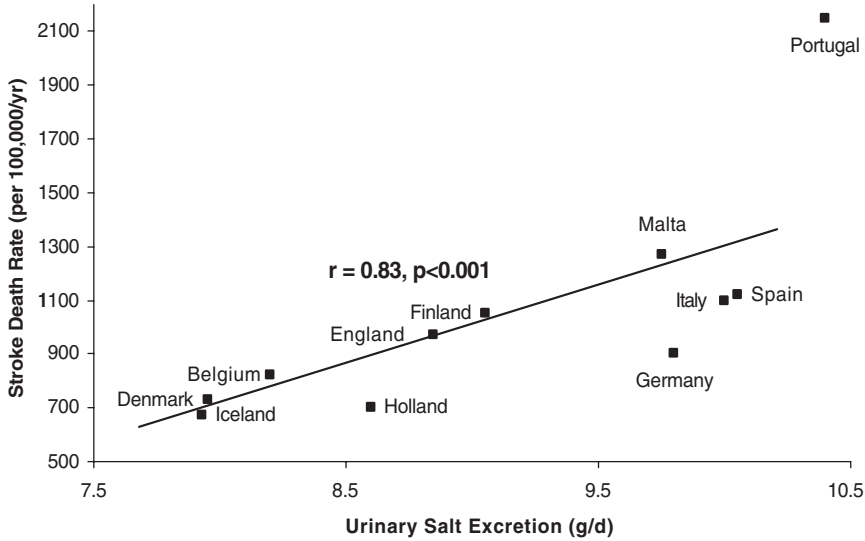

Figure 4 Regression line for death rate from stroke versus urinary salt excretion recorded in European countries taking part in the INTERSALT study. Reproduced with permission from the *Journal of Human Hypertension* (64).

cardiovascular disease and blood pressure is not linear, but exponential, and the relationship is steeper for stroke than for myocardial infarction. The benefit of reducing salt intake by a modest 3 g/day has been estimated to reduce the prevalence of stroke and myocardial infarction by 22% and 16%, respectively (48). Based on their more recent meta-analysis, He & MacGregor (39) estimated the effect of a DASH-like reduction in salt intake from 12–3 g/day for the U.K. population. This analysis suggests if the current WHO target of 5–6 g/day could be achieved in the United Kingdom, ∼15,000 deaths from stroke and a further ∼30,000 from myocardial infarction would be prevented. Impressive as the figures are, they may actually underestimate the benefit, since during DASH-sodium and other intervention studies the falls in blood pressure were larger than the meta-analysis results themselves.

A recent analysis has emphasized just how cost-effective nonpersonal health interventions can be to governments in preventing cardiovascular disease. Such interventions could include a national reduction in salt intake via processed food (60). It was estimated that around 20 million disability life-years could be saved worldwide by this approach. Nonetheless, governments have been slow in addressing the public health importance of a lowered salt intake. The United Kingdom has recently taken a lead in this with their Food Standards Agency, which set a goal of reaching a 6 g/day target by 2010 (http://www.salt.gov.uk/index.shtml). However, even this modest goal is only going to be achieved with the active support

of the food industry, as ~80% of our dietary salt is "hidden" within prepared and processed food. This poses a particular bar to the prospect of reducing intake still further to 3 g/day, where cardiovascular benefits are even larger. Labeling food products with their sodium content would seem an important good starting point, but even here a consensus is still lacking (71). Assuming this can be surmounted, a reasonable strategy would be to reduce salt intake through processed food in annual small steps. This would produce no noticeable change in the taste of our processed food nor confound food technologists who rely on salt to enhance its succulence and shelf life.

Critics have argued that implementation of a public health initiative to lower salt intake, especially if it is to happen with food industry support, requires evidence from an outcome trial. Yet other dietary and lifestyle changes have been adopted without this evidence. There are no outcome trials, for example, showing that stopping cigarette smoking, increasing fruit and vegetable intake, exercising, or losing weight affect coronary disease mortality. What should convince us of the need to reduce our salt intake is the size and consistency of the evidence base that it will affect both our blood pressure and reduce our risk of cardiovascular disease. This evidence comes from epidemiology, migration, intervention, animal, and genetic studies and dwarfs the evidence available to support any other lifestyle change.

That said, salt restriction is always worthwhile in subjects taking specific antihypertensive agents. For example, dietary manipulation of patients receiving amiloride or triamterene should be beneficial, because these act competitively with sodium for transport via ENaC. In addition, there is evidence that reducing salt intake increases the efficacy of angiotensin-converting enzyme inhibitors because of the renin-angiotensin-aldosterone axis activation that salt depletion induces (92).

CONCLUSIONS

Overall it seems very clear that the body's handling of salt is key to our cardiovascular health, and recent evidence strongly supports the use of saliuretics (as prescription thiazide diuretics) for first-line therapy of hypertension and hence the prevention of coronary heart disease (3). The real controversy is not whether salt affects blood pressure, but rather whether the current body of evidence supports a reduction in salt intake in the general population. Dietary manipulations tend to have poor compliance rates in the long term (54), but given the increasing prevalence of hypertension and the steep relation between stroke risk and blood pressure, any strategy that reduces stroke burden in the general population must be taken very seriously. The public health and budgetary implications are surely irresistible. We could invest more effort in clinical, biochemical, and pharmacologic phenotyping of hypertensive subjects to identify those who will derive most benefit from a low salt intake. Alternatively, the simpler strategy is to target the ~80% of dietary salt that comes to us through food processing, to achieve a population-wide salt intake of 5–6 g/day. It does not seem reasonable that implementing this should require outcome data from randomized intervention trials—even supposing it were

still ethical and fundable. Other lifestyle changes have been accepted on vastly inferior evidence, but the gulf separating the "pro" and "anti" low-salt camps still needs to be closed. This will take either further reasoned argument or public and government pressure.

ACKNOWLEDGMENTS

Kevin M. O'Shaughnessy and Fiona E. Karet acknowledge the support of the British Heart Foundation and the Wellcome Trust, respectively.

The *Annual Review of Nutrition* is online at http://nutr.annualreviews.org

LITERATURE CITED

1. *2003 Report of a Joint WHO/FAO Expert Consultation*. Diet, nutrition and the prevention of chronic disease. World Health Org., Geneva
2. Adeyemo AA, Omotade OO, Rotimi CN, Luke AH, Tayo BO, Cooper RS. 2002. Heritability of blood pressure in Nigerian families. *J. Hypertens.* 20:859–63
3. Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial Collaborative Research Group. 2003. Diuretic versus alpha-blocker as first-step antihypertensive therapy: final results from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Hypertension* 42:239–46
4. Ascherio A, Rimm EB, Hernan MA, Giovannucci EL, Kawachi I, et al. 1998. Intake of potassium, magnesium, calcium, and fiber and risk of stroke among US men. *Circulation* 98:1198–204
5. Ball CO, Meneely GR. 1957. Observations on dietary sodium chloride. *J. Am. Dent. Assoc.* 33:366–70
6. Barker DJ, Osmond C, Golding J, Kuh D, Wadsworth ME. 1989. Growth in utero, blood pressure in childhood and adult life, and mortality from cardiovascular disease. *Br. Med. J.* 298:564–67
7. Bartter FC, Pronove P, Gill JR Jr, MacCardle RC. 1962. Hyperplasia of the juxtaglomerular complex with hyperaldosteronism and hypokalemic alkalosis. A new syndrome. *Am. J. Med.* 33:811–28
8. Berghoff RS, Geraci AS. 1929. The influence of sodium chloride on blood pressure. *Br. Med. J.* 56:395–97
9. Bettinelli A, Bianchetti MG, Girardin E, Caringella A, Cecconi M, et al. 1992. Use of calcium excretion values to distinguish two forms of primary renal tubular hypokalemic alkalosis: Bartter and Gitelman syndromes. *J. Pediatr.* 120:38–43
10. Biemesderfer D, Pizzonia J, Abu-Alfa A, Exner M, Reilly R, et al. 1993. NHE3: a Na^+/H^+ exchanger isoform of renal brush border. *Am. J. Physiol.* 265:F736–42
11. Biemesderfer D, Rutherford PA, Nagy T, Pizzonia JH, Abu-Alfa AK, Aronson PS. 1997. Monoclonal antibodies for high-resolution localization of NHE3 in adult and neonatal rat kidney. *Am. J. Physiol.* 273:F289–99
12. Birkenhager R, Otto E, Schurmann MJ, Vollmer M, Ruf EM, et al. 2001. Mutation of BSND causes Bartter syndrome with sensorineural deafness and kidney failure. *Nature Genet.* 29:310–14
13. Botero-Velez M, Curtis JJ, Warnock DG. 1994. Brief report: Liddle's syndrome revisited - a disorder of sodium reabsorption in the distal tubule. *N. Engl. J. Med.* 330:178–81
14. Canessa CM, Schild L, Buell G, Thorens B, Gautschi I, et al. 1994. Amiloride-sensitive

epithelial Na^+ channel is made of three homologous subunits. *Nature* 367:463–67
15. Cappuccio FP, MacGregor GA. 1991. Does potassium supplementation lower blood pressure? A meta-analysis of published trials. *J. Hypertens.* 9:465–73
16. Chang SS, Grunder S, Hanukoglu A, Rosler A, Mathew PM, et al. 1996. Mutations in subunits of the epithelial sodium channel cause salt wasting with hyperkalaemic acidosis, pseudohypoaldosteronism type 1. *Nature Genet.* 12:248–53
17. Cheek DB, Perry JW. 1958. A salt wasting syndrome in infancy. *Arch. Dis. Child.* 33:252–56
18. Chen SY, Bhargava A, Mastroberardino L, Meijer OC, Wang J, et al. 1999. Epithelial sodium channel regulated by aldosterone-induced protein SGK. *Proc. Natl. Acad. Sci. USA* 96:2514–19
19. Cherchovich GM, Capek K, Jefremova Z, Pohlova I, Jelinek J. 1976. High salt intake and blood pressure in lower primates (*Papio hamadryas*). *J. Appl. Physiol.* 40:601–4
20. Choate KA, Kahle KT, Wilson FH, Nelson-Williams C, Lifton RP. 2003. WNK1, a kinase mutated in inherited hypertension with hyperkalemia, localizes to diverse Cl^--transporting epithelia. *Proc. Natl. Acad. Sci. USA* 100:663–68
21. Cierpial MA, McCarty R. 1987. Hypertension in SHR rats: contribution of maternal environment. *Am. J. Physiol.* 253:H980–84
22. Corbett WT, Kuller LH, Blaine EH, Damico FJ. 1979. Utilization of swine to study the risk factor of an elevated salt diet on blood pressure. *Am. J. Clin. Nutr.* 32:2068–75
23. Corvol P, Persu A, Gimenez-Roqueplo AP, Jeunemaitre X. 1999. Seven lessons from two candidate genes in human essential hypertension: angiotensinogen and epithelial sodium channel. *Hypertension* 33:1324–31
24. Cruz DN, Shaer AJ, Bia MJ, Lifton RP, Simon DB. 2001. Gitelman's syndrome revisited: an evaluation of symptoms and health-related quality of life. *Kidney Int.* 59:710–17
25. Curtis JJ, Luke RG, Dustan HP, Kashgarian M, Whelchel JD, et al. 1983. Remission of essential hypertension after renal transplantation. *N. Engl. J. Med.* 309:1009–15
26. Dahl LK. 1960. Possible role of salt intake in the development of essential hypertension. In *Essential Hypertension*: *An International Symposium*, ed. P Cottier, KD Bock, pp. 61–75. Berlin: Springer Verlag
27. Dahl LK, Heine M, Tassinari L. 1962. Effects of chronic excess salt ingestion: evidence that genetic factors play an important role in susceptibility to experimental hypertension. *J. Exp. Med.* 115:1173–90
28. Denton D, Weisinger R, Mundy NI, Wickings EJ, Dixson A, et al. 1995. The effect of increased salt intake on blood pressure of chimpanzees. *Nature Med.* 1:1009–16
29. Disse-Nicodeme S, Achard JM, Desitter I, Houot AM, Fournier A, et al. 2000. A new locus on chromosome 12p13.3 for pseudohypoaldosteronism type II, an autosomal dominant form of hypertension. *Am. J. Hum. Genet.* 67:302–10
30. Dodic M, Moritz K, Koukoulas I, Wintour EM. 2002. Programmed hypertension: kidney, brain or both? *Trends Endocrinol. Metab.* 13:403–8
31. Elliott P, Stamler J, Nichols R, Dyer AR, Stamler R, et al. 1996. INTERSALT revisited: further analyses of 24 hour sodium excretion and blood pressure within and across populations. INTERSALT Cooperative Research Group. *Br. Med. J.* 312:1249–53
32. Estevez R, Boettger T, Stein V, Birkenhager R, Otto E, et al. 2001. Barttin is a Cl^- channel beta-subunit crucial for renal Cl^- reabsorption and inner ear K^+ secretion. *Nature* 414:558–61
33. Gitelman HJ, Graham JB, Welt LG. 1966. A new familial disorder characterized by hypokalemia and hypomagnesemia. *Trans. Assoc. Am. Phys.* 79:221–35
34. Gordon RD, Geddes RA, Pawsey CG, O'Halloran MW. 1970. Hypertension and severe hyperkalaemia associated with suppression of renin and aldosterone and

completely reversed by dietary sodium restriction. *Australas. Ann. Med.* 19:287–94

35. Gouldsborough I, Ashton N. 1998. Effect of cross-fostering on neonatal sodium balance and adult blood pressure in the spontaneously hypertensive rat. *Clin. Exp. Pharmacol. Physiol.* 25:1024–31
36. Gow IF, Dockrell M, Edwards CR, Elder A, Grieve J, et al. 1992. The sensitivity of human blood platelets to the aggregating agent ADP during different dietary sodium intakes in healthy men. *Eur. J. Clin. Pharmacol.* 43:635–38
37. Hansson JH, Nelson-Williams C, Suzuki H, Schild L, Shimkets R, et al. 1995. Hypertension caused by a truncated epithelial sodium channel gamma subunit: genetic heterogeneity of Liddle syndrome. *Nature Genet.* 11:76–82
38. Harrap SB. 2003. Where are all the blood-pressure genes? *Lancet* 361:2149–51
39. He FJ, MacGregor GA. 2003. How far should salt intake be reduced? *Hypertension* 42:1093–99
40. He J, Ogden LG, Vupputuri S, Bazzano LA, Loria C, Whelton PK. 1999. Dietary sodium intake and subsequent risk of cardiovascular disease in overweight adults. *J. Am. Med. Assoc.* 282:2027–34
41. Institute of Medicine of the National Academies. 2004. *Dietary Reference Intakes for Water, Potassium, Sodium, Chloride and Sulfate*. Washington, DC: Natl. Acad. Press. 640 pp.
42. INTERSALT Cooperative Research Group. 1988. INTERSALT: an international study of electrolyte excretion and blood pressure. Results for 24 hour urinary sodium and potassium excretion. *Br. Med. J.* 297:319–28
43. Jeunemaitre X. 2003. Renin-angiotensin-aldosterone system polymorphisms and essential hypertension: Where are we? *J. Hypertens.* 21:2219–22
44. Kahle KT, Wilson FH, Leng Q, Lalioti MD, O'Connell AD, et al. 2003. WNK4 regulates the balance between renal NaCl reabsorption and K^+ secretion. *Nature Genet.* 35:372–76
45. Kerem E, Bistritzer T, Hanukoglu A, Hofmann T, Zhou Z, et al. 1999. Pulmonary epithelial sodium-channel dysfunction and excess airway liquid in pseudohypoaldosteronism. *N. Engl. J. Med.* 341:156–62
46. Kim HS, Krege JH, Kluckman KD, Hagaman JR, Hodgin JB, et al. 1995. Genetic control of blood pressure and the angiotensinogen locus. *Proc. Natl. Acad. Sci. USA* 92:2735–39
47. Kurtz TW, Al Bander HA, Morris RC Jr. 1987. "Salt-sensitive" essential hypertension in men. Is the sodium ion alone important? *N. Engl. J. Med.* 317:1043–48
48. Law MR, Frost CD, Wald NJ. 1991. By how much does dietary salt reduction lower blood pressure? III—Analysis of data from trials of salt reduction. *Br. Med. J.* 302:819–24
49. Ledingham JM, Ashton N. 2005. Remodelling of mesenteric arteries in genetically hypertensive rats cross-fostered from birth to normotensive Wistar rats. *Clin. Exp. Pharmacol. Physiol.* 32:859–64
50. Liddle G, Bledsoe T, Coppage W. 1963. A familial renal disorder simulating primary aldosteronism but with negligible aldosterone secretion. *Trans. Assoc. Am. Phys.* 76:199–213
51. Lifton RP, Gharavi AG, Geller DS. 2001. Molecular mechanisms of human hypertension. *Cell* 104:545–56
52. Lind L, Lithell H, Gustafsson IB, Pollare T, Ljunghall S. 1993. Calcium metabolism and sodium sensitivity in hypertensive subjects. *J. Hum. Hypertens.* 7:53–57
53. Luft FC, Miller JZ, Weinberger MH, Grim CE, Daugherty SA, Christian JC. 1987. Influence of genetic variance on sodium sensitivity of blood pressure. *Klin. Wochenschr.* 65:101–9
54. Luft FC, Morris CD, Weinberger MH. 1997. Compliance to a low-salt diet. *Am. J. Clin. Nutr.* 65:698–703S
55. Luft FC, Weinberger MH. 1997. Heterogeneous responses to changes in dietary salt

intake: the salt-sensitivity paradigm. *Am. J. Clin. Nutr.* 65:612–17S

56. Mansfield TA, Simon DB, Farfel Z, Bia M, Tucci JR, et al. 1997. Multilocus linkage of familial hyperkalaemia and hypertension, pseudohypoaldosteronism type II, to chromosomes 1q31-42 and 17p11-q21. *Nature Genet.* 16:202–5
57. Materson BJ, Reda DJ, Cushman WC, Massie BM, Freis ED, et al. 1993. Single-drug therapy for hypertension in men. A comparison of six antihypertensive agents with placebo. The Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents. *N. Engl. J. Med.* 328:914–21
58. Meneton P, Jeunemaitre X, de Wardener HE, MacGregor GA. 2005. Links between dietary salt intake, renal salt handling, blood pressure, and cardiovascular diseases. *Physiol. Rev.* 85:679–715
59. Murphy CA, McCarty R. 1989. Maternal environment and development of high blood pressure in Dahl hypertensive rats. *Am. J. Physiol.* 257:H1396–401
60. Murray CJ, Lauer JA, Hutubessy RC, Niessen L, Tomijima N, et al. 2003. Effectiveness and costs of interventions to lower systolic blood pressure and cholesterol: a global and regional analysis on reduction of cardiovascular-disease risk. *Lancet* 361:717–25
61. Nagata C, Takatsuka N, Shimizu N, Shimizu H. 2004. Sodium intake and risk of death from stroke in Japanese men and women. *Stroke* 35:1543–47
62. Naray-Fejes-Toth A, Canessa C, Cleaveland ES, Aldrich G, Fejes-Toth G. 1999. SGK is an aldosterone-induced kinase in the renal collecting duct. Effects on epithelial Na^+ channels. *J. Biol. Chem.* 274:16973–78
63. Neri LC, Johansen HL. 1978. Water hardness and cardiovascular mortality. *Ann. NY Acad. Sci.* 304:203–21
64. Perry IJ, Beevers DG. 1992. Salt intake and stroke: a possible direct effect. *J. Hum. Hypertens.* 6:23–25
65. Province MA, Kardia SL, Ranade K, Rao DC, Thiel BA, et al. 2003. A meta-analysis of genome-wide linkage scans for hypertension: the National Heart, Lung and Blood Institute Family Blood Pressure Program. *Am. J. Hypertens.* 16:144–47
66. Rathaus M, Bernheim J. 2002. Oxygen species in the microvascular environment: regulation of vascular tone and the development of hypertension. *Nephrol. Dial. Transplant.* 17:216–21
67. Romero MF, Boron WF. 1999. Electrogenic Na^+/HCO_3^- cotransporters: cloning and physiology. *Annu. Rev. Physiol.* 61:699–723
68. Sacks FM, Svetkey LP, Vollmer WM, Appel LJ, Bray GA, et al. 2001. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. *N. Engl. J. Med.* 344:3–10
69. Safar ME. 2000. Pulse pressure, arterial stiffness, and cardiovascular risk. *Curr. Opin. Cardiol* 15:258–63
70. Schultheis PJ, Clarke LL, Meneton P, Miller ML, Soleimani M, et al. 1998. Renal and intestinal absorptive defects in mice lacking the NHE3 Na^+/H^+ exchanger. *Nature Genet.* 19:282–85
71. Sharp D. 2004. Labelling salt in food: If yes, how? *Lancet* 364:2079–81
72. Shimkets RA, Warnock DG, Bositis CM, Nelson-Williams C, Hansson JH, et al. 1994. Liddle's syndrome: heritable human hypertension caused by mutations in the beta subunit of the epithelial sodium channel. *Cell* 79:407–14
73. Shore AC, Markandu ND, MacGregor GA. 1988. A randomized crossover study to compare the blood pressure response to sodium loading with and without chloride in patients with essential hypertension. *J. Hypertens.* 6:613–17
74. Simon DB, Bindra RS, Mansfield TA, Nelson-Williams C, Mendonca E, et al. 1997. Mutations in the chloride channel gene, CLCNKB, cause Bartter's syndrome type III. *Nature Genet.* 17:171–78

75. Simon DB, Karet FE, Hamdan JM, DiPietro A, Sanjad SA, Lifton RP. 1996. Bartter's syndrome, hypokalaemic alkalosis with hypercalciuria, is caused by mutations in the Na-K-2Cl cotransporter NKCC2. *Nature Genet.* 13:183–88
76. Simon DB, Karet FE, Rodriguez-Soriano J, Hamdan JH, DiPietro A, et al. 1996. Genetic heterogeneity of Bartter's syndrome revealed by mutations in the K^+ channel, ROMK. *Nature Genet.* 14:152–56
77. Simon DB, Nelson-Williams C, Bia MJ, Ellison D, Karet FE, et al. 1996. Gitelman's variant of Bartter's syndrome, inherited hypokalaemic alkalosis, is caused by mutations in the thiazide-sensitive Na-Cl cotransporter. *Nature Genet.* 12:24–30
78. Snieder H, Harshfield GA, Treiber FA. 2003. Heritability of blood pressure and hemodynamics in African- and European-American youth. *Hypertension* 41:1196–201
79. Snyder PM, Steines JC, Olson DR. 2004. Relative contribution of Nedd4 and Nedd4-2 to ENaC regulation in epithelia determined by RNA interference. *J. Biol. Chem.* 279:5042–46
80. Srinivasan SR, Dalferes ER Jr, Wolf RH, Radhakrishnamurthy B, Foster TA, Berenson GS. 1984. Variability in blood pressure response to dietary sodium intake among African green monkeys (*Cercopithecus aethiops*). *Am. J. Clin. Nutr.* 39:792–96
81. Staub O, Dho S, Henry P, Correa J, Ishikawa T, et al. 1996. WW domains of Nedd4 bind to the proline-rich PY motifs in the epithelial Na^+ channel deleted in Liddle's syndrome. *EMBO J.* 15:2371–80
82. Strautnieks SS, Thompson RJ, Gardiner RM, Chung E. 1996. A novel splice-site mutation in the gamma subunit of the epithelial sodium channel gene in three pseudohypoaldosteronism type 1 families. *Nature Genet.* 13:248–50
83. Svetkey LP, Moore TJ, Simons-Morton DG, Appel LJ, Bray GA, et al. 2001. Angiotensinogen genotype and blood pressure response in the Dietary Approaches to Stop Hypertension (DASH) study. *J. Hypertens.* 19:1949–56
84. Swift PA, Markandu ND, Sagnella GA, He FJ, MacGregor GA. 2005. Modest salt reduction reduces blood pressure and urine protein excretion in black hypertensives: a randomized control trial. *Hypertension* 46:308–12
85. Taubes G. 1998. The (political) science of salt. *Science* 281:898–907
86. Taubes G. 2000. A DASH of data in the salt debate. *Science* 288:1319
87. Tripodi G, Valtorta F, Torielli L, Chieregatti E, Salardi S, et al. 1996. Hypertension-associated point mutations in the adducin alpha and beta subunits affect actin cytoskeleton and ion transport. *J. Clin. Invest.* 97:2815–22
88. Tuomilehto J, Jousilahti P, Rastenyte D, Moltchanov V, Tanskanen A, et al. 2001. Urinary sodium excretion and cardiovascular mortality in Finland: a prospective study. *Lancet* 357:848–51
89. Verhaar MC, Stroes E, Rabelink TJ. 2002. Folates and cardiovascular disease. *Arterioscler. Thromb. Vasc. Biol.* 22:6–13
90. Ward R. 1995. Familial aggregation and genetic epidemiology of blood pressure. In *Hypertension*, ed. JH Laragh, BM Brenner, pp. 67–88. New York: Raven
91. Weinman EJ, Cunningham R, Wade JB, Shenolikar S. 2005. The role of NHERF-1 in the regulation of renal proximal tubule sodium-hydrogen exchanger 3 and sodium-dependent phosphate cotransporter 2a. *J. Physiol.* 567:27–32
92. Weir MR, Chrysant SG, McCarron DA, Canossa-Terris M, Cohen JD, et al. 1998. Influence of race and dietary salt on the antihypertensive efficacy of an angiotensin-converting enzyme inhibitor or a calcium channel antagonist in salt-sensitive hypertensives. *Hypertension* 31:1088–96
93. Wilson FH, Disse-Nicodeme S, Choate

KA, Ishikawa K, Nelson-Williams C, et al. 2001. Human hypertension caused by mutations in WNK kinases. *Science* 293:1107–12

94. Wilson FH, Kahle KT, Sabath E, Lalioti MD, Rapson AK, et al. 2003. Molecular pathogenesis of inherited hypertension with hyperkalemia: the Na-Cl cotransporter is inhibited by wild-type but not mutant WNK4. *Proc. Natl. Acad. Sci. USA* 100:680–84
95. Yang CL, Angell J, Mitchell R, Ellison DH. 2003. WNK kinases regulate thiazide-sensitive Na-Cl cotransport. *J. Clin. Invest.* 111:1039–45
96. Zoccali C, Mallamaci F. 2000. The salt epidemic: old and new concerns. *Nutr. Metab. Cardiovasc. Dis.* 10:168–71

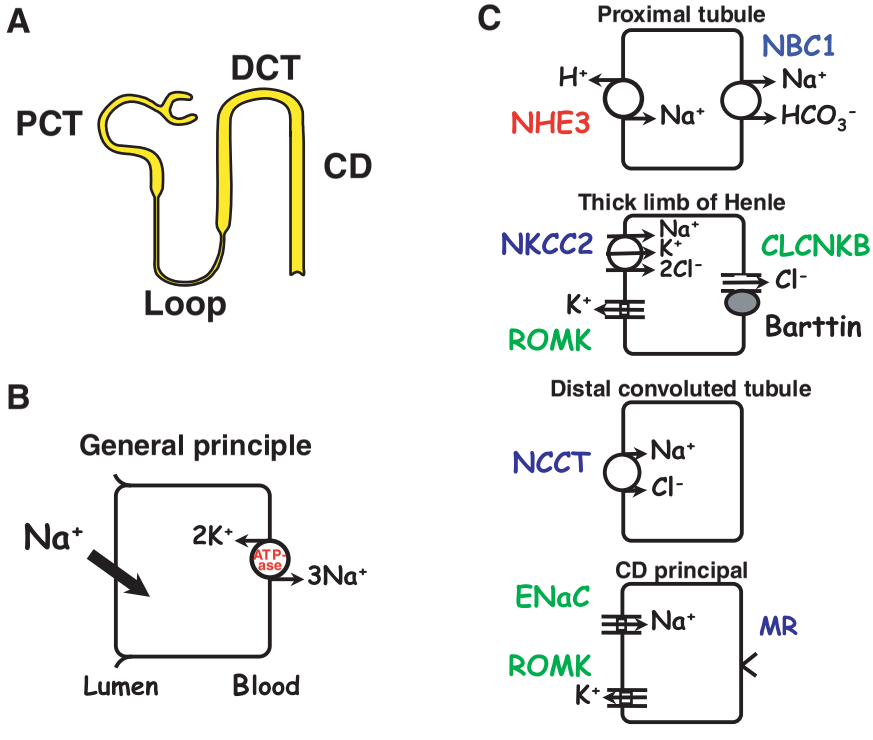

Figure 1 Molecular pathways of sodium reabsorption in the nephron. (*A*) A cartoon of a nephron with different segments labeled: PCT, proximal convoluted tubule, DCT, distal convoluted tubule; CD, collecting duct. (*B*) General principle of sodium reabsorption across the apical surface driven by electrogenic activity of the basolateral Na/K-ATPase. (*C*) Individual cells contain different sodium transporters as described in the text. *Blue*, cotransporters; *green*, channels; *red*, ATP-dependent exchanger. Fine regulation occurs in the collecting duct via the aldosterone-activated mineralocorticoid receptor (MR). ENaC, epithelial Na channel; NCCT, renal tubular Na-Cl cotransporter; NKCC2, sodium-potassium-chloride cotransporter, ROMK, renal outer medullary K channel.

Annual Review of Nutrition
Volume 25, 2005

CONTENTS