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REVIEW

The molecular basis of blood pressure variation

Hakan R. Toka · Jacob M. Koshy · Ali Hariri

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Abstract Advances in genetic mapping and sequencing techniques have led to substantial progress in the study of rare monogenic (Mendelian) forms of abnormal blood pressure. Many disease-defining pathways for hypertension have been identified in the past two decades. Perturbations in renal salt handling appear to be a common mechanism underlying these rare syndromes of hypertension. Excess activation at various points in the mineralocorticoid signaling pathway and malfunctioning of the autonomic (specifically sympathetic) nervous system have both been implicated in inducing hypertension, while complementary studies examining low blood pressure phenotypes have identified novel pathways exclusively linked to renal salt wasting in either the thick ascending limb or the distal nephron. The genetic defects and the physiological and cellular pathways affected in these various disorders are reviewed here. Importantly, studies have suggested that genetic variation affecting these same genes and pathways may play an important role in explaining the variation of blood pressure levels in the general population. The investigation of rare syndromes of human blood pressure variation has important implications for improving the diagnosis and treatment of hypertension.

Keywords Pseudohypoaldosteronism · Liddle's syndrome · Pheochromocytoma · Bartter's syndrome · Gitelman's syndrome · Essential hypertension

H. R. Toka · J. M. Koshy
Department of Nephrology, Brigham and Women's Hospital,
Harvard Medical School,
Boston, MA, USA

A. Hariri
Nephrology and Internal Medicine and Scientific Affairs, Takeda Pharmaceuticals of North America,
Deerfield, IL, USA

H. R. Toka (✉)
Department of Nephrology, Brigham and Women's Hospital,
75 Francis Street, MRB4,
Boston, MA 02215, USA
e-mail: htoka@partners.org

Introduction

Hypertension is a substantial public health problem affecting approximately 25 % of the adult population in industrialized societies and over 1 billion people worldwide [1]. It is a major risk factor for many causes of morbidity and mortality in the general population, including stroke, myocardial infarction, congestive heart failure, and end-stage renal disease [2]. Despite the important role of hypertension as a cause of disease, its pathogenesis remains largely unknown. Extensive investigations over the last several decades have revealed that hypertension has a multifactorial etiology, including demographic, dietary, and genetic factors. Known demographic components are numerous and include age, gender, and body mass [3]. Dietary factors include salt, potassium, and calcium intake [4]. The influence of genetic factors on blood pressure (BP) variation is known from twin studies and studies of biological versus adopted siblings. Monozygotic twins show greater concordance of BP variation than dizygotic twins, and biological siblings have similar BP values when compared with adopted siblings [5, 6]. The identification of genes underlying BP variation has the capacity not only to define primary physiologic mechanisms, but also to reveal disease mechanisms and thereby develop novel therapies. Different approaches have been made to study the molecular basis of BP variation, including in vitro and in vivo studies, animal models, and population

genetics. The most successful approach has been the investigation of Mendelian (monogenic) forms of arterial hypertension and hypotension in men, where single genes have a large effect on BP [7]. In the last two decades, a number of disease-causing mutations have been identified in various genes, and several disease mechanisms have been described [8]. In the 1990s, the identification of a disease gene for BP variation was mainly achieved by studying large pedigrees of individuals with BP variation in conjunction with advances in genotyping technology and computational (linkage) analysis. Advances in analyzing polymorphic microsatellite markers on a genome-wide level were followed by single nucleotide polymorphism technology in the 2000s. In addition, the candidate gene approach has been successful in conditions that had been previously studied in detail by physiologists. In the last few years, new advances in sequencing ("next generation sequencing") and computational technology have made it possible to identify additional disease genes in small pedigrees and single individuals with extreme phenotypes [9, 10]. Importantly, genetic studies in the general population have shown that rare allelic variations of Mendelian disease genes affecting BP have implications for the genetic structure of BP variation in the general population. Participants of the Framingham Heart Study (FHS) were screened for allelic variations in rare disease genes affecting renal salt handling. Several allelic gene variants were identified and proven or inferred to be functional in lowering BP [11]. In the following report, several rare conditions eliciting high and low BP will be reviewed and compared.

Genes that increase BP

Pathways of enhanced salt reabsorption in the collecting duct

Glucocorticoid-remediable aldosteronism (familial hyperaldosteronism type I)

The BP in patients with glucocorticoid-remediable aldosteronism (GRA) is salt sensitive and increases with salt intake. Laboratory tests show that these patients have mild hypokalemia and metabolic alkalosis. Renin levels are typically low, while aldosterone values can be elevated (Table 1). Patients with this condition are often suspected of having primary hyperaldosteronism. However, computed tomography (CT) scanning of the adrenal glands is negative for (unilateral) adrenal adenomas. A family history of hypertension is often positive, suggesting autosomal dominant inheritance. The BP in GRA improves with all diuretics, including blockers of the epithelial sodium channel (ENaC) in the distal nephron. A distinguishing biochemical feature of GRA is the presence of steroid metabolites not normally found in urine. Urine testing in affected individuals is positive for 18-hydroxycortisol and 18-oxocortisol. Recognition of these abnormal products in the urine helped solve the etiology of this condition. Linkage analysis of a large kindred with GRA localized the responsible gene(s) to chromosome 8q21. The enzyme 11-β-hydroxylase (*CYP11B1*), expressed in the zona fasciculata of the adrenal gland, resides within this locus. *CYP11B1* is responsive to adrenocorticotropic hormone and involved in the terminal step of glucocorticoid biosynthesis. The gene for aldosterone synthase (*CYPB11B2*) resides at the same locus on chromosome 8q21, and this gene has a highly similar DNA sequence (approx. 95 %) to *CYB11B1* and encodes an enzyme involved in mineralocorticoid synthesis. In affected individuals, a chimeric gene is formed by an unequal crossing-over at chromosomal location 8q21, consisting of the promoter (regulatory) region of the 11-β-hydroxylase gene and the structural portion of the aldosterone synthase gene. The protein of this chimeric gene performs all of the same actions as aldosterone; however, protein expression is regulated by the adrenocorticotropic hormone (ACTH) and not by angiotensin 2 (Fig. 1). Metabolism of this chimeric gene product results in the unusual urine metabolites mentioned above. Steroid treatment with prednisone ameliorates hypertension in GRA by suppressing the adrenal zona fasciculata, giving this condition its name [12, 13].

Apparent mineralocorticoid excess

The biochemical presentation of apparent mineralocorticoid excess (AME) is similar to that of GRA (Table 1). In contrast to GRA, urine analysis is negative for abnormal steroid metabolites, but the urinary free cortisol to cortisone ratio is increased (ratio>0.5) despite normal cortisol levels. This finding helped to identify the disease gene for AME, which is inherited in an autosomal recessive fashion. Glycyrrhetinic acid was found to inhibit the enzyme 11-β-hydroxysteroid-dehydrogenase (11-β-HSD), which converts cortisol to cortisone in renal tubular epithelial cells. In the distal renal tubule, the kidney-specific isoform of 11-β-HSD "protects" the mineralocorticoid receptor (MR) from cortisol, which has the same affinity for the MR as aldosterone. Candidate gene analysis showed that individuals with AME have loss-of-function mutations in a renal isoform of 11-β-HSD (11-β-HSD2), rendering the product incapable of converting cortisol to cortisone (Fig. 1). The hypertension in this condition responds to both spironolactone and ENaC blockers. Individuals ingesting large amounts of licorice, which contains glycyrrhetinic acid, and individuals treated with carbenoxolone, which also contains glycyrrhetinic acid and is licensed in the UK for treatment of mucosal ulcerations, develop features of AME [14, 15].

Table 1 Monogenic forms of elevated blood pressure

Syndromes of elevated BP[a]	Mode of inheritance	Serum K^+	pH	Serum renin	Serum aldosterone	Treatment of choice[b]	Locus	Gene
GRA	AD	↓	↑	↓	↑(N)	SPLN and/or ENaC-blocker	8q21	Chimeric gene: *CYP11B1*/*CYP11B2*
AME	AR	↓	↑	↓	↓	SPLN and/or ENaC-blocker	16q22	*HSD11B2*
Liddle's	AD	↓	↑	↓	↓	ENaC-blocker	16p13	*SCNN1B*
							16p13	*SCNN1G*
HiP	AD	↓	↑	↓	↓	ENaC-blocker	4q31	*NR3C2* (MR)
APA	AD/de novo	↓	↑	↓	↑	SPLN and/or ENaC-blocker	11q24	*KCNJ5* (Kir3.4)
CAH	AR	↓	↑	↓	↓	SPLN and/or ENaC-blocker	10q24	*CYP17A1*
							8q24	*CYP11B1*
PHA II	AD	↑	↓	↓	N(↑)	Thiazide	12p13	*WNK1*
							17q21	*WNK4*
							2q36	*CUL3*
							5q31	*KLHL3*
HBS	AD	N	N	N (↓)	N	No specific treatment	12p12	?
Pheo	AD	↓	N	↑	↑	α-Blocker	10q11	*Ret*
							17q11	*NF1*
							3p25	*VHL*
							1p36/1q23/11q23	*SDHB/SDHC/SDHD*
Mitochondria	Maternal	N	N	N	N	No specific treatment	Mitochondrial Nucl. 4263-4331	*tRNA-Ile*

AD, Autosomal-dominant; BP, blood pressure; K^+, potassium; N, Normal

[a] GRA, Glucocorticoid-remediable aldosteronism; AME, apparent mineralocorticoid excess; HiP, hypertension exacerbated in pregnancy; APA, aldosterone-producing adrenal adenomas; CAH, congenital adrenal hyperplasia; PAH II, pseudohypoaldosteronism type 2; HBS, Bilginturan's syndrome; Pheo, pheochromocytoma

[b] ENaC, Epithelial sodium channel; SPLN, spironolactone

Liddle's syndrome

In 1963, Grant W. Liddle described patients with an autosomal dominant form of hypertension associated with hypokalemia, metabolic alkalosis, and low aldosterone levels [16] (Table 1). Liddle speculated that his patients had a distal tubular defect of enhanced sodium reabsorption. Renal transplantation in Liddle's patients who developed renal failure "cured" their hypertension, suggesting that the etiology of this condition resided within the kidney. The hypertension in affected individuals did not respond to spironolactone treatment. However, affected individuals showed significant improvement with blockers of ENaC [17]. Candidate gene analysis of ENaC identified gain-of-function mutations in two out of three subunits as the responsible cause for Liddle's syndrome. Missense mutations and deletions in the cytoplasmic tails of the β- or γ-subunits of ENaC, which share approximately 35 % identity in their amino acid sequences, lead to impaired deactivation of the channel in the distal nephron [18, 19]. Disease-causing mutations typically occur in the proline-rich PY motif (PPPXY) of the cytoplasmic tails of these subunits. This domain interacts with WW-domains of proteins that are known for their ubiquitination and degradation of cell surface proteins. The PY motif of the cytoplasmic tails is also important for endocytosis via clathrin-coated pits [20]. As a consequence, internalization of the ENaC channels is impaired, and the ENaC channels remain active on the apical cell surface (Fig. 1). This mechanism explains the superb efficacy of ENaC blockers, such as amiloride and triameterene, in the treatment of this disease.

Syndrome of hypertension exacerbated in pregnancy

Candidate gene screening of the MR gene (*NR3C2*) in patients with features resembling Liddle's syndrome, who tested negative for ENaC gene mutations, led to the identification of one family with activating mutations in *NR3C2* [21]. One index case was found to have a heterozygous mutation at codon 810 of the MR that resulted in a leucine (L) substitution for serine (S). All four affected family members carried the same MR-S810L mutation, whereas

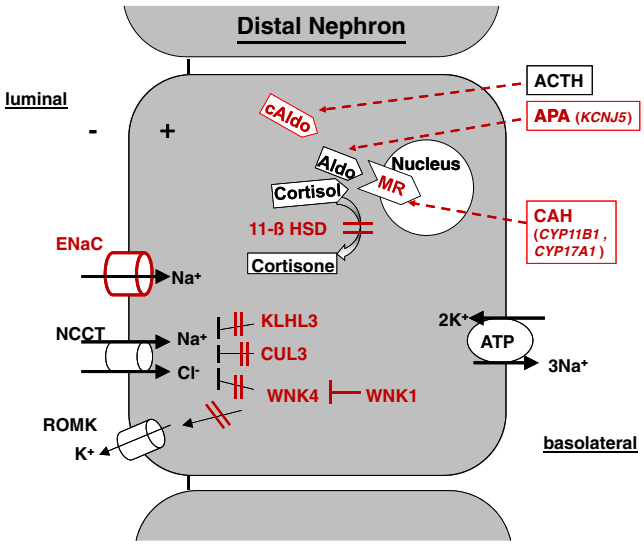

Fig. 1 Mutations in genes expressed in distal nephron epithelia cause salt retention and blood pressure (BP) elevation. Schematic illustration of ten molecular mechanisms (*red*) leading to increased salt reabsorption in distal nephron epithelia. *Red double lines* indicate loss-of-function effect on downstream target(s). *WNK1* gain-of-function mutations lead to increased suppression of WNK4, which has dual function at baseline (NCCT activation and ROMK suppression). *Aldo* Aldosterone, *cAldo* chimeric aldosterone, *MR* mineralocorticoid receptor, *APA* aldosterone-producing adrenal adenoma, *CAH* congenital adrenal hyperplasia, *ACTH* adrenocorticotropic hormone, *DOC* deoxycorticosterone, *Cul3* Cullin 3, *KLHL3* Kelch-like 3, *11-β-HSD* 11-β hydroxysteroid dehydrogenase, *NCCT* Na^+–Cl^- cotransporter, *ROMK* renal outer medullary K^+ channel

unaffected members were negative. The mode of transmission was autosomal dominant (Table 1). Interestingly, affected women in this family exhibited a worsening of hypertension in pregnancy (HiP), suggesting that progesterone acted as an agonist of the mutated MR-S810L. Structural protein analysis revealed that the mutated MR gene allowed for MR activation by steroids lacking the 21-hydroxyl group, which under normal conditions is not possible. The leucine residue at position 810 lies within helix 5 of the ligand-binding domain of the MR and creates a novel interaction with alanine at a position of MR helix 3. This modification explains why, in in vitro studies, compounds that are normally antagonists, such as spironolactone, act as agonists in MR-S810L [21].

Aldosterone-producing adrenal adenomas (familial hyperaldosteronism type III)

At least 5 % of patients referred for evaluation of primary hypertension have aldosterone-producing adrenal adenomas (APA, or unilateral adrenal hyperplasia) [22]. As in GRA and AME, patients with APA show findings consistent with excessive aldosterone secretion (Table 1). Family history is often negative. Patients are identified due to hypokalemia and frequently feature a characteristic adrenal mass on CT scans. Adrenal vein sampling demonstrates predominant aldosterone secretion from the gland harboring the tumor, which is crucial for the correct diagnosis as it allows APA to be distinguished from idiopathic hyperaldosteronism (familial hyperaldosteronism type II). Surgical removal of the affected adrenal gland ameliorates hypertension in most patients [22]. Lifton and colleagues performed exome sequencing of 22 adrenal adenoma tissues and identified that approximately one-third of all adenomas harbored novel somatic mutations at highly conserved residues (G151R and L168R) of the inwardly rectifying potassium channel *KCNJ5* (Kir3.4) [23]. *KCNJ5* was further implicated as a cause of a Mendelian form of primary aldosteronism through the identification of a family (father and both daughters) with familial adrenal adenomas and severe hypertension [24]. Mutational analysis in this family revealed a unique germline mutation within a highly conserved residue of *KCNJ5* (T158A). Structural proteomics and in vitro experiments suggest that these rare *KCNJ5* mutations alter Kir3.4 channel function and lead to chronic depolarization of adrenal zona glomerulosa cells, thereby causing constitutive aldosterone production as well as adrenal cell proliferation [25] (Fig. 1).

Congenital adrenal hyperplasia

Congenital adrenal hyperplasia (CAH) refers to several autosomal recessive diseases resulting from mutations in genes encoding enzymes mediating biochemical steroidogenesis in the adrenal gland. In CAH, the adrenal glands secrete excessive or deficient amounts of sex hormones and mineralocorticoids during prenatal development [26]. Poor cortisol production is a hallmark of these conditions. CAH is often classified into the common classical ("salt-wasting" and "simple virilizing" mostly due to 21-α-hydroxylase deficiency) and the rare non-classical forms (<5–10 %), which can be associated with hypertension due to elevated adrenocorticotropic hormone (ACTH) levels. Loss-of-function mutations in *CYP11B1* (11-β-hydroxylase) and *CYP17A1* (cytochrome P450 17A1, also known as 17α-hydroxylase) are both causes of rare forms of CAH [26]. Both cortisol and sex steroids are decreased in CAH, leading to increased mineralocorticoid precursor production. The aldosterone precursors 11-deoxy corticosterone (DOC) and corticosterone are elevated, activating the MR (Fig. 1). Patients typically develop hypertension in childhood due to volume expansion and feature hypokalemia and metabolic alkalosis (Table 1). Treatment with glucocorticoids suppresses ACTH, thereby returning mineralocorticoid precursor production back toward normal and lowering the BP [27]. Female virilization (11-β-hydroxylase deficiency) and ambiguous genitalia in genetic males or failure of the ovaries to function at puberty in genetic females (17-α-hydroxylase deficiency) are other features of CAH.

Pathway of enhanced salt reabsorption in the distal convoluted tubule associated with impaired potassium secretion

Pseudohypoaldosteronism type 2 (PHA II, also known as Gordon's syndrome or familial hyperkalemia and hypertension) is a unique form of hypertension associated with hyperkalemia and metabolic acidosis transmitted in an autosomal dominant fashion [28] (Table 1). Hypercalciuria has been reported in some cases, making this syndrome a near mirror image of Gitelman's syndrome, which is described further below [29]. Renin activity in PHA II is typically suppressed, and aldosterone levels can be normal or slightly elevated. Thiazide diuretics represent a highly effective treatment for this syndrome and also commensurate with salt-sensitivity. The hypertension is chloride dependent because the exchange of sodium bicarbonate or citrate infusions for sodium chloride infusion was found to ameliorate BP elevation [30]. In recent years, several genes have been identified for the etiology of PHA II. Intronic deletions in the kinase *WNK1* and missense mutations in the kinase *WNK4* have been identified in large pedigrees of this condition by linkage analysis [31]. Both kinases belong to a novel kinase family that is lacking lysine (K) at a typical location, giving them their name ("With No K"). Both of these kinases are expressed in the distal nephron and have been implicated in the regulation of several transporters and channels since their discovery. Dominant gain-of-function mutations in *WNK1* and loss-of-function mutations in *WNK4* lead to increased salt reabsorption in the distal nephron by activating the Na^+–Cl^- cotransporter (NCCT) regardless of volume status, resulting in salt-sensitive hypertension and inhibition of K^+ excretion despite marked hyperkalemia. The role of NCCT activation in the pathophysiology of PHA II explains why this condition is so susceptible to treatment with thiazide diuretics. At baseline, WNK1 functions as a suppressor of WNK4 by associating with WNK4 in a protein complex involving the kinase domains. WNK4 has also been found to regulate the renal outer medullary K^+ channel (ROMK) in the distal convoluted tubule (DCT) [32]. Recently, two more gene defects for PHA II have been identified by exome sequencing [33]. The majority of patients with PHA II in this study (87 %) were negative for WNK mutations and 52 such kindreds were included. Many of these did not display the usual autosomal-dominant inheritance; rather, a recessive model was suggested. Novel, protein-altering allelic variants were identified primarily in two genes. Twenty-four PHA II index cases revealed novel mutations in the gene *KLHL3* (Kelch-like 3) that were predominantly at positions conserved among orthologs. Among the remaining index cases of PHA II without mutations in *WNK1*, *WNK4*, or *KLHL3*, 17 were identified with novel allelic variants in the gene *CUL3* (Cullin 3). Eight of these mutations were de novo and not present in parents. The molecular mechanism of KLHL3 and CUL3 in causing PHA II remains unclear; however, both proteins are expressed in the DCT and co-localize with WNK1, WNK4, and NCCT. Impaired ubiquitination of NCCT from the luminal cell surface in the DCT has been speculated as a mechanism for PHA II development in patients with KLHL3 and CUL3 mutations [33] (Fig. 1). The phenotype of patients with different gene defects in PHA II differs. Patients with CUL3 appear more severely affected as they develop PHA II at younger age and present with more severe hyperkalemia and also a failure to thrive. However, thiazide diuretics are the treatment of choice in all forms of PHA II due to their inhibition of NCCT [29] (Table 1).

Pathways affecting the autonomic (sympathetic) regulation of BP

Hypertension with brachydactyly (Bilginturan's syndrome)

Autosomal dominant hypertension with brachydactyly (HBS) was first described in 1973 [34]. The affected family members were short in stature, developed hypertension in childhood, and died typically of stroke before the age of 50. The clinical findings of short metacarpal bones (= brachydactyly type E), cone-shaped epiphysis, and short endphalanx of the thumb (= brachydactyly type B) are 100 % concordant with the elevated BP values in identified families [35]. Contrary to the previously described syndromes, HBS does not feature any associated biochemical abnormalities, and BP levels do not appear to be salt-sensitive (Table 1). Evaluation of the renin–angiotensin–aldosterone axis, as well as catecholamines, has revealed no abnormalities [36]. Diuretics do not play a significant role in the treatment of this condition, and patients typically require multiple anti-hypertensive drugs [37]. Autonomic nervous system testing has revealed an abnormal baroreceptor reflex response, resulting in an excessive increase of BP with sympathetic stimuli [38]. The BP of affected individuals at baseline is much more sensitive to the alpha-agonist phenylephrine than that of controls. This difference is diminished when the baroreceptor reflex mechanism is blocked with the ganglion blocker trimethaphan. All tested affected patients (n=15) in the originally described family feature neurovascular anomalies in the area of the left ventrolateral medulla oblongata in MRI studies, whereas these anomalies are absent in unaffected family members (n=12) [39]. It is unknown if neurovascular arterial compression of the brainstem in this location is responsible for the abnormal baroreceptor function and hypertension in this syndrome. The gene(s) for this condition was (were) located on chromosome 12p [35]. A complex rearrangement of the HBS locus has been identified, and several promising candidate genes

have been screened, but no definitive underlying cause has been as yet identified. It has been speculated that the rearrangement at this locus could affect microRNA expression and cause translational repression of gene transcripts or gene silencing [40].

Hereditary familial pheochromocytoma

Pheochromocytoma is caused by catecholamine-producing adrenal tumors and is associated with various symptoms depending on the type and secretory pattern of the produced catecholamine(s). Hypertension can present as paroxysmal, labile hypertension, complicated by orthostatic hypotension, as well as persistent hypertension. Hypokalemia can often be found, and renin and aldosterone levels can be elevated due to decreased intravascular volume [41]. The frequency of hereditary familial forms of pheochromocytoma has been reported to be approximately 25 %. The majority of these are associated with the type II multiple endocrine neoplasia syndrome (MEN II) and caused by gain-of-function mutations in the *RET* proto-oncogene [42]. In addition to pheochromocytoma, MEN II features medullary thyroid cancer (types IIA and IIB), hyperparathyroidism (type IIA), and mucosal neuromas (type IIB). Including *RET*, more than ten gene defects have been associated with pheochromocytoma. Other examples are neurofibromatosis type 1 (NF1), Von Hippel–Lindau disease (VHL), and familial extra-adrenal paragangliomas (SDHB, SDHC, SDHD) [42]. The genes encoding for the succinate dehydrogenase subunits B (*SDHB*), C (*SDHB*), and D (*SDHD*) are three of four proteins forming the succinate dehydrogenase protein complex, which participates in the Krebs cycle and in mitochondrial electron chain transport. The treatment of choice is surgical resection of the affected adrenal gland(s) or paraganglioma, respectively. Treatment with irreversible alpha-blockade prior to surgery is mandatory to prevent hypertensive complications [41].

Pathway with unknown mechanism: mitochondrial gene mutation in *tRNA-Ile* resembling metabolic syndrome

Richard Lifton and colleagues described a familial form of hypertension, hypomagnesemia, and hyperlipidemia along the maternal lineage of a large family, indicating mitochondrial inheritance of this syndrome [43]. Sequencing of the mitochondrial genome of the maternal lineage identified a homoplasmic mutation substituting cytidine for uridine immediately 5′ to the mitochondrial tRNA anti-codon for isoleucin (Ile). In silico analysis showed that uridine at this position is almost invariant among tRNAs, stabilizing the tRNA anticodon loop. Hypertension, hypomagnesemia, and hypercholesterolemia each showed 50 % penetrance among adults on the maternal lineage. The prevalence of hypertension on the maternal lineage showed marked age dependence, increasing from 5 % in subjects under 30 years of age to 95 % in those over 50 years of age . The mechanism of BP elevation in this syndrome is as yet unexplained. In vivo nuclear magnetic resonance spectroscopy of skeletal muscle in one affected patient showed decreased ATP production (in the setting of normal Krebs cycle function) [43]. Given the known loss of mitochondrial function with aging due to increased mitochondrial mutations, increasing BP could be secondary to the loss of ATP production, which has been associated with hypertension in the animal model [43]. Another possibility is the increased presence of reactive oxygen species secondary to mitochondrial dysfunction that has been associated with hypertension as well [44]. Epidemiological studies have shown that children of hypertensive mothers are more likely to develop hypertension, also suggesting that the mitochondrial genome could be associated with inheriting hypertension [45, 46].

Genes that decrease BP

Pathway of renal salt wasting in the thick ascending limb: Bartter's syndrome

Barrter's syndrome is a rare defect of the thick ascending limb (TAL) of the loop of Henle [47]. All patients with this condition feature varying degrees of hypokalemic metabolic alkalosis and low-to-normal BP with elevated renin levels (Table 2). Some patients also have hypercalciuria (Bartter's types 1, 2 and 5). Most of these findings are identical to those of patients who are on loop diuretics. To date, five different disease genes have been identified for this syndrome, all encoding for proteins facilitating salt reabsorption in the TAL (Fig. 2). Bartter's syndrome is classified into five different genetic subtypes, which differ in disease severity. The transmission of Bartter's syndrome is typically autosomal recessive except for type 5, which is transmitted in an autosomal-dominant fashion. Neonatal Bartter's syndrome is the most common form (approx. 90 % of all patients) and is typically noticed during pregnancy due to polyhydramnios (excess amniotic fluid). Neonatal infants feature severe polyuria and polydipsia. Life-threatening volume contraction may result if the infant does not receive adequate fluids. The majority of infants are hypercalciuric and will develop nephrocalcinosis, which can progress to renal failure. Failure to thrive is a typical occurrence in children with neonatal Bartter's syndrome, which is caused by loss-of-function mutations in the Na^+–K^+–$2Cl^-$ cotransporter (NKCC2, Bartter's type 1) and the renal outer medullary K^+ channel (ROMK, Bartter's type 2), both of which are expressed at the apical membrane of TAL epithelia [48, 49]. In comparison, the classic Bartter's syndrome (type 3) is caused by

Table 2 Monogenic forms of low BP

Syndrome[a]	Mode of inheritance	K^+	pH	Renin	Aldosterone	Treatment	Loci	Gene
Bartter's	AR	↓	↑	↑	↑	Increase salt intake	15q21	*SLC12A1* (type 1)
	AR	↓	↑	↑	↑		11q24	*KCNJ1* (type 2)
	AR	↓	↑	↑	↑		1p36	*CLCNKB* (type 3)
	AR	↓	↑	↑	↑		1p32	*BSND* (type 4)
	AD	↓	↑	↑	↑		3q21	*CASR* (type 5)
Gitelman's	AR	↓	↑	↑	↑	Increase salt intake	16q13	*SLC12A3* (NCCT)
PHA I	AD	↑	↓	↑	↑	Increase salt intake	4q31	*NR3C2* (type 1A)
							12p13	*SCNN1A* (type 1B)
							16p13	*SCNN1B* (type 1B)
							16p13	*SCNN1G* (type 1B)
SeSAME/EAST	AR	↓	↑	↑	↑	Increase salt intake	1q23	*KCNJ10* (Kir4.1)
RTD	AR	↑	↓	↓ or ↑	↓	Vasopressors	1q32	*REN*
							1q42	*AGT*
							3q24	*ACE*
							17q23	*AGT1R*

AR, Autosomal-recessive

[a]PHA I, Pseudohypoaldosteronism type 1; RTD, renal tubular dysgenesis; SeSAME, seizures, sensorineural hearing loss, ataxia, mental retardation, and electrolyte imbalance; EAST, epilepsy, ataxia, sensorineural deafness, and tubulopathy

loss-of-function mutations in the basolateral Cl^- channel Kb (CLCNKB) and is usually diagnosed at school age or later, although symptoms of renal salt wasting may occur earlier in life [50]. In classic Bartter's syndrome, increased urinary calcium excretion is significantly milder, and kidney stones can develop later in life, if at all. Renal function is typically normal; however, progression to end-stage renal disease has been described. Since CLCNKB is also expressed in the DCT, type III Bartter's syndrome is classified by some authors as a mixed disorder of the TAL and DCT or as a disorder of the thiazide–furosemide pharmacotype [51]. Mild hypomagnesemia can be present in classic Bartter's syndrome. Type 4 Bartter's syndrome is caused by mutations in Barttin (*BSND*), which is an accessory β-subunit of the CLCNKB [52]. Since Barttin is also expressed in the inner ear (where it interacts with the Cl^- channel CLCNKA), patients with Bartter's type 4 also suffer from sensorineural deafness. Gain-of-function mutations in the calcium-sensing receptor gene (CASR) feature renal salt wasting and hypercalciuria [53]. Although parathyroid hormone (PTH) levels are severely suppressed in this syndrome, which is also known as autosomal-dominant hypocalcemia (ADH), this condition is classified by some as Bartter's type 5 due to the expression of the CASR on the basolateral membrane of TAL epithelia. However, rather than being considered a variant of Bartter's syndrome with specific dysfunction of TAL epithelia, this condition could also be interpreted as a phenocopy of Bartter's syndrome.

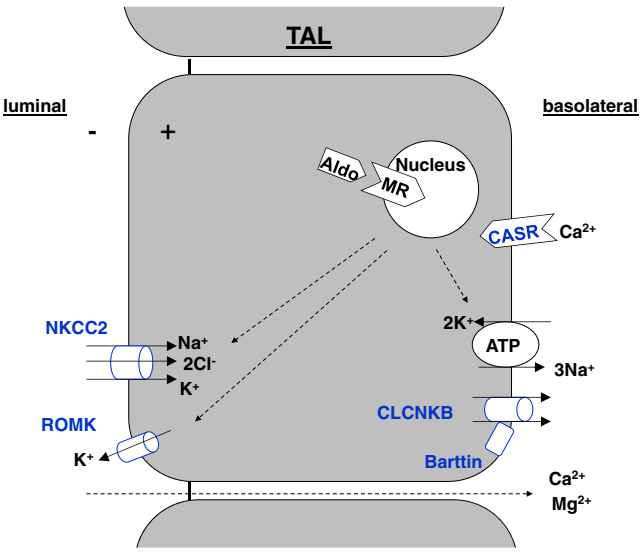

Fig. 2 Mutations in genes expressed in thick ascending limb (*TAL*) epithelia cause Bartter's syndrome. Schematic illustration of five molecular mechanisms (*blue*) leading to renal salt wasting in epithelia of the TAL. *CASR* Calcium-sensing receptor, *NKCC2* Na^+–K^+-$2Cl^-$ cotransporter, *CLCNKB* Cl^- channel Kb. For other abbreviations, see caption to Fig. 1

Pathways of renal salt wasting in the distal nephron

Gitelman's syndrome

Patients with Gitelman's syndrome present with symptoms identical to those who are on thiazide diuretics. Lifton and colleagues performed linkage analysis in several unrelated families with Gitelman's syndrome and identified the locus for the thiazide-sensitive NCCT gene (*SLC12A3*). Several

homozygous or compound heterozygous loss-of-function mutations in *SLC12A3* were identified in their study [54], which inactivate NCCT expressed in the apical membrane of DCT epithelia (Fig. 3). The clinical symptoms are a mirror image of those of PHA II, with the exception of hypomagnesemia, and include hypochloremic metabolic alkalosis, hypokalemia, and hypocalciuria (Table 2). Affected individuals are typically asymptomatic; however, muscular cramps, weakness/fatigue, and irritability have been described. More severe symptoms, such as tetany and paralysis, are rare. Individuals with heterozygous loss-of-function mutations in NCCT may have a survival benefit due to a lower BP and increased bone mineral density [11, 55].

Pseudohypoaldosteronism type 1

Pseudohypoaldosteronism type 1 (PHA I) is characterized by salt wasting resulting from renal unresponsiveness to mineralocorticoids [56, 57]. Patients may present with neonatal renal salt wasting with hyperkalemic acidosis despite high aldosterone levels (Table 2). Two genetic subtypes can be distinguished; type I A, which is inherited in an autosomal dominant fashion, and type I B, which is transmitted in an autosomal recessive pattern. PHA I A is caused by loss-of-function mutations in the MR gene and is typically milder than PHA I B [56]. It could be considered as a mirror image of the syndrome of hypertension in pregnancy. Patients improve with age and usually become asymptomatic without treatment when they reach adulthood. Some adult patients are found to have elevated aldosterone levels, however, they lack a history of the disease. This observation suggested that only those infants whose salt homeostasis is "stressed" by intercurrent illness and volume depletion develop clinically recognized PHA I. The recessive form, PHA 1B, is caused by loss-of-function mutations in any one of the three genes encoding the α-, β- or γ-subunits of ENaC, leading to decreased channel activity and renal salt wasting (Fig. 3) [57]. PHA 1B is a mirror image of Liddle's syndrome. Patients with this form can feature a severe systemic disorder starting in infancy and persisting into adulthood.

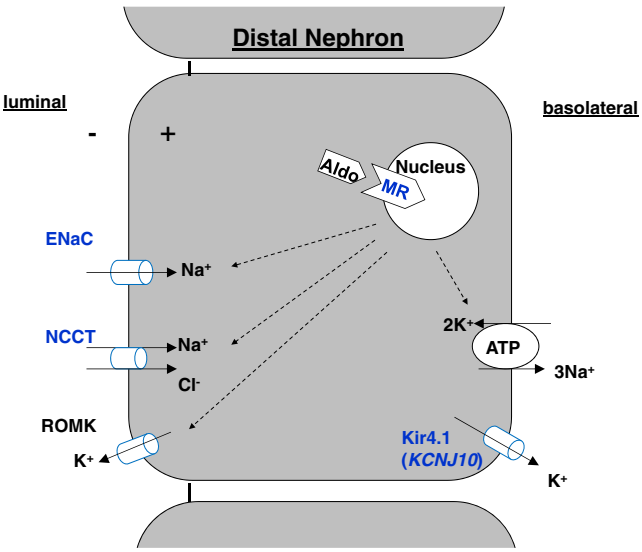

Fig. 3 Mutations in genes expressed in distal nephron epithelia cause salt wasting, electrolyte abnormalities, and low blood pressure. Schematic illustration of four molecular mechanisms (*blue*) leading to renal salt wasting in distal nephron epithelia. *ENaC* Epithelial Na^+ channel, *Kir4.1* K^+ channel, inwardly rectifying, subfamily J, member 10. For other abbreviations, see captions to Figs. 1 and 2

SeSAME/EAST syndrome

The SeSAME (seizures, sensorineural hearing loss, ataxia, mental retardation, and electrolyte imbalance) or EAST (epilepsy, ataxia, sensorineural deafness, and tubulopathy) syndrome features renal salt wasting and electrolyte imbalance, and its study has added considerable new insight into renal electrolyte homeostasis in the distal nephron. This syndrome is accompanied by several additional findings giving this condition its names. Lifton and colleagues named it the SeSAME syndrome in order to describe the presence of seizures, sensorineural hearing loss, ataxia, mental retardation and electrolyte imbalance [58]. Bockenhauer and colleagues named it the EAST syndrome for its association with apparent epilepsy, ataxia, sensorineural deafness, and renal tubulopathy [59]. The mode of inheritance is autosomal recessive, and consanguinity has been described in some families. The responsible gene, *KCNJ10*, was identified by linkage analysis and encodes for the K^+-channel Kir4.1, which is expressed in the basolateral membranes of the DCT, connecting tubule (CNT), and CD epithelia. The identified electrolyte and acid–base abnormalities are similar to those seen in Gitelman's syndrome and include hypokalemia, hypomagnesemia, and metabolic alkalosis (Table 2). Renin and aldosterone levels are elevated. Patients typically have normal BP values but still crave salt, suggesting that they compensate for renal salt losses with an increased consumption of salt to maintain normal BP values [59]. In vitro studies suggest that loss-of-function mutations in *KCNJ10* impair the activity of the Na^+–K^+ ATPase, which is also located at the basolateral membrane of epithelia of the same nephron segments. Loss of Kir4.1 function probably impairs K^+ cycling at the basolateral membrane and thereby inhibits the Na^+–K^+ ATPase function and Na^+ reabsorption [58]. The additional features seen in this syndrome are due to the expression of Kir4.1 in neuronal tissue and in cells of the inner ear. *KCNJ10*-deficient mice exhibit a striking pathology of the entire central nervous system and display renal salt wasting and volume contraction [60].

Severe hypotension due to renal tubular dysgenesis

Autosomal recessive renal tubular dysgenesis (RTD) is a severe developmental disorder of abnormal renal tubular formation characterized by persistent fetal oligoanuria frequently associated with in utero or perinatal death [61]. Parental consanguinity is present in approximately one-third of all reported families [62]. Surviving newborn infants display severe and refractory hypotension that requires vasopressor treatment, respiratory assistance, and dialysis after birth. Death often occurs due to pulmonary hypoplasia and respiratory failure from early-onset oligohydramnios (Potter sequence). Gubler et al. reported that to date only four patients have survived after days or weeks of intensive care [62]. The absence or paucity of differentiated proximal tubules is the histopathologic hallmark of this disorder, which is often associated with postnatal skull ossification defects (hypocalvaria). In RTD, all tubules appear to be abnormally developed, primitive, and reminiscent of collecting tubules. RTD can also be found in children of women using angiotensin-converting-enzyme inhibitors (ACEi) during pregnancy [63]. Hypocalvaria is also present in this acquired (secondary) form of RTD, also known as ACEi fetopathy. The genetic forms of RTD are caused by loss-of-function mutations in four genes encoding for proteins of the renin–angiotensin system. These genes are shown in Table 2 and include *REN* (renin), *AGT* (angiotensinogen), *ACE*, and *AGT1R* (angiotensin II receptor type 1). In one study involving 160 cases, no correlation could be established between the clinical course of the disease and the type of mutation[62].

Molecular basis of essential hypertension

The genetic causes of (essential) hypertension in the general population remain unknown, probably due to the polygenic nature of BP homeostasis involving many different systems, including vasculature, the central and autonomic nervous system, the kidney, and various different hormonal pathways [64]. It is probable that multiple genes with small effects determine overall BP levels by either lowering or increasing BP. In the last two decades, several DNA sequence-based strategies of gene identification were applied to identify genes for essential hypertension, including hypothesis-based (candidate gene analysis, candidate gene

Table 3 Genome-wide association studies for systolic and diastolic BP or hypertension

GWAS	Chromosome loci	Nearest gene(s) at locus	Kidney expression
CHARGE: - n = 29,136 (Europeans) - P < 4 x 10^{-7}	1p36 11p15 12q21, 12q24 18p11	- *CASZ1* - *PLEKHA7* - *ATP2B1* , *ATXN2* / *TBX3* / *TBX5* / *TRAFD1* - *C18orf 1*	+ + + , + / + / + / + +
Global BPgen: - n = 134,258 (Europeans) & n = 12,889 (Indian Asians) - P < 5 x 10^{-7}	1p36 3q26 4q21 10q21, 10q24 12q24 15q24 17q21	- *MTHFR* / *NPPB* / *CLCN6* - *MDS1* - *FGF5* / *C4orf22* / *PRDM8* - *C10orf107* / *TMEM26* , *CYP17A1* / *NT5C2* - *SH2B3* / *ATXN2* - *CYP1A1* / *CYP1A2* - *ZNF652* / *PHB*	+ / + / + + + / + / + ± / + , ± / + + / + + / + + / +
AGEN-BP: - n = 50,373 (East Asians) - P < 5 x 10^{-8}	1p13,1p36 2q24 4q21, 4q25 5p13 10q24 12q21, 12q24	- *CAPZA1* , *CASZ1* - *FIGN* / *GRB14* - *FGF5* , *ENPEP* - *NPR3* - *CYP17A1* / *NT5C2* / *CNNM2* - *ATP2B1* , *TBX3* / *RPL6* / *PTPN11* / *ALDH2*	+ , + + / + + , + + + / + / + + , + / + / + / ±
IC BP GWAS: - n = 200,000 (Europeans) - P < 5 x 10^{-9}	1p13,1p36 3p22, 3p23, 3q26 4q21, 4q22, 4q32 5p13, 5q33 6p21, 6p22 10p12,10q21,10q23,10q24 11p15, 11q22 12q21, 12q24 15q24, 15q25, 17q11, 17q21 20p12, 20q13	- *MOV10* , *MTHFR* / *NPPB* - *ULK4* , *SLC4A7* , *MECOM (MDS1)* - *FGF5* , *SLC39A8* , *GUCY1A3* / *GUCY1B3* - *NPR3* , *EBF1* - *BAT2* / *BAT5* , *HFE* - *CACNB2* , *C10orf107* , *PLCE1* , *CYP17A1* / *NT5C2* - *ADM* / *PLEKHA7*, *FLJ32810* / *TMEM133* - *ATP2B1* , *SH2B3* / *TBX3* / *TBX5* - *CYP1A1* / *ULK3* , *FURIN* / *FES* - *GOSR1* , *ZNF652* - *JAG1* , *GNAS* / *EDN3*	+ , + / + + , ± , + + , + , + / + + , + + / + , + ± / ± / + , ± / + + / + , + / + + , + / + / + + / + , + / + + , + + , ± / +

GWAS, Genome-wide association study

[a] CHARGE, Cohorts for Heart and Aging Research in Genome Epidemiology; Global BPgen, Global Blood Pressure Genetics; AGEN-BP, Asian Genetic Epidemiology Network Blood Pressure; IC BP GWAS, International Consortium Blood Pressure. CHARGE and IC BP GWAS SNP data were also analyzed for HTN (BP as a dichotomous trait)

[b] Candidate genes reported twice or more are marked in red. The *CYP17A1* locus was identified in three studies and is the only gene known to cause monogenic hypertension (marked in blue)

[c] Kidney expression of listed genes was called positive (+) if renal expression was shown in any of three different databases (GUDMAP, Human Protein Atlas, GeneCards). Kidney expression was listed as "±" if the expression data were contradictive between databases

association studies) and hypothesis-free [linkage analysis, genome-wide association studies (GWAS)] strategies. Most gene loci for essential hypertension have been identified by GWAS, which require a large sample size and population stratification to succeed. Additional limitations of GWAS are the frequent inability to replicate findings in independent data sets and the lack of causal (functional) allelic gene variations at the identified loci.

Four large GWAS for essential hypertension with 29,000–200,000 participants identified 29 gene loci determining systolic and diastolic BP as quantitative traits [65–68] (Table 3). Most of the identified loci have no obvious connections to known pathways affecting BP and contribute only minimally to phenotypic variation, explaining <1 % of systolic and diastolic BP variance in these cohorts, despite an estimated BP heritability of 30–60 % [5, 6, 64]. Two of the BP loci, 1p36 and 12q24, were identified in all four GWAS despite the varying ancestry of the study populations. Interestingly, genes located at 1p36 include *MTHFR* (methylene-tetrahydrofolate reductase) and *NPPB* (brain natriuretic peptide). *MTHFR* has been associated with pre-ecclampsia [69], and deletions in *NPPB* have been associated with salt-sensitive hypertension in the mouse [70]. Another interesting candidate gene is *SLC4A7* (Na^+–$HCO3^-$ cotransporter 3) on 3p23. *SLC4A7*-deficient mice develop arterial hypertension, probably by inhibition of NO-mediated vasorelaxation [71]. *CYP17A1* on 10q24 is the only locus previously identified in a rare syndrome of BP variation (loss-of-function mutations cause CAH). Similar to the genes responsible for rare forms of BP variation, most of the genes found at the "GWAS loci" for essential hypertension are expressed in the kidney, underscoring the importance of the kidney in BP regulation (Table 3).

One (candidate gene-based) study showing that rare functional variants do determine BP in the general population was conducted in approximately 5,000 participants of the FHS population [11]. Several rare, heterozygous mutations in *SLC12A3* (NCCT), *SLC12A1* (NKCC2), and *KCNJ1* (ROMK) were identified, and a causal reduction of BP was postulated based on data obtained from comparative genomics, genetics, and biochemistry. In the heterozygous state, 30 mutations in these three genes were associated with protection from BP changes. This study underlined the contribution of genes altering renal salt handling on BP homeostasis and showed the importance of studying rare forms of hypertension with extreme phenotypes to unravel the genetics of hypertension. The identification of the ROMK pathway as a potentially important player in BP regulation in the general population was particularly interesting since it could motivate the investigation of a new antihypertensive diuretic agent that might not produce the hypokalemia seen with the known loop and thiazide diuretics.

Conclusion

Guyton and colleagues postulated over 3 decades ago that the kidney plays a central role in BP regulation by managing urinary sodium excretion ("pressure natriuresis") [72]. Although this hypothesis has been debated over several decades, there is overwhelming clinical evidence that sodium intake is associated with hypertension and that diuretic therapy is beneficial. The vast majority of genes identified in rare forms of hypertension are expressed in the kidney, which supports Guyton et al.'s hypothesis that renal salt handling is the final determinant of (abnormal) BP homeostasis [7, 8]. These syndromes have led us to understand the primary physiology of BP regulation and taught us about disease mechanisms, which can lead to arterial hypertension, hypotension, and abnormal electrolyte and acid–base homeostasis. Some of the genes discussed in this review have been tested in the FHS population and have been shown to have an effect on BP variation in the general population [11]. Based on the FHS data, it is probable that the combined effects of rare independent mutations in genes described in this review may account for a substantial fraction of BP variation in the general population. Therefore, continuing to study these rare conditions is of great importance, and further knowledge will enable us to understand, prevent, and treat hypertension better than we do at present and lay the foundation for future individualized medical care based on genetic predisposition.

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