Is Hypertension a Disorder of Volume Control? What Is the Evidence?

Graeme Mindel Aubrey R. Morrison

Department of Medicine, Washington University School of Medicine, St. Louis, Mo., USA

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Abstract

The etiological factors responsible for the hypertensive phenotype are complex and several experimental and clinical observations point to a major role of the kidney as being responsible. Genetic studies of uncommon diseases which express monogenetic inheritance all have in common a dysregulation of Na^+ balance and volume expansion. Furthermore, epidemiological data suggest an increased incidence of hypertension in communities with high excretory rates of Na^+ . Experimental data also suggest that low birth weight is associated with an increase in the frequency of hypertension later in life and raises the possibility that intrauterine imprinting may contribute to the expression of the phenotype. Upregulation of the $\text{Na}^+/\text{K}^+/\text{2Cl}^-$ and thiazide-sensitive transporters in low birth weight animals may provide the physiological basis for these observations. In addition, low birth weight is associated with a decrease in nephron number. Therefore, low nephron number may induce adaptive changes in utero which influence volume homeostasis later in life and subtle gain of function mutations in one or more of these transporters may unmask

defects in volume homeostasis with increasing salt intake. Finally, the high prevalence of hypertension in functionally anephric patients seems to respond to sustained maintenance of 'dry weight' through ultrafiltration.

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Worldwide, elevation of blood pressure is a common trait and in the USA affects about 15–20% of the adult population. It contributes directly or indirectly to about 220,000 deaths annually from stroke, myocardial infarction and renal failure [1]. The definition of hypertension has evolved over several decades away from arbitrary values towards an emphasis on the levels of blood pressure that are associated with vascular damage and increased cardiovascular morbidity and mortality. This generates an enormous problem that physicians, healthcare providers and patients must grapple with, since individuals aged 55–65 have a lifetime probability of 90% for the development of hypertension [2] as currently defined.

In the mid 20th century, two prevailing views on essential hypertension existed. The first championed by Lord Platt suggested that hypertension resulted from a defect in a gene or genes each of which were sufficient to produce the phenotype, resulting in two populations, those who are normotensive or hypertensive. The second prevailing view was that of Sir Thomas Pickering, who

Fig. 1. Model of pathogenesis of hypertension.

suggested that hypertension resulted from the cumulative effect of several dysregulated genes, which individually were not sufficient to result in the hypertensive phenotype. As such, blood pressure was a continuum with hypertension being one of the extremes of blood pressure variation in the community. This latter view has received some support from a large body of experimental work which has led to a hypothesis championed by Oliver Smithies who suggests that ‘essential hypertension results from contributions of genetic variation that are not the same in all affected persons and that individually may not cause sufficient deviation from normality to be harmful’. This has led to the concept of multifactorial determinants of blood pressure in which genetics and other epigenetic factors such as gender, body mass, age and environment all contribute to the observed phenotype and this concept is illustrated in figure 1.

Currently the majority of hypertension is believed to fall into the category of disorders with complex inheritance and as such presents several challenges to the geneticist. A complimentary approach to the large body of physiologic information is the identification of genetic factors contributing to the pathogenesis of hypertension. If key mutations can be found, they should provide a rational springboard from which the pathophysiology of hypertension can be understood, especially since evidence from epidemiology, twin studies and adoptive studies, suggests a role for heredity in 25–40% of human hypertension [3]. The latter approach has been exploited efficiently by Lifton et al. [4] who have identified genes which influence blood pressure variation at the low and high end of the spectrum. What is important for this discussion is

that, without exception, the diseases whose molecular pathogenesis has been defined by this approach, all directly or indirectly affect salt balance and hence influence the status of the extracellular volume (ECV) (table 1).

The control of ECV is not completely understood, nevertheless several physiological systems have been identified which affect sodium handling by the kidney. Indeed the kidney is the organ which assumes primacy in the efferent arm of the physiological control homeostatic mechanism. One of the best studied systems in this regard is the renin/angiotensin/aldosterone axis. This axis is comprised of angiotensinogen (*AGT*), which circulates in plasma where it is the substrate for proteolytic cleavage by renin, produced in the juxtaglomerular apparatus of the mammalian kidney. *AGT* circulates in plasma at concentrations close to the K_m for renin, thus changes in the level of *AGT* will produce significant changes in the levels of circulating angiotensin I (AI), the product of cleavage of *AGT* by renin. AI is subsequently cleaved to angiotensin II (AII) by angiotensin-converting enzyme (ACE) in the lung and other tissues, increases vascular smooth muscle tone, and enhances the secretion of aldosterone from the adrenal glomerulosa through the AT1 receptor. Aldosterone binds to the mineralocorticoid receptor in the distal convoluted tubule to promote Na^+ reabsorption through genomic and non-genomic mechanisms. Several mutations in various key players along the renin/angiotensin/aldosterone axis have been identified. These mutations have been associated with an elevated blood pressure and have in common Na^+ retention as the physiologic root of this observed phenotype.

Table 1. Mutations affecting circulating mineralocorticoid hormones

Disorder	Genetics	Pathogenesis	Clinical features
Polymorphisms in the human angiotensinogen (<i>AGT</i>) gene		Increased promoter activity → increased circulating AGT → Na ⁺ retention and hypertension	Only 2 kindreds identified. Effect may be modest and the physiologic importance is not fully understood
Glucocorticoid remediable aldosteronism	Autosomal dominant with complete penetrance	Unequal crossing over between aldosterone synthase and 11 β -hydroxylase → chimeric gene expressed in the zona fasciculata encoding aldosterone synthase under the control of ACTH	Excess mineralocorticoid secretion with normal to elevated aldosterone levels despite suppressed plasma renin activity. Variable hypokalemic metabolic alkalosis. Suppression of aldosterone secretion by exogenous administration of glucocorticoids
Syndrome of apparent mineralocorticoid excess	Autosomal recessive	Homozygous loss of function of 11 β -hydroxysteroid dehydrogenase type II gene → cortisol exerting a mineralocorticoid effect with Na ⁺ retention, volume expansion and hypertension	Early onset hypertension. Hypokalemic metabolic alkalosis. Low plasma renin and aldosterone levels
<i>Mutations in the mineralocorticoid receptor</i>			
Geller's syndrome	Autosomal dominant	Missense mutation in the mineralocorticoid receptor S810R → activation of the mineralocorticoid receptor by steroids lacking 21-hydroxyl groups such as progesterone	Early onset hypertension prior to the age of 20. Accelerated hypertension during pregnancy with suppression of the renin-angiotensin system
<i>Mutations in renal ionic channels and transporters</i>			
Liddle syndrome	Autosomal dominant	Enhanced activity of the epithelial sodium channel (ENAC) → increased Na ⁺ transport → volume expansion and hypertension	Onset of hypertension in adolescents and young adults. Low renin and aldosterone. Hypokalemic metabolic alkalosis
Gordon's syndrome (pseudohypoaldosteronism type II)	Autosomal dominant	Mutations in the WNK 1 and 4 genes → increased expression of the thiazide-sensitive transporter on the apical membrane of the DCT → enhanced NaCl reabsorption with volume expansion and hypertension	Hyperkalemia. Hyperchloremic non-anion gap metabolic acidosis. Low to normal plasma renin activity and aldosterone
Mutations in the α -adducin gene		Adducin is a cytoskeletal protein. Expression of the mutant protein → alteration in the actin polymerization → increased Na ⁺ reabsorption through the kidney	Homozygous mutations have been expressed as a form of salt-sensitive hypertension in an Italian kindred

Mutations in *AGT*

Two kindreds have been identified, one in Salt Lake City and the other in Paris, in which elevation of blood pressure is linked to polymorphisms in the human *AGT* gene [5, 6]. The M235T variant has been associated with another mutation in nucleotide -6 from the initiation site of transcription [7] and which results in increased promoter activity in a heterologous expression system. This mutation would therefore be expected to result in an increase in circulating *AGT* and based on the discussion

above would result in Na⁺ retention and increased BP. This interpretation has gained support from experiments in mice where one through four copies of the *AGT* gene were sequentially added on a null background [8]. With each additional copy of the *AGT* gene the blood pressure was proportionally elevated confirming that the levels of circulating *AGT* could influence BP in an intact animal.

Glucocorticoid Remediable Aldosteronism

Glucocorticoid remediable aldosteronism is an autosomal dominant trait, producing hypertension of early onset and associated with suppressed plasma renin activity [9]. It arises as a consequence of a gene duplication consisting of an unequal crossing over between aldosterone synthase and steroid 11 β -hydroxylase. This results in the presence of a chimeric gene ectopically expressed in the zona fasciculata, which encodes aldosterone synthase and whose expression is under the control of ACTH [4, 10]. This results in excess mineralocorticoid secretion, Na⁺ retention, volume expansion and hypertension.

Syndrome of Apparent Mineralocorticoid Excess

This is an autosomal recessive disease whose clinical features are onset of early hypertension, hypokalemic metabolic alkalosis, suppressed plasma renin and absence of circulating aldosterone. This disease is a consequence of homozygous loss-of-function in the 11 β -hydroxysteroid dehydrogenase type-2 gene in the distal renal tubule [11]. The absence of this enzyme allows cortisol to act as a mineralocorticoid to promote Na⁺ retention, volume expansion and hypertension.

Mutations in the Mineralocorticoid Receptor

Recently a kindred was identified with an activating mutation of the mineralocorticoid receptor which demonstrated autosomal dominant transmission [12]. This resulted from a missense mutation, S810R, and all carriers of the mutation developed hypertension before age 20. Another feature of the affected kindred was that, while wild-type receptor was not activated by progesterone, the mutant receptor was fully activated by this steroid, thus providing the basis for an accelerated hypertension in affected females with pregnancy. As with the above genetic abnormalities in the renin/angiotensin/aldosterone axis, the physiology of a constitutively active mineralocorticoid receptor would cause excessive Na⁺ retention, volume expansion and hypertension.

Mutations in the renin/angiotensin/aldosterone axis are uncommon disorders which lead to elevated blood pressure associated with Na⁺ retention and volume expansion. Nevertheless, the evidence placing the kidney as a major player in the pathogenesis of salt-sensitive hyper-

tension is very compelling. Experimental evidence in rats from Dahl et al. [13] and others [14] has demonstrated through cross-transplantation experiments that the defect which allowed the expression of the phenotype resides in the kidney. There is also clinical evidence that suggests that hypertension in African Americans could be cured with transplantation of kidneys from normotensive donors [15]. These observations are supported by epidemiological data showing a strong correlation between the frequency of hypertension in large populations and the levels of urinary Na⁺ excretion (a surrogate for Na⁺ intake) [16]. Finally, there is evidence for a gene influencing blood pressure on chromosome 17, obtained by genome wide scans of subjects from the Framingham Study [17]. This QTL is of particular interest because it is syntenic with a QTL on chromosome 10 in rats [18, 19], linked to hypertension in several studies of spontaneously hypertensive rats, and syntenic to a QTL on chromosome 11 in the mouse [20], linked to salt sensitivity in a hypertensive mouse strain.

The kidney is the major organ charged with the defense of the ECV and does this through signals which influence a number of channels and transporters along the length of the nephron. The kidney excretes under normal conditions and with a full complement of nephrons, 0.5–1.0% of the filtered load of sodium. It accomplishes this fine regulation through a phenomenon known as glomerulotubular balance and the appropriate level of coordinated Na⁺ reabsorption. This delicate balance can be disrupted by a malfunction directly or indirectly, from loss-of-function or gain-of-function of one or more transport proteins or channels that orchestrate this homeostatic function.

Epidemiological studies have suggested a correlation between hypertension late in life and intrauterine growth retardation [21–24]. The correlation is with low birth weight, rather than prematurity, and suggests that the in utero environment is responsible for imprinting and programming of blood pressure. Compared to white Americans, hypertension in African Americans is more prevalent, occurs earlier in life, is more severe and is more often associated with end-organ damage [25]. National Health and Nutrition Examination Survey (NHANES) data, looking at trends in prevalence, awareness, treatment and control of hypertension in the USA, indicated that non-Hispanic black race/ethnicity was independently associated with increased rates of hypertension [26]. African American infants weigh on average 200–300 g less at birth than do European American infants resulting in a two- to threefold higher risk for low birth weight and very low birth weight among black infants compared with

white infants. Although infant mortality has decreased among all races during the past two decades, the overall black-white gap for infant mortality has widened. The basis for this disparity is unclear but numerous factors have been associated with increased risk for having a low birth weight infant including socioeconomic status, the age and health of the mother, prenatal care and maternal anthropometrics [27]. There are both animal and human data linking low birth weight with reduced nephron mass. In an animal study, Leroy and co-workers [28] showed that full-term rat pups with intrauterine growth retardation had lower kidney weights and a reduced number of glomeruli than pups in the normal weight group. It is therefore a possibility that low birth weight may be a significant contributing factor to the observed racial differences in hypertension severity and cardiovascular outcomes. Furthermore, the higher salt intake in the African American population may further exacerbate this disparity.

In an experimental model of intrauterine growth retardation, Manning et al. [29] demonstrated upregulation of the $\text{Na}^+/\text{K}^+/\text{2Cl}^-$ and Na^+/Cl^- electroneutral transporters in the mammalian nephron. If the function of these two transporters correlated with the levels of their expression, they would be expected to enhance Na^+ reabsorption and thus volume expansion. It should not be surprising therefore if gain-of-function mutations were identified in transporters along the mammalian nephron, they could result in an increase in ECV and hypertension. Such mutations have been identified.

Liddle's Syndrome

Liddle's syndrome is characterized by hypertension with its onset in early childhood and associated with hypokalemic alkalosis. The molecular defect in these patients is a result of mutations in either the C-terminus of the β or γ subunits of the epithelial sodium channel (ENaC) [30, 31]. This C-terminus carries a PPPXY motif which interacts with the WW motifs of Nedd4-1 and -2, proteins that interact with the ubiquitin ligase and are responsible for recycling of β and γ subunits in clathrin-coated pits [32–34]. This mutation increases the number of functioning channels in the apical membrane of the distal nephron and enhances Na^+ reabsorption resulting in volume expansion.

Pseudohypoaldosteronism Type II (Gordon's Syndrome)

This is an autosomal dominant disorder, genes for which have been mapped in different families to chromosome 17, 1 or 12 [35, 36]. The hypertension has been attributed to renal Na^+ retention. Mutations in WNK1 and 4 genes have been identified in some families and appear to be the molecular basis for the observed phenotype [37] in some of the families but not all. It is interesting to note that the defect in WNK1 families is associated with a fivefold increase in kinase expression (gain of function) while the defect in WNK4 is associated with a loss-of-function of the kinase with increased expression of the thiazide-sensitive transporter on the apical membrane of the DCT.

Mutations in the α -Adducin Gene

Identification of a candidate gene in the Milan hypertensive rat which encoded the α and β isoforms of adducin [38] led to the identification of families which expressed this mutation and in whom the homozygous mutation was expressed as salt-sensitive hypertension [39]. The point mutations identified were in α (F316Y) and β (Q529R) isoforms of adducin in the rat [38] and in the human α -adducin, the SNP identified a Gly406Trp on chromosome 4 as being associated with salt-sensitive hypertension [39]. The heterodimer of α - and β -adducin interacts with F-actin and spectrin [38, 40] and in vitro experiments have demonstrated that the expression of the mutant protein is associated with a significant increase in the expression of Na^+K^+ -ATPase in renal epithelia and which is associated with an increase in $V_{\max}$ of the transporter. This would be expected to lower the Na^+ activity in transporting epithelia with an increase in secondary active transport through the Na^+/H^+ exchanger and will therefore account for the enhanced Na^+/Li^+ countertransport seen in these families. This mutation would therefore increase Na^+ reabsorption, resulting in volume expansion.

Based on a large body of work throughout his scientific career, Guyton [41, 42] has demonstrated that there is a pressure natriuresis system in the mammalian kidney which is activated within hours to days to defend the level of ECV to 'normal' limits. This system is believed to have infinite gain and is the only system endowed with the ability to completely restore ECV to normal when deviations occur. Small changes in ECV can have significant

changes in blood pressure [41], and as a result it is conceivable that polymorphisms in the multiple channels and transporters along the nephron which produce subtle alterations in function could be unmasked with a high Na^+ intake. This could be the underlying basis for the increased frequency of hypertension in communities which have increased rates of Na^+ ingestion. The observations in Gordon's syndrome also underscore the possibility that hypertension may result from mutations in proteins which alter the function of the transporters and channels, thus providing the potential for mutations in several renal proteins to influence Na^+ handling by the kidney through direct and indirect mechanisms.

We have already pointed out that there are a number of genetic conditions that are associated with alterations in sodium transport in the tubules. Others have reviewed in detail the numerous possible mechanisms of acquired renal injury as a cause of salt-sensitive hypertension and the pathways through which this is achieved [43].

An emerging concept is that congenital reduction in the number of nephrons may limit the filtration of sodium, resulting in sodium retention and an elevation of blood pressure [44]. This has been alluded to previously by Guyton and co-workers [45] in the analysis of the kidney's role in different types of hypertension. Under normal conditions, equilibrium is achieved at an arterial pressure of 100 mm Hg, i.e., intake and output of water and salt are matched. Where there has been loss of renal mass, equilibrium is achieved at a higher arterial pressure. Furthermore, when the intake of salt and water are increased, the diminished renal mass kidneys demonstrate a considerably greater increase in the blood pressure than the normal kidney. This may suggest a reduced capacity to filter or excrete the sodium load – in essence a rightward shift in the pressure natriuresis curve. It is also worth mentioning the effect of non-steroidal anti-inflammatory drugs (NSAIDs). Inhibition of intrarenal prostaglandins may result in intrarenal vasoconstriction with sodium retention and development of hypertension. In addition, cyclooxygenase-2-derived prostaglandin E_2 is found in the thick ascending limb of the loop of Henle where it inhibits sodium reabsorption. NSAID-induced inhibition of prostaglandin E_2 can therefore result in salt and water retention. NSAIDs and cyclooxygenase inhibitors vary in their effect on blood pressure but this effect is most pronounced in patients with hypertension, impaired renal function and in individuals who demonstrate salt sensitivity.

In our aging population, because of the higher incidence of arthritic related symptoms, the use of NSAIDs

and COX2i may take on a greater significance. These individuals have a reduced renal mass and a greater tendency to salt sensitivity and so the use of these agents may be associated with a greater degree of incident hypertension. It is clear that blood pressure control is a major problem in functionally anephric individuals. If one looks at the distribution of both systolic and diastolic blood pressure measurements in the dialysis population, then approximately 80% of dialysis patients will have hypertension as defined by the JNC VII criteria with a systolic blood pressure >140 mm Hg and a diastolic blood pressure >90 mm Hg [46]. There are a variety of reasons postulated for the development of hypertension in the dialysis patient. These include: volume loss, increased vasopressor activity or decreased vasodilator activity, and hormones including parathyroid hormone and erythropoietin. Despite all of these possibilities it is clear that volume reduction is associated with improved blood pressure control. This is best demonstrated in the Tassin study group in France in which patients received longer periods of dialysis (24 h/week) with greater degrees of ultrafiltration. Virtually none of these patients required antihypertensive medication because of improved ultrafiltration [47]. It is interesting to note that this same group observed a phenomenon, which they have termed the 'lag phenomenon'. This describes a set of circumstances in which, despite reduction of the ECV, significant changes in the mean arterial pressure were only seen weeks to months later (fig. 2). They postulated that this may occur as a result of a reversal in the sequence of hemodynamic modifications described by Guyton when patients with chronic kidney disease are exposed to a saline load [48]. Based on Guyton's principles, it is probable that improved ECV control in dialysis patients, achieved by greater degrees of ultrafiltration, will eventually result in a reduction in the peripheral vascular resistance. Once the dialysis patient reaches his or her true 'dry weight', the reduction in the peripheral vascular resistance is associated with the observed improvement in the mean arterial pressure, a process which may take several weeks to months.

Recently, Keller and co-workers [49] demonstrated that the number of glomeruli is lower in the kidneys of patients with hypertension than in the kidneys of matched normotensive controls. Whether the cause of this reduced nephron mass is genetic or epigenetic is unknown. Equally plausible is that the resulting reduced nephron number could have been due to intrauterine events as discussed earlier and hypertension expressed as a consequence of the reduced nephron number. Experimental data in rats

Fig. 2. Pre-dialysis blood pressure and post-dialysis weight in 712 Tassin study patients. Anti-HT = Antihypertensive therapy [from 48, with permission].

[50, 51] and sheep [52] suggest that uninephrectomy predisposes these animals to the development of hypertension later in life. There is a suggestion that removal of a kidney also predisposes patients to the development of hypertension later in life and that males are more likely to exhibit an elevated blood pressure [53–55]. However, there is a significant body of accumulating data in the donors of kidneys for transplantation that the uncomplicated reduction of 50% of nephrons produced by donor nephrectomy is not associated with an increased incidence of hypertension nor increased rates of ESRD [56–58]. This occurs in spite of hyperfiltration in the remaining solitary kidney. This suggests, first, that a simple reduction of up to 50% of the complement of nephrons in humans is insufficient to produce hypertension in spite of the physiological adaptations, and second, that the reduction of nephron number in the neonatal period which is associated with hypertension later in life must occur as a result of other factors present in the developing kidney in which nephron ‘plasticity’ allows for enhanced expression of transporters, which is not seen in the fully differentiated adult kidney.

It is clear that an elevated blood pressure can induce functional adaptive changes in the resistance vessels in the arterial tree. However, equally well documented is the observation of structural changes in the vessels which can eventually lead to end-organ damage which may not be reversible. This may therefore account for the inability to reverse blood pressure to normal with pharmacological

reversal of the physiological derangements observed in some of the genetic syndromes described above and makes a powerful argument for aggressive blood pressure control early in the natural history of this very important disease. The concept proposed in this review will be further supported if new hypertensive genes express themselves through a dysregulation of Na^+ homeostasis and volume control.

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