The molecular basis of hypertension

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Hypertension is a substantial public health problem affecting about 25% of the population in industrialized societies. The disorder is responsible for many common causes of morbidity and mortality. Despite the important role of hypertension as a cause of disease, its pathogenesis remains largely unknown. The application of genetic approaches to rare monogenic (Mendelian) forms of hypertension and hypotension has begun to delineate molecular pathways underlying human blood pressure variation, defining disease pathogenesis and identifying targets for therapeutic intervention. In all cases the pathophysiology is altered net renal salt reabsorption. Mutations are either affecting circulating mineralocorticoid hormones or renal ion channels and transporters. Examples are glucocorticoid-remediable aldosteronism (GRA), Liddle's syndrome, the syndrome of hypertension exacerbated in pregnancy, and apparent mineralocorticoid-excess (AME). Recently, alterations in genes of a novel serine-threonine kinase family (WNK1 and WNK4) were identified causing pseudohypoaldosteronism type II. The molecular pathway of this syndrome remains unclear. Additionally, there is the syndrome of hypertension associated with brachydactyly type E (Bilginturan's syndrome), for which the molecular mechanism has yet to be identified.

Key words: hypertension, molecular basis.

Hypertension is a substantial public health problem affecting 25% of the adult population in industrialized societies[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. From extensive investigations over the last decades it is known that hypertension has a multifactorial determination. These factors include demographic, dietary and genetic factors. Known demographic factors are age, gender and body mass[3]. Dietary factors include e.g. salt, potassium and calcium intake[4]. The influence of genetic factors are known from twin studies[5] and studies of biological versus adopted siblings[6]. Monozygotic twins show greater concordance of blood pressure than dizygotic twins, and biological siblings show higher similarity of blood pressure values than adopted siblings[7].

The identification of genes underlying hypertension has the capacity to define primary physiologic mechanisms and thereby clarify disease mechanisms and pathways. Different approaches have been made to study the genetics of hypertension. One of these approaches is the investigation of Mendelian (monogenic) forms of blood pressure variation, where single genes have a large effect on blood pressure[8]. The most progress in the research of the molecular mechanisms of hypertension has been made by investigations in monogenic forms of blood pressure variation. Mutations in 19 genes have been identified as causing abnormal blood pressure variation. Mutations in 10 genes cause monogenic forms of hypertension and mutations in 9 genes cause monogenic forms of hypotension. Numerous disease mechanisms have been defined[9].

In the following report, six syndromes are reviewed. The molecular mechanisms of the first four syndromes have been defined. The genetic alterations in glucocorticoid-remediable

aldosteronism, Liddle's syndrome, hypertension in pregnancy and apparent mineralocorticoid-excess cause increased renal salt and volume reabsorption resulting in hypertension[9]. The mechanism of pseudohypoaldosteronism type II remains unclear, although alterations in two genes of a novel serine-threonine kinase family (WNK1 and WNK4) have been recently identified[10]. The gene(s) responsible for Bilginturan's syndrome has been mapped to chromosome 12p[11], but has yet to be identified.

Glucocorticoid-remediable aldosteronism (GRA)

Patients with glucocorticoid-remediable aldosteronism have an autosomal dominant hypertension and are usually suspected of having primary aldosteronism. They have a volume expansion and a salt-sensitive form of hypertension, tend to metabolic alkalosis with hypokalemia, and respond to both thiazide diuretics and spironolactone. The latter fact suggested that mineralocorticoid products may be involved. Patient renin values are low while the aldosterone values can be elevated (Table I). They also have 18-hydroxy- and 18- oxocortisol, steroids not normally found in urine. Recognizing these abnormal products led to solving the mystery. Prednisone replacement ameliorates the hypertension, causes the abnormal steroids to disappear, and gives the syndrome its name. The abnormal cortisol derivatives and the favorable effects of glucocorticoid treatment suggested that the zona fasciculata, which express the gene for 17 β-hydroxylase (CYP17) and is ACTH-responsive, was the source of the excess mineralocorticoids. Two distinct gene poroducts, 11-β-hydroxylase (CYP11B1) and aldosterone synthase (CYP11B2), perform the terminal steps in glucocorticoid and mineralocorticoid biosynthesis, respectively. A linkage analysis in a large pedigree localized the responsible gene to chromosome 8q, exactly at the site where the genes for 11 β-hydroxylase and aldosterone synthase also reside[12]. In affected individuals, a chimeric gene consisting of the promotor-regulatory region of 11-β-hydroxylase and the structural portion of aldosterone synthase is located between CYP11B1 and CYP11B2. The chimeric gene results from a meiotic mismatch and unequal crossing over (Fig. 1). The protein product performs all reactions required for aldosterone production: however, the protein is

Table I. Monogenic (Mendelian) forms of hypertension are compared regarding potassium (K^+), pH, renin, aldosterone (Aldo), specific treatment, gene loci and gene. In contrast to the other syndromes, the hypertension and brachydactyly syndrome (HBS) is not salt-sensitive and features normal (N) values for the shown parameters

Syndrome	K^+	pH	Renin	Aldo	Treatment	Loci	Gene
GRA	↓	↑	↓	↑	Spironolactone, Amiloride	8q	Chimeric gene (CYP11B1/ CYP11B2)
Liddle's syndrome	↓	↑	↓	↓	Amiloride	16p	β and γ subunit of ENaC
AME	↓	↑	↓	↓	Spironolactone, Amiloride	16q	11-β-HSD
MR	↓	↑	↓	↓	None, multiple drug therapy	4q	MR
PHA type II	↑	↓	↓	↓	Hydrochloro-thiazide	12p 17q 1q	WNK1 WNK4 ?
HBS	N	N	N (↓)	N	None, multiple drug therapy	12p	?

GRA: glucocorticoid-remediable aldosteronism; AME: apparent mineralocorticoid-excess; MA: mineralocorticoid receptor; PHA II: pseudohypoaldosteronism type II.

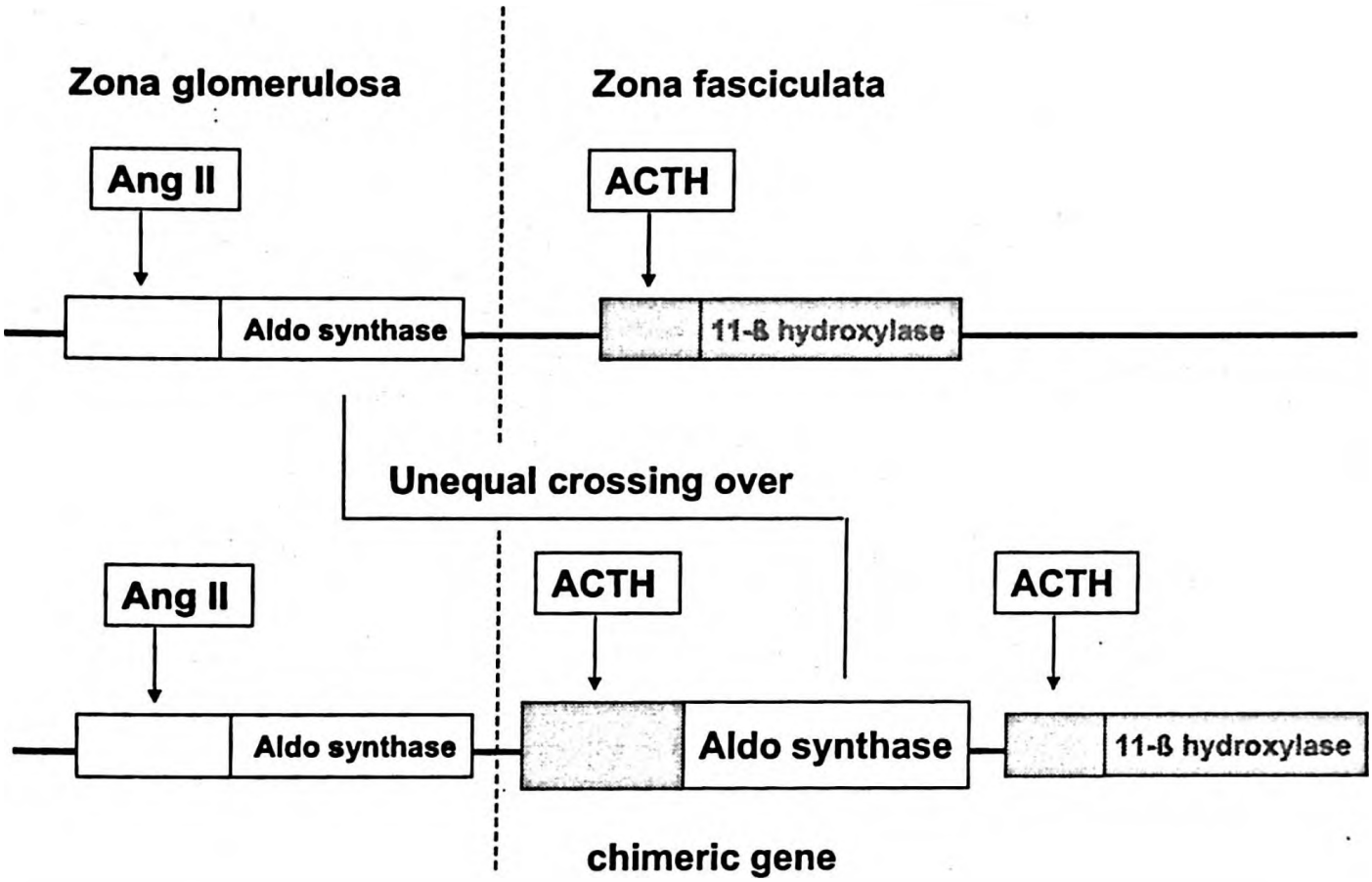

Fig. 1. A chimeric gene is formed by meiotic mismatch and unequal crossing over with the promoter region of the 11-β-hydroxylase gene (dark box) and the coding region of the aldosterone synthase gene (white box). As a result, the aldosterone synthase gene is under control of ACTH in the zona fasciculata. Ang II = angiotension II; aldo: aldosterone; ACTH: adrenocorticotropic hormone.

ACTH rather than angiotensin II-dependent. Ectopic expression of this protein in the zone fasciculata permits the formation of 18-hydroxy- and 18-oxocortisol, the biochemical hallmarks of GRA. Finally, suppressing steroid genesis in the zona fasciculata with exogenous glucocorticoids alleviates the hypertension.

Liddle's syndrome

Grant Liddle described patients with autosomal dominant monogenic hypertension who also tended to have metabolic alkalosis with hypokalemia. His patients had low renin and low aldosterone values, and did not respond to spironolactone, while thiazides and triamterene reduced the blood pressure (Table I). This observation suggested that they probably did not have a form of mineralocorticoid excess. Liddle speculated that they would show a distal tubular defect of enhanced sodium and chloride reabsorption. A renal transplant performed on a patient with Liddle's syndrome who developed renal failure cured the disease, providing strong evidence that the problem resided within the kidneys rather than in a regulatory system[13]. Shimkets et al.[14] subsequently localized the responsible gene of a family with Liddle's syndrome to chromosome 16p, and were able to show that the gene encodes for the β-subunit of the epithelial sodium channel (ENaC). The channel is amiloride-and triamterene-sensitive, explaining the efficacy of these drugs in the syndrome. The channel remains inappropriately permeable even in the face of high salt intake, thereby explaining the salt-sensitive hypertension. Subsequently, a mutation in the γ-subunit of ENaC has been found, which can also result in Liddle's syndrome[15]. The molecular mechanisms of Liddle's syndrome involve missense mutations or deletions in the cytoplasmic tails of β- or γ-subunits of ENaC. As a consequence, the channels are not internalized (clathrin-coated pits pathway) or degraded (ubiquitination by WW domain containing proteins), and instead remain activated on the cell surface[16]. Figure 2 shows a schematic illustration of ENaC removal from the cell surface.

Apparent mineralocorticoid-excess (AME)

Apparent mineralocorticoid-excess resembles the syndrome observed in persons ingesting large amounts of licorice. Licorice gluttony and treatment with carbenoxolone both cause a volume expansion, low renin, low aldosterone and a salt-sensitive form of hypertension, which may also feature metabolic alkalosis and hypokalemia. Interestingly, the hypertension responds to both thiazide and spironolactone, but no abnormal steroid products are present in the urine. Both licorice and carbenoxolone contain glycyrrhetinic acid, which was found to inhibit the enzyme 11-β-hydroxysteroid dehydrogenase (11-β-HSD). 11-β-hydroxysteroid dehydrogenase is responsible for converting cortisol to cortisone (Fig. 3). In the distal renal tubule, this step is crucial for protecting the mineralocorticoid receptor, which has the same affinity for cortisol as it does for aldosterone. This step protects us all from developing AME. Inhibition of 11-β-HSD results in AME. Interestingly, AME may also occur as a rare, autosomal recessive form of hypertension. Needless to say, the 11-β-HSD gene, which has a renal-specific isoform, was a good candidate gene for this condition.

The clinical clues helful in resolving this condition were: volume dependent salt-sensitive hypertension, tendency to hypokalemia and metabolic alkalosis, low renin and low aldosterone values, responsiveness to both thiazides and spironolactone despite absence of aldosterone or any abnormal mineralocorticoid products, and resemblance to licorice gluttony (Table I). Mune et al.[17] solved the mystery. In eight of nine families, mutations in the renal-specific isoform gene for 11-β-HSD were found,

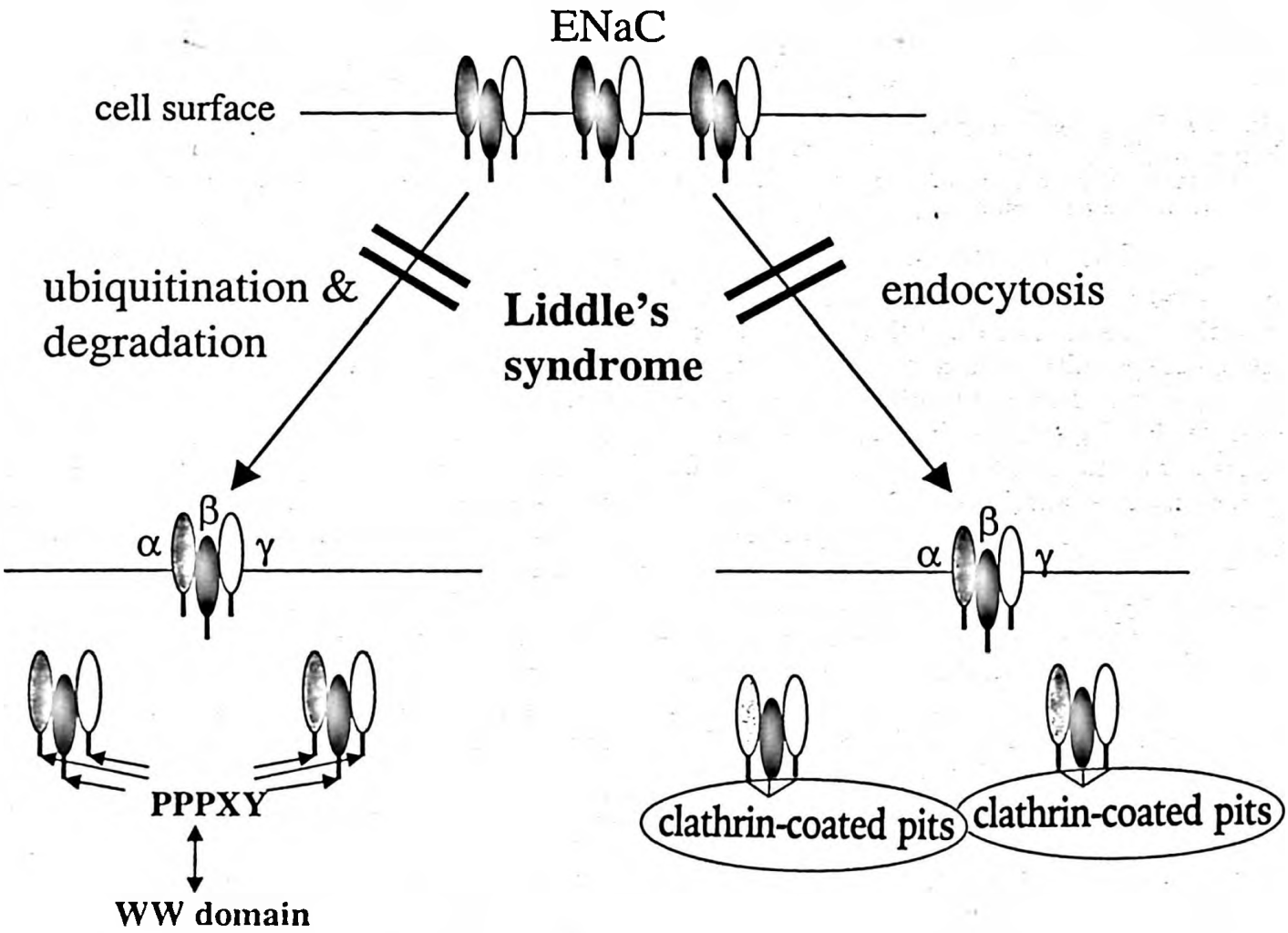

Fig. 2. Two pathways are shown for the removal of the epithelial sodium channel ENaC from the cell surface. One pathway is endocytosis by clathrin-coated pits. The other one is ubiquitination and degradation by WW-domain containing proteins specifically interacting with an amino acid sequence at the C-termini of the α-, β- and γ-subunits of ENaC. This amino acid sequence is called PY motif (PPPXY). In Liddle's syndrome missense mutations in the PY motif or deletions of the C-termini of the β- or γ-subunits cause Liddle's syndrome, inhibiting both pathways.

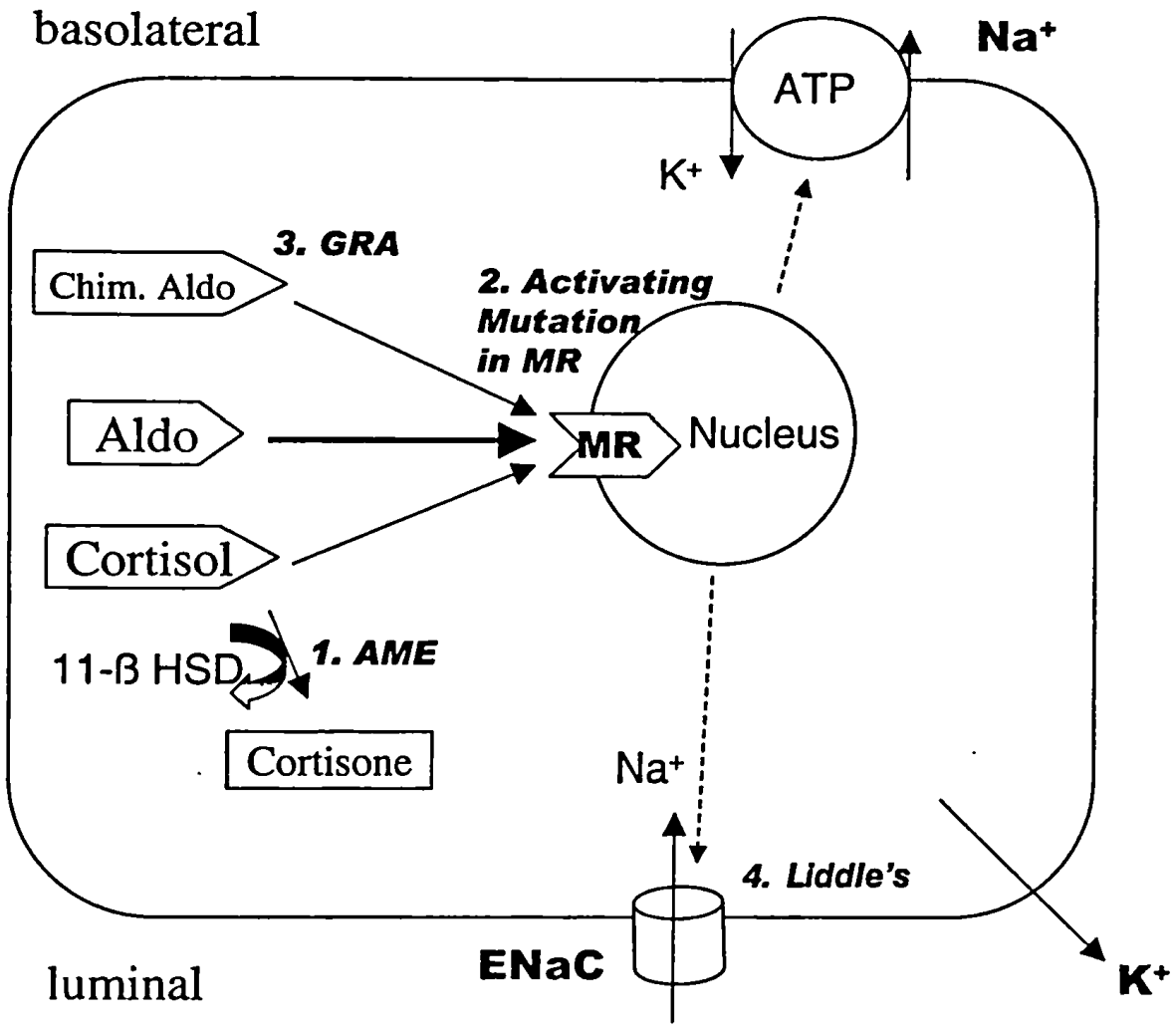

Fig. 3. A schematic illustration of a cortical collecting duct cell is shown. The mineralocorticoid receptor (MR) has the same affinity for cortisol as for aldosterone (aldo). The enzyme 11-β-hydroxysteroid dehydrogenase (11-β-HSD) "protects" the MR by metabolizing cortisol to cortisone, which has no affinity. A mutated or an inhibited enzyme results in an intracellular concentration of cortisol and an increased activation of the MR (1). Molecular mechanisms of the other syndromes are also shown. A mutated MR can result in an altered configuration and activation by steroids lacking a 21-hydroxyl group (2). A chimeric gene product (chim. aldo) in GRA causes an Ang II-independent activation of the MR (3). The increased MR activity causes enhanced Na^+ reabsorption (ENaC, Na-K-ATPase) and K^+ excretion. An increased presence and activity of ENaC at the cell surface in Liddle's syndrome has the same effect (4). GRA: glucocorticoid-remediable aldosteronism; AME: apparent mineralocorticoid-excess.

which indeed rendered the product incapable of converting cortisol to cortisone. Thus, the mineralocorticoid receptor is unprotected from cortisol in these patients and cortisol functions to occupy the mineralocorticoid receptor.

Activating mutations in the mineralocorticoid receptor (hypertension in pregnancy)

Geller et al.[18] recently presented a new Mendelian form of hypertension caused by an activating mutation in the mineralocorticoid receptor. The investigators screened for mutations in the mineralocorticoid receptor in seven unrelated patients referred for possible monogenic hypertension with the single-strand conformation polymorphism (SSCP) technique. One patient had a heterozygous mutation at codon 810 in the mineralocorticoid receptor gene, resulting in a leucine for serine substitution. This residue lies in the hormone-binding domain. The index case had severe hypertension, as did four relatives. Four other relatives had no hypertension. Affected persons all exhibited the leucine for serine substitutions, had low plasma renin activities, and low aldosterone concentrations. Since the phenotype resembles Liddle's syndrome (Table I), the investigators ruled out the presence of ENaC mutations. The authors speculate that the mineralocorticoid receptor gene mutation is an activating mutation in the receptor.

Interestingly, affected women exhibit a worsening of hypertension during pregnancy, suggesting that progesterone occupancy of the receptor results in activation rather than inhibition of aldosterone-like effects (Fig. 4). Similarly, spironolactone makes the blood pressure elevation worse, rather than better.

Geller et al.[18] were successful in elucidating the mechanism of the mutation. Their work is a good example of a successful cooperation between molecular genetics and structural proteomics. The MR-S810L mutation allows mineralocorticoid receptor activation by steroids lacking 21-hydroxyl groups. The L810 residue in helix 5 of the ligand-binding domain makes a new van der Waals interaction with alanine (A) at position 773 in helix 3. This interaction eliminates the requirement for the 21-hydroxyl group of aldosterone to interact with asparagine (N) at position 770 in helix 3. The modification explains why compounds that are normally antagonists now are agonists for the receptor.

Pseudohypoaldosteronism type II (PHA II)

PHA II features familial hypertension with hyperkalemia, normal glomerular filtration rate, suppressed plasma renin activity, normal or elevated aldosterone levels and metabolic acidosis[19]. Thiazide diuretics are highly effective in this syndrome, commensurate with salt sensitivity (Table I). The hypertension is chloride-dependent because exchange of sodium bicarbonate or sodium citrate infusion for sodium chloride improves blood pressure[20]. PHA II is a heterogeneous disease. Three gene loci were mapped to the chromosomes 1q, 12p and 17[21,22]. Two genes in which alterations cause PHA II have been recently identified. WNK1 (#12p) an WNK4 (#17q) belong to a novel serine-threonine kinase family in which lysine (K) in the catalytic domain is substituted by cysteine (with no lysine = WNK)[23].

Wilson et al.[10] identified large intronic deletions in intron 1 of WNK1 in two families (Fig. 5A).

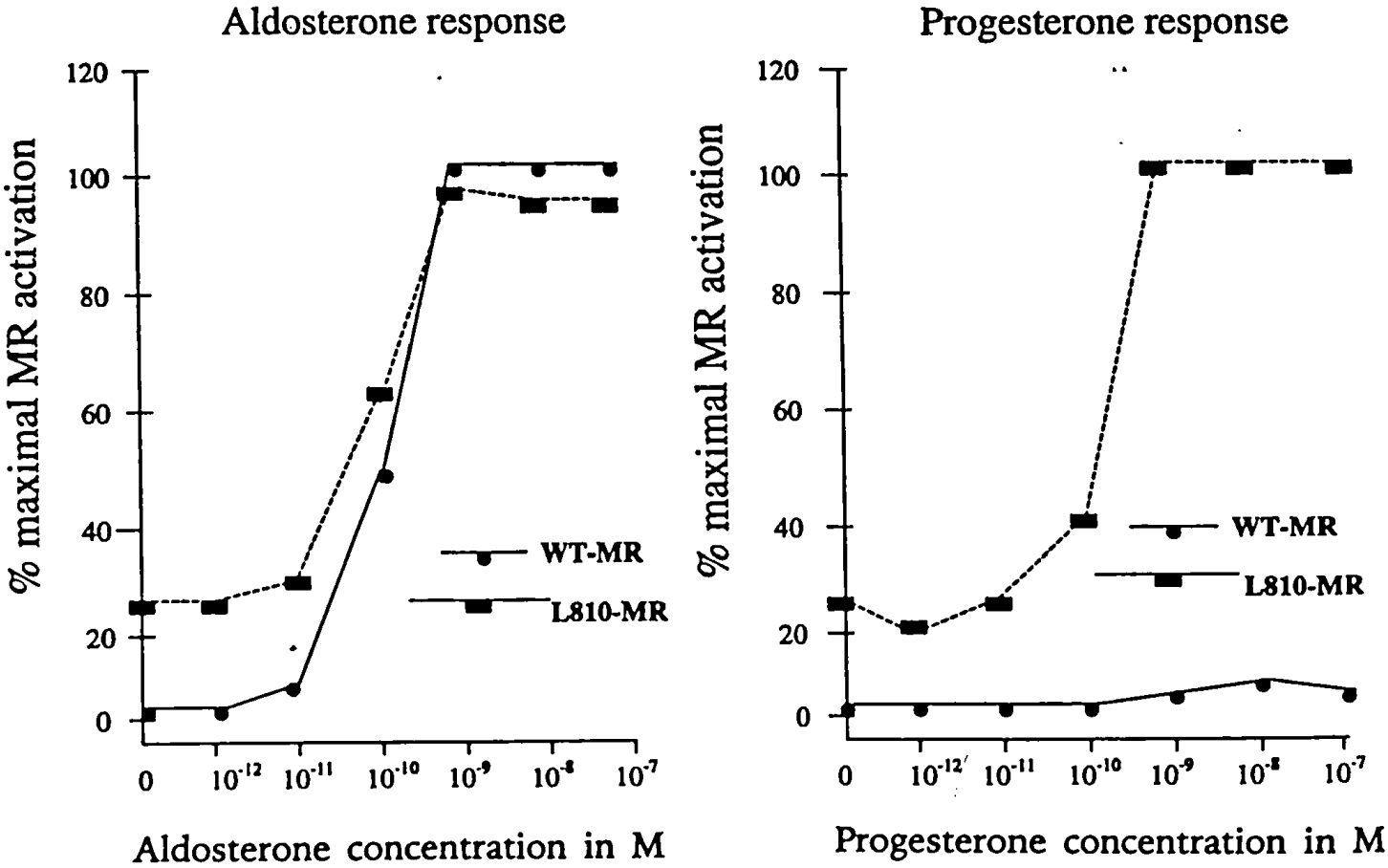

Fig. 4. Dose-response curves of the mutant MR and ML810S versus wildtype (WT) MR are shown. Activation of the MR was measured by induction of luciferase. The mutant MR shows a constitutive activation without stimulation. Otherwise, the response to increasing concentrations of aldosterone is similar to the WT MR. The WT MR shows no activation with progesterone lacking the 21-hydroxy group. The mutant MR ML810S is activated by progesterone with no difference to aldosterone response. MR: mineralocorticoid receptor.

Quantitative RT-PCR from blood leukocytes showed some evidence for gain-of-function mechanism. Patients showed a five-fold increased expression compared to intrafamilial controls (Fig. 5B). A 10 kilobase transcript is highly expressed in the kidney. Immunohistochemistry reveals that WNK1 localizes to the distal convoluted tubule (DCT) and cortical collecting duct (CCD) in the distal nephron of the kidney, and is expressed throughout the cytoplasm.

Missense mutations in WNK4 were identified in four families. The charge-changing mutations cluster in a span of four amino acids which are highly conserved among the WNK family. WNK4 is smaller than WNK1 (16 versus 156 kilobases) and shares 76% identity with WNK1 in the kinase domain and first coil-domain. WNK4 is exclusively expressed in the kidney, in intercellular junctions in the DCT and CCD, and is part of the tight junction complex.

The mechanism of these alterations in the kinases causing PHA II is unclear. The authors speculate that the action of the altered kinases increases paracellular chloride conductance in the CCD, thereby increase salt reabsorption and vascular volume, while concomitantly dissipating the electrical gradient and diminishing potassium and proton secretion[10].

Bilginturan's syndrome

Bilginturan et al.[24] described in 1974 a family with autosomal dominant hypertension associated with type E brachydactyly (Fig. 6). Affected family members had a dramatic increase in blood pressure with age and died before the age of 50 years by multiple strokes. The Turkish kindred were re-examined in 1994[25]. The hypertension can be easily distinguished from other monogenic hypertensive syndromes described thus far. The patients are not salt-sensitive and have normal renin, angiotensin, aldosterone and catecholamine responses. By measuring plasma renin activity (PRA) and plasma aldosterone in supine and upright positions, other conditions

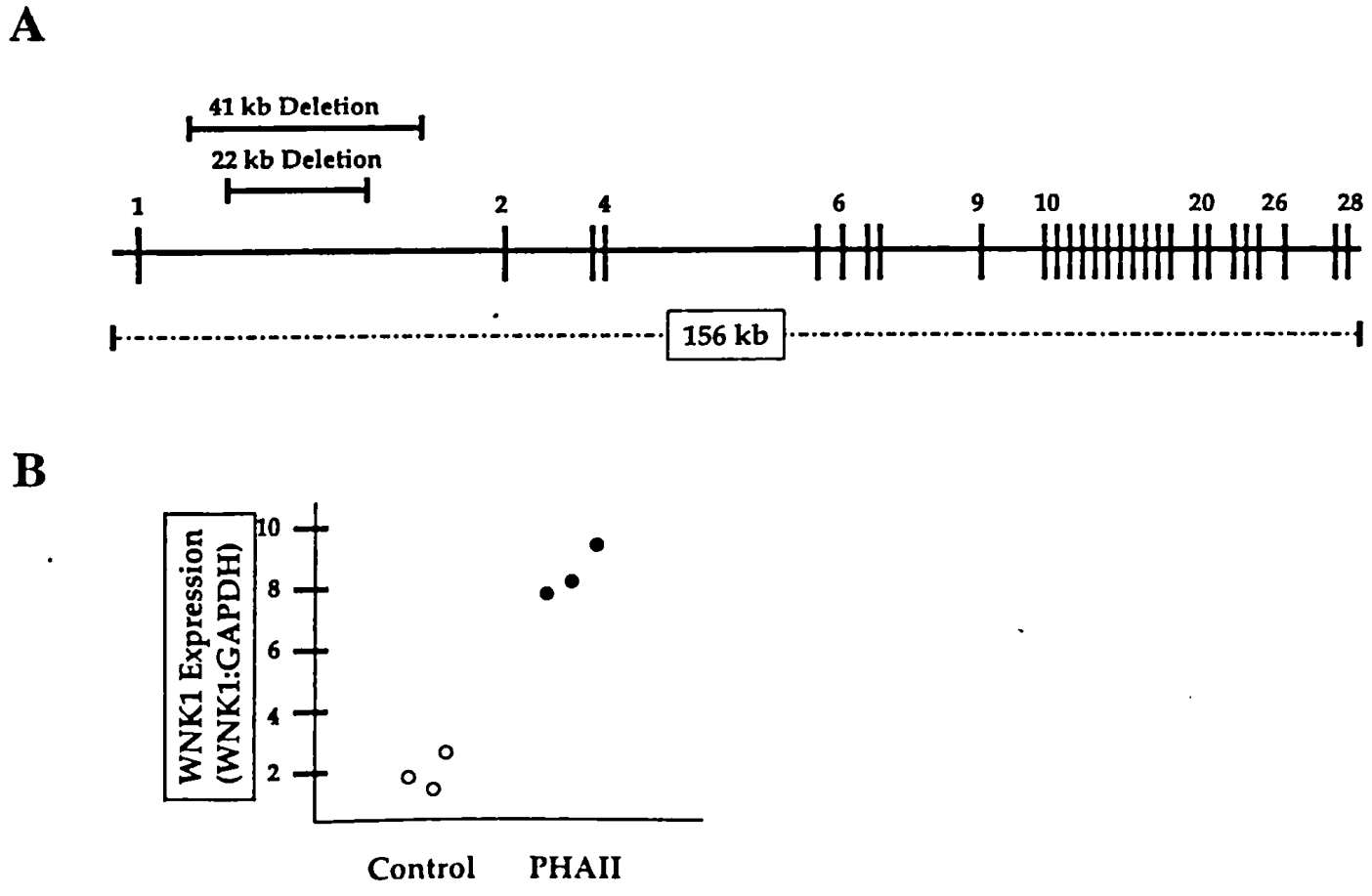

Fig. 5. (A) Genomic structure of WNK1. The intronic deletions identified in two families are located in intron 1 and are 41 or 22 kilobase respectively in size (B) RT-PCR from blood leukocytes in the 22kb deletion family shows five-fold increase in expression compared to two not affected family members and one control. PHA II: pseudohypoaldosteronism.

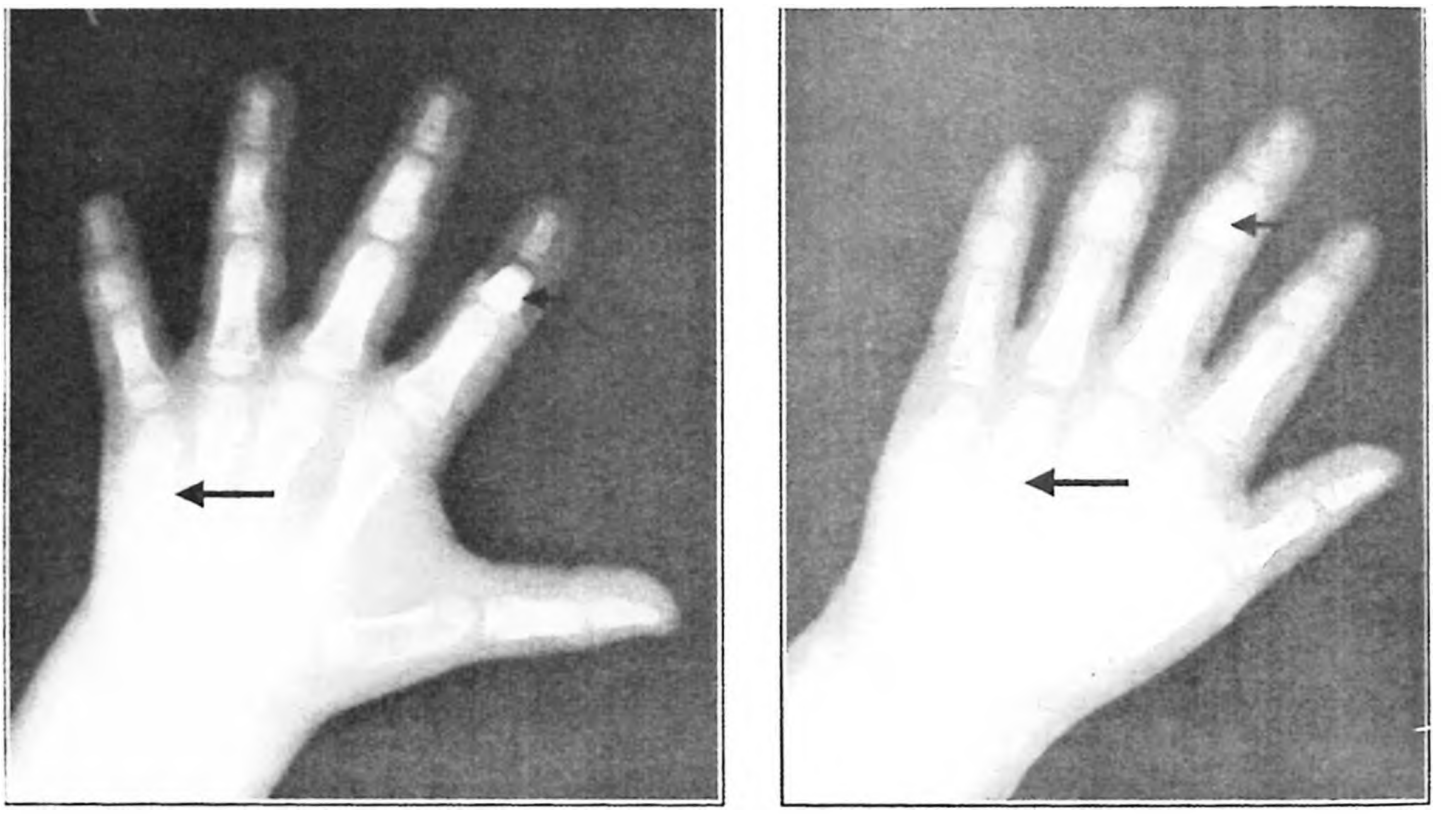

Fig. 6. Hand X-rays of a six-year-old Turkish boy and a 5 1/2-year-old Japanese boy with brachydactyly type E. The large arrows indicate the shortened metacarpal bones, which define this form of brachydactyly. The phalanges are also shortened. Additionally, cone-shaped epiphyses are present (small arrows).

can be excluded[26]. In glucocorticoid-remediable aldosteronism, PRA should be low while aldosterone concentrations are on the high normal side. In Liddle'syndrome, apparent mineralocorticoid excess, PHA II and mutations in the mineralocorticoid receptor, PRA and aldosterone levels should both be low. However, in autosomal dominant hypertension with brachydactyly, PRA and aldosterone values are normal. Table I shows the phenotypical distinction of this syndrome.

The phenotyping efforts showed that patients do not respond to any particular form of medication[27]. Beta-blocker, calcium antagonists, alpha-blocker and ACE inhibitor all improve blood pressure without significant difference. A multi-drug therapy is required for the treatment of patients.

The mechanism of the hypertension is unknown. However, an additional phenotype was discovered, which may provide a clue. Intra-operative observations[28,29], anatomical studies[30], and magnetic resonance imaging (MRI)[31] have demonstrated a posterior fossa neurovascular anomaly in patients with essential hypertension. This anomaly is believed to represent neurovascular compression (NVC) of the left ventrolateral medulla oblongata.

To test the hypothesis of whether NVC is present in patients with Bilginturan's syndrome, MRI was performed in 27 family members. All 15 affected family members had evidence for NVC. All had left sided PICA (posterior inferior cerebellar artery) or vertebral artery loops, while six had bilateral NVC. None of the nonaffected family members had NVC. These MRI data suggest NVC at the left ventrolateral medulla oblongata as an intermediate phenotype of this syndrome[32].

Based on these results, detailed autonomic testing was performed[33]. In young patients with monogenic hypertension, the hypotheses of whether or not the hypertension was mediated through sympathetic activation and of whether changes in increased sympathetic nerve traffic, vascular sensitivity, or impaired baroreflex buffering would contribute to the phenotype were tested. The average blood pressure during complete ganglionic blockade with trimethaphan was 139/83 mmHg and 90/50 mmHg in patients and controls, respectively.

However, sympathetic stimuli like cold pressor, hand-grup testing, and upright posture all increased blood pressure excessively. In contrast, muscle sympathetic nerve activity (tested by microneurography) was not increased at rest or during cold pressor test. The dose of the alpha-agonist phenylephrine that increased systolic blood pressure 12.5 mmHg was 8 μg in patients and 135 μg in control subjects before ganglionic blockade and 5 μg in patients and 13 μg in control subjects during ganglionic blockade (Fig. 7). Patients reacted with 16.9-fold increased sensitivity to phenylephrine at baseline compared to controls. During ganglionic blockade (baroreceptor reflex blocked) this difference was diminished to 2.6-fold.

These results suggest that in patients with Bilginturan's syndrome, basal blood pressure is increased independent of autonomic activity. However, sympathetic stimuli cause an excessive increase in blood pressure. Increased sympathetic nerve traffic or increased vascular sensitivity cannot explain this excessive response. A possible explanation is that the ability of the baroreflex to buffer changes in vascular tone is severely impaired. The hypertension could be related to abnormal baroreceptor reflex function.

A genome wide screen was performed to identify the responsible gene(s). The gene for Bilginturan's syndrome was mapped to the short arm of chromosome 12[34]. Additional families with the same syndrome and a chromosome 12p deletion syndrome in a Japanese child narrowed down the critical area[35,36]. The chromosomal region of interest is completely cloned and candidate genes are investigated.

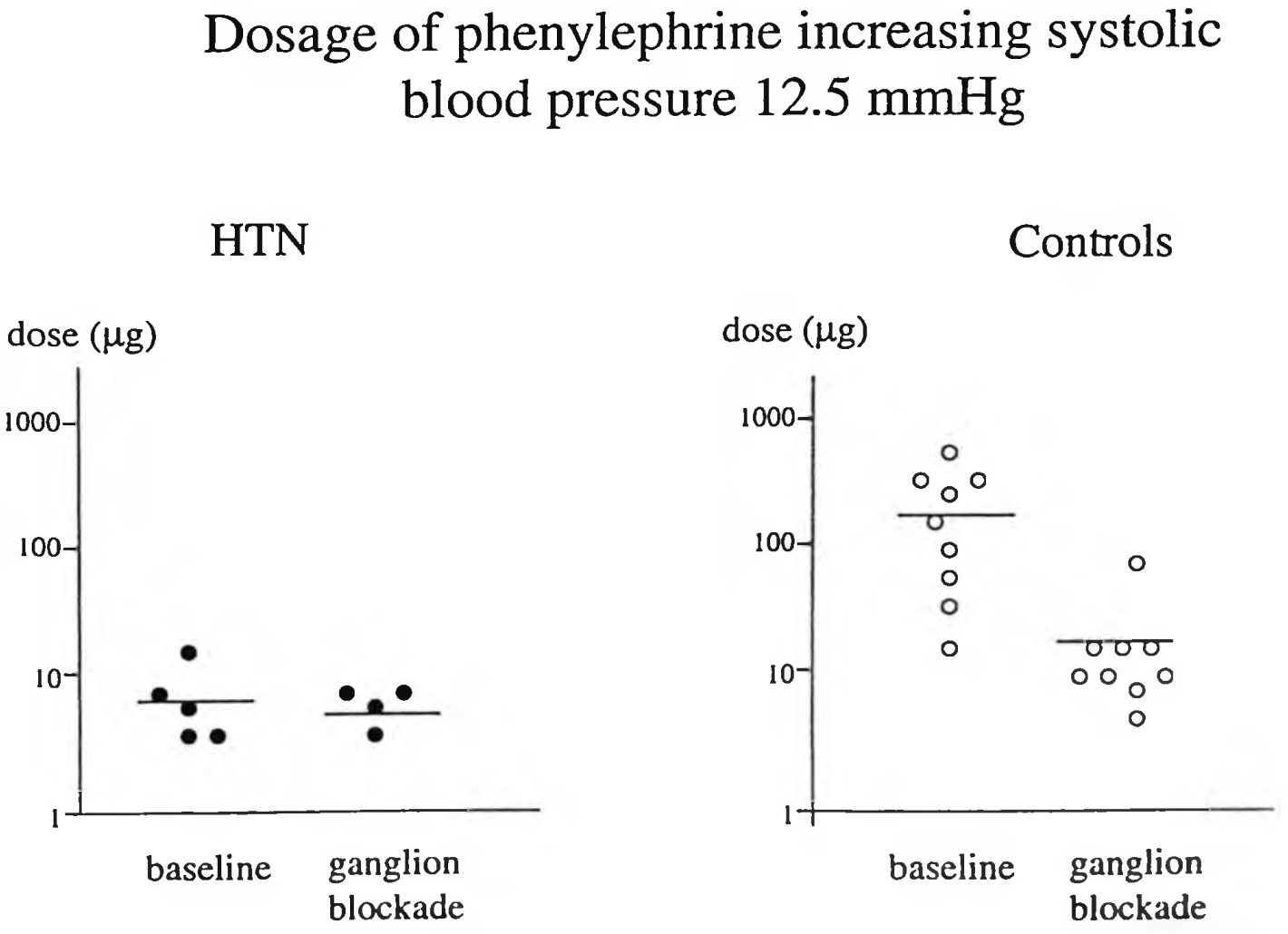

Fig. 7. Doses of phenylephrine, which increase blood pressure 12.5 mmHg before and during ganglion blockade with trimethaphan. The sensitivity to the alpha-agonist phenylephrine at baseline significantly higher (16.9-fold) in patients (HTN, black symbols) compared to controls. After interruption of the baroreflex during ganglion blockade this difference is diminished (2.6-fold).

Summary

The focus of this review was on Mendelian forms of hypertension. However, much is to be learned from Mendelian causes of hypotension. Lifton and colleagues have elucidated mutations in the ENaC alpha-subunit causing pseudohypoaldosteronism type I, three mutations involving transporters in the loop of Henle causing Bartter's syndrome, and mutations in the sodium chloride cotransporter causing Gitelman's syndrome. These conditions also speak to the issue of hypertension because they address problems in sodium handling, volume homeostasis and blood pressure regulation. Similarly, a mutation in the norepinephrine transporter has been described causing orthostatic hypotension, tachycardia, and syncope[37]. The lessons learned from these Mendelian syndromes of human blood pressure variation have been profound. They may lead us to understand the primary physiology of blood pressure regulation and disease mechanisms involved in hypertension of the general population. This progress may allow us to diagnose hypertension earlier and perhaps treat it better than we do today.

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