Renal Tubular Disorders

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Inherited renal tubular disorders involve a variety of defects in renal tubular transport processes and their regulation. These disorders generally are transmitted as single gene defects (Mendelian traits), and they provide a unique resource to dissect the complex molecular mechanisms involved in tubular solute transport. An integrated approach using the tools of molecular genetics, molecular biology, and physiology has been applied in the 1990s to identify defects in transporters, channels, receptors, and enzymes involved in epithelial transport. These investigations have added substantial insight into the molecular mechanisms involved in renal solute transport and the molecular pathogenesis of inherited renal tubular disorders. This chapter focuses on the inherited renal tubular disorders, highlights their molecular defects, and discusses models to explain their underlying pathogenesis.

CHAPTER

12

Overview of Renal Tubular Disorders

OVERVIEW OF RENAL TUBULAR DISORDERS INHERITED AS MENDELIAN TRAITS

Inherited disorder	Transmission mode	Defective protein
Renal glucosuria	?AR, AD	Sodium-glucose transporter 2
Glucose-galactose malabsorption syndrome	AR	Sodium-glucose transporter 1
Acidic aminoaciduria	AR	Sodium-potassium–dependent glutamate transporter
Cystinuria	AR	Apical cystine-dibasic amino acid transporter
Lysinuric protein intolerance	AR	Basolateral dibasic amino acid transporter
Hartnup disease	?	?
Blue diaper syndrome	AR	Kidney-specific tryptophan transporter
Neutral aminoacidurias:	AR	?
Methioninuria		
Iminoglycinuria		
Glycinuria		
Hereditary hypophosphatemic rickets with hypercalciuria	AR	? Sodium-phosphate cotransporter
X-linked hypophosphatemic rickets	X-linked dominant	Phosphate-regulating with endopeptidase features on the X chromosome
Inherited Fanconi's syndrome isolated disorder	AR and AD	?
Inherited Fanconi's syndrome associated with inborn errors of metabolism	AR	–
Carbonic anhydrase II deficiency	AR	Carbonic anhydrase type II
Distal renal tubular acidosis	AR	?
	AD	Basolateral anion exchanger (AE1)
Bartter-like syndromes:		
Antenatal Bartter variant	AR	NKCC2, ROMK, ClC-K2
Classic Bartter variant	AR	ClC-K2b
Gitelman's syndrome	AR	NCCT
Pseudohypoparathyroidism:		
Type Ia	AD	Guanine nucleotide–binding protein
Type Ib	?	
Low-renin hypertension:		
Glucocorticoid-remedial aldosteronism	AD	Chimeric gene (11β-hydroxylase and aldosterone synthase)
Liddle's syndrome	AD	β and γ subunits of the sodium channel
Apparent mineralocorticoid excess	AR	11-β-hydroxysteroid dehydrogenase
Pseudohypoaldosteronism:		
Type 1	AR and AD	α and β subunits of the sodium channel
Type 2 (Gordon's syndrome)	AD	?
Nephrogenic diabetes insipidus:		
X-linked	X-linked recessive	Arginine vasopressin 2 receptor
Autosomal	AR and AD	Aquaporin 2 water channel
Urolithiases:		
Cystinuria	AR	Apical cystine–dibasic amino acid transporter
Dent's disease	X-linked	Renal chloride channel (ClC-5)
X-linked recessive nephrolithiasis	X-linked	Renal chloride channel (ClC-5)
X-linked recessive hypophosphatemic rickets	X-linked	Renal chloride channel (ClC-5)
Hereditary renal hypouricemia	AR	? Urate transporter

AD—autosomal dominant; AR—autosomal recessive; ClC-K2—renal chloride channel; NCCT—thiazide-sensitive cotransporter; NKCC2—bumetanide-sensitive cotransporter; ROMK—inwardly rectified.

FIGURE 12-1

Inherited renal tubular disorders generally are transmitted as autosomal dominant, autosomal recessive, X-linked dominant, or X-linked recessive traits. For many of these disorders, the identification of the disease-susceptibility gene and its associated defective protein product has begun to provide insight into the molecular pathogenesis of the disorder.

Renal Glucosuria

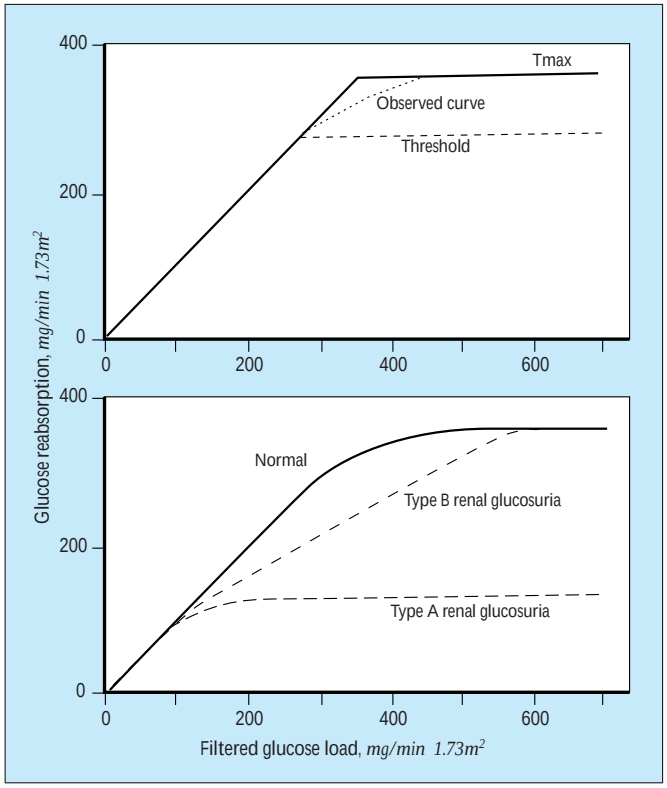

FIGURE 12-2

Physiology and pathophysiology of glucose titration curves. Under normal physiologic conditions, filtered glucose is almost entirely reabsorbed in the proximal tubule by way of two distinct sodium-coupled glucose transport systems. In the S1 and S2 segments, bulk reabsorption of glucose load occurs by way of a kidney-specific high-capacity transporter, the sodium-glucose transporter-2 (SGLT2) [1]. The residual glucose is removed from the filtrate in the S3 segment by way of the high-affinity sodium-glucose transporter-1 (SGLT1) [2]. This transporter also is present in the small intestine.

As are all membrane transport systems, glucose transporters are saturable. The top panel shows that increasing the glucose concentration in the tubular fluid accelerates the transport rate of the glucose transporters until a maximal rate is achieved. The term *threshold* applies to the point that glucose first appears in the urine. The maximal overall rate of glucose transport by the proximal tubule SGLT1 and SGLT2 is termed the *Tmax*. Glucose is detected in urine either when the filtered load is increased (as in diabetes mellitus) or, as shown in the bottom panel, when a defect occurs in tubular reabsorption (as in renal glucosuria). Kinetic studies have demonstrated two types of glucosuria caused by either reduced maximal transport velocity (type A) or reduced affinity of the transporter for glucose (type B) [3]. Mutations in the gene encoding SGLT1 cause glucose-galactose malabsorption syndrome, a severe autosomal recessive intestinal disorder associated with mild renal glucosuria (type B). Defects in SGLT2 result in a comparatively more severe renal glucosuria (type A). However, this disorder is clinically benign. Among members of the basolateral glucose transporter (GLUT) family, only GLUT1 and GLUT2 are relevant to renal physiology [4]. Clinical disorders associated with mutations in the genes encoding these transporters have yet to be described. (*From* Morris and Ives [5]; with permission.)

Aminoacidurias

CLASSIFICATION OF INHERITED AMINOACIDURIAS

Major categories	Forms	OMIM number*	Amino acids involved
Acidic amino acids	Acidic aminoaciduria	222730	Glutamate, aspartate
Basic amino acids and cystine	Cystinuria	220100, 600918, 104614	Cystine, lysine, arginine, ornithine
	Lysinuric protein intolerance	222690, 222700, 601872	Lysine, arginine, ornithine
	Isolated cystinuria	238200	Cystine
	Lysinuria	–	Lysine
Neutral amino acids	Hartnup disease	234500, 260650	Alanine, asparagine, glutamine, histidine, isoleucine, leucine, phenylalanine, serine, threonine, tryptophan, tyrosine, valine
	Blue diaper syndrome	211000	Tryptophan
	Iminoglycinuria	242600	Glycine, proline, hydroxyproline
	Glycinuria	138500	Glycine
	Methioninuria	–	Methionine

*OMIM—Online Mendelian Inheritance in Man (accessible at http://www3.ncbi.nlm.nih.gov/omin/).

FIGURE 12-3

Over 95% of the filtered amino acid load is normally reabsorbed in the proximal tubule. The term *aminoaciduria* is applied when more than 5% of the filtered load is detected in the urine. Aminoaciduria can occur in the context of metabolic defects, which elevate plasma amino acid concentrations and thus increase the glomerular filtered load. Aminoaciduria can be a feature of generalized proximal tubular dysfunction caused by toxic nephropathies or Fanconi's syndrome. In addition, aminoaciduria can arise from genetic defects in one of the several amino acid transport systems in the proximal tubule. Three distinct groups of inherited aminoacidurias are distinguished based on the net charge of the target amino acids at neutral pH: acidic (negative charge), basic (positive charge), and neutral (no charge) [5].

Acidic aminoaciduria involves the transport of glutamate and aspartate and results from a defect in the high-affinity sodium-potassium–dependent glutamate transporter [6]. It is a clinically benign disorder.

Four syndromes caused by defects in the transport of basic amino acids or cystine have been described: cystinuria, lysinuric protein intolerance, isolated cystinuria, and isolated lysinuria. Cystine actually is a neutral amino acid that shares a common carrier with the dibasic amino acids lysine, arginine, and ornithine. The transport of all four amino acids is disrupted in cystinuria. The rarer disorder, lysinuric protein intolerance, results from defects in the basolateral transport of dibasic amino acids but not cystine. Increased intracelluar concentrations of lysine, arginine, and ornithine are associated with disturbances in the urea cycle and consequent hyperammonemia [7].

Disorders involving the transport of neutral amino acids include Hartnup disease, blue diaper syndrome, methioninuria, iminoglycinuria, and glycinuria. Several neutral amino acid transporters have been cloned and characterized. Clinical data suggest that Hartnup disease involves a neutral amino acid transport system in both the kidney and intestine, whereas blue diaper syndrome involves a kidney-specific tryptophan transporter [5]. Methioninuria appears to involve a separate methionine transport system in the proximal tubule. Case reports describe seizures, mental retardation, and episodic hyperventilation in affected patients [8]. The pathophysiologic basis for this phenotype is unclear. Iminoglycinuria and glycinuria are clinically benign disorders.

ROSENBERG CLASSIFICATION OF CYSTINURIAS

Category	Phenotype	Intestinal transport defect
I		
Heterozygote	No abnormality	
Homozygote	Cystinuria, basic aminoaciduria, cystine stones	Cystinine, basic amino acids
II		
Heterozygote	Excess excretion of cystine and basic amino acids	
Homozygote	Cystinuria, basic aminoaciduria, cystine stones	Basic amino acids only
III		
Heterozygote	Excess excretion of cystine and basic amino acids	
Homozygote	Cystinuria, basic aminoaciduria, cystine stones	None

From Morris and Ives [5]; with permission.

FIGURE 12-4

In this autosomal recessive disorder the apical transport of cystine and the dibasic amino acids is defective. Differences in the urinary excretion of cystine in obligate heterozygotes and intestinal amino acid transport studies in homozygotes have provided the basis for defining three distinct phenotypes of cystinuria [9]. Genetic studies have identified mutations in the gene (SCL3A1) encoding a high-affinity transporter for cystine and the dibasic amino acids in patients with type I cystinuria [10,11]. In patients with type III cystinuria, SCL3A1 was excluded as the disease-causing gene [12]. A second cystinuria-susceptibility gene recently has been mapped to chromosome 19 [13].

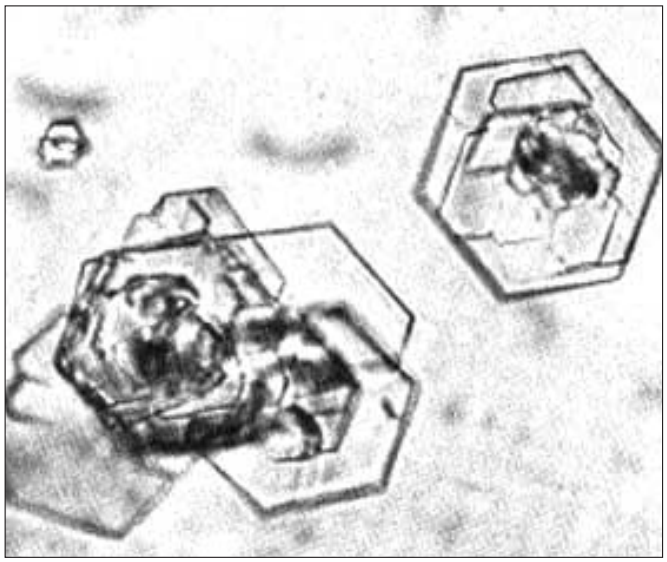

FIGURE 12-5

Urinary cystine crystals. Excessive urinary excretion of cystine (250 to 1000 mg/d of cystine/g of creatinine) coupled with its poor solubility in urine causes cystine precipitation with the formation of characteristic urinary crystals and urinary tract calculi. Stone formation often causes urinary tract obstruction and the associated problems of renal colic, infection, and even renal failure. The treatment objective is to reduce urinary cystine concentration or to increase its solubility. High fluid intake (to keep the urinary cystine concentration below the solubility threshold of 250 mg/L) and urinary alkalization are the mainstays of therapy. For those patients refractory to conservative management, treatment with sulfhydryl-containing drugs, such as D-penicillamine, mercaptopropionylglycine, and even captopril can be efficacious [14,15].

Renal Hypophosphatemic Rickets

INHERITED FORMS OF HYPOPHOSPHATEMIC RICKETS

Disorder	Vitamin D	Parathyroid hormone	Serum calcium	Urinary calcium	Treatment
X-linked hypophosphatemic rickets	Low, low normal	Normal, high normal	Low, normal	Elevated	Calciferol, phosphate supplementation
Hereditary hypophosphatemic rickets with hypercalciuria	Elevated	Low, low normal	Normal	Elevated	Phosphate supplementation

Vitamin D—1,25-dihydroxy-vitamin D_3

FIGURE 12-6

Several inherited disorders have been described that result in isolated renal phosphate wasting. These disorders include X-linked hypophosphatemic rickets (HYP), hereditary hypophosphatemic rickets with hypercalciuria (HHRH), hypophosphatemic bone disease (HBD), autosomal dominant hypophosphatemic rickets (ADHR), autosomal recessive hypophosphatemic rickets (ARHR), and X-linked recessive hypophosphatemic rickets (XLRH). These inherited disorders share two common features: persistent hypophosphatemia caused by decreased renal tubular phosphate (Pi) reabsorption (expressed as decreased ratio of plasma concentration at which maximal phosphate reabsorption occurs [TmP] to glomerular filtration rate [GFR], [TmP/GFR], a normogram derivative of the fractional excretion of Pi); and associated metabolic bone disease, *eg,* rickets in children or osteomalacia in adults [5]. These disorders can be distinguished on the basis of the renal hormonal response to hypophosphatemia, the biochemical profile, and responsiveness to therapy. In addition, the rare disorder XLRH is associated with nephrolithiasis. The clinical features of the two most common disorders HYP and HHRH are contrasted here. Whereas both disorders have defects in renal Pi reabsorption, the renal hormonal response to hypophosphatemia is impaired in HYP but not in HHRH. Indeed, in children with HHRH, phosphate supplementation alone can improve growth rates, resolve the radiologic evidence of rickets, and correct all biochemical abnormalities except the reduced TmP GFR [5].

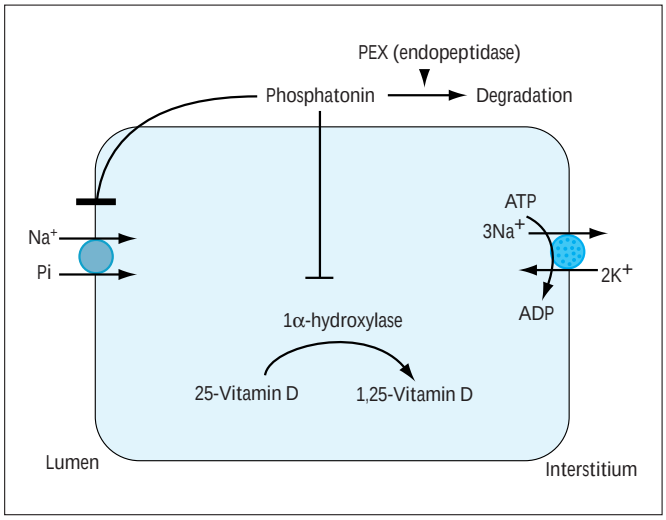

FIGURE 12-7

Proposed pathogenesis of X-linked hypophosphatemic rickets (HYP). HYP, the most common defect in renal phosphate (Pi) transport, is transmitted as an X-linked dominant trait. The disorder is characterized by growth impairment in children, metabolic bone disease, phosphaturia, and abnormal bioactivation of vitamin D [16]. Cell culture, parabiosis, and transplantation experiments have demonstrated that the defect in HYP is not intrinsic to the kidney but involves a circulating humoral factor other than parathyroid hormone [16,17].

Phosphate is transported across the luminal membrane of the proximal tubule by a sodium-phosphate cotransporter (NaPi). This transporter is regulated by multiple hormones. Among these is a putative phosphaturic factor that has been designated phosphatonin [18]. It is postulated that phosphatonin inhibits Pi reabsorption by way of the sodium-coupled phosphate cotransporter, and it depresses serum 1,25-dihydroxy-vitamin D_3 production by inhibiting 1-α-hydroxlase activity and stimulating 24-hydroxylase activity. Positional cloning studies in families with HYP have identified a gene, designated PEX (phosphate-regulating gene with homologies to endopeptidases on the X chromosome), that is mutated in patients with X-linked hypophosphatemia [19]. PEX, a neutral endopeptidase, presumably inactivates phosphatonin. Defective PEX activity would lead to decreased phosphatonin degradation, with excessive phosphaturia and deranged vitamin D metabolism. A similar scenario associated with increased phosphatonin production has been proposed as the basis for oncogenic hypophosphatemic osteomalacia, an acquired disorder manifested in patients with tumors of mesenchymal origin [17].
Na^+—sodium ion; K^+—potassium ion.

Fanconi's Syndrome

INHERITED FANCONI'S SYNDROME

Disorder	OMIM number*
Idiopathic	227700, 227800
Cystinosis	219800, 219900, 219750
Hepatorenal tyrosinemia (tyrosinemia type I)	276700
Hereditary fructose intolerance	229600
Galactosemia	230400
Glycogen storage disease type I	232200
Wilson's disease	277900
Oculocerebrorenal (Lowe's) syndrome	309000
Vitamin-D–dependent rickets	264700

*OMIM—Online Mendelian Inheritance in Man (accessible at http://www3.ncbi.nlm.nih.gov/omin/).

From Morris and Ives [5]; with permission.

FIGURE 12-8

Fanconi's syndrome is characterized by two components: generalized dysfunction of the proximal tubule, leading to impaired net reabsorption of bicarbonate, phosphate, urate, glucose, and amino acids; and vitamin D–resistant metabolic bone disease [20]. The clinical manifestations in patients with either the hereditary or acquired form of Fanconi's syndrome include polyuria, dehydration, hypokalemia, acidosis, and osteomalacia (in adults) or impaired growth and rickets (in children). Inherited Fanconi's syndrome occurs either as an idiopathic disorder or in association with various inborn errors of metabolism.

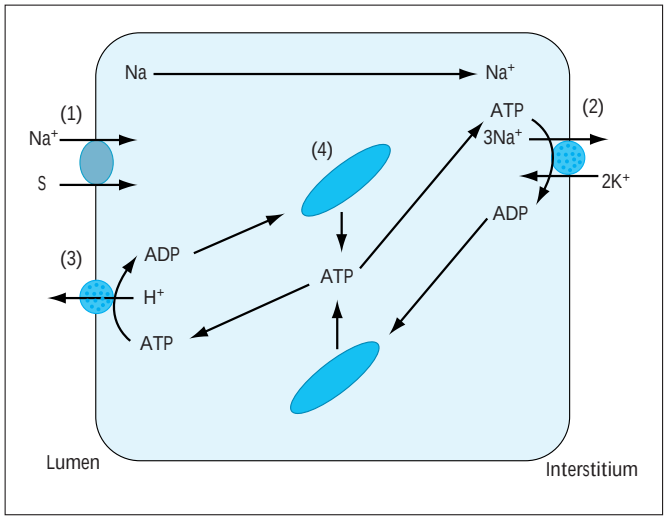

FIGURE 12-9

Proposed pathogenic model for Fanconi's syndrome. The underlying pathogenesis of Fanconi's syndrome has yet to be determined. It is likely, however, that the various Mendelian diseases associated with Fanconi's syndrome cause a global disruption in sodium-coupled transport systems rather than a disturbance in specific transporters. Bergeron and coworkers [20] have proposed a pathophysiologic model that involves the intracellular gradients of sodium, adenosine triphosphate (ATP), and adenosine diphosphate (ADP). A transepithelial sodium gradient is established in the proximal tubule cell by sodium (Na) entry through Na-solute cotransport systems (Na-S) (1) and Na exit through the sodium-potassium adenosine triphosphatase (Na-K ATPase) (2). This Na gradient drives the net uptake of cotransported solutes. A small decrease in the activity of the Na-K ATPase cotransporter may translate into a proportionally larger increment in the Na concentration close to the luminal membrane, thus decreasing the driving force that energizes all Na-solute cotransport systems. Concomitantly, reciprocal ATP and ADP gradients are established in the cell by the activity of membrane bound ATPases (Na-K ATPase (2) and hydrogen-ATPase (3)) and mitochondrial (4) ATP synthesis. A small reduction in mitochondrial rephosphorylation of ADP may result in a juxtamembranous accumulation of ADP and a reciprocal decrease in ATP, altering the ADP-ATP ratio and downregulating pump activities. Therefore, a relatively small mitochondrial defect may be amplified by the effects on the intracellular sodium gradients and ADP-ATP gradients and may lead to a global inhibition of Na-coupled transport. H^+—hydrogen ion.

Renal Tubular Acidoses

INHERITED RENAL TUBULAR ACIDOSES

Disorder	Transmission mode
Isolated proximal RTA	Autosomal recessive
Carbonic anhydrase II deficiency	Autosomal recessive
Isolated distal RTA	Autosomal dominant
Distal RTA with sensorineural deafness	Autosomal recessive

RTA—renal tubular acidosis.

FIGURE 12-10

Renal tubular acidosis (RTA) is characterized by hyperchloremic metabolic acidosis caused by abnormalities in renal acidification, *eg*, decreased tubular reabsorption of bicarbonate or reduced urinary excretion of ammonium (NH_4^+). RTA can result from a number of disease processes involving either inherited or acquired defects. In addition, RTA may develop from an isolated defect in tubular transport; may involve multiple tubular transport abnormalities, *eg*, Fanconi's syndrome; or may be associated with a systemic disease process. Isolated proximal RTA (type II) is rare, and most cases of proximal RTA occur in the context of Fanconi's syndrome. Inherited forms of classic distal RTA (type I) are transmitted as both autosomal dominant and autosomal recessive traits. Inherited disorders in which RTA is the major clinical manifestation are summarized.

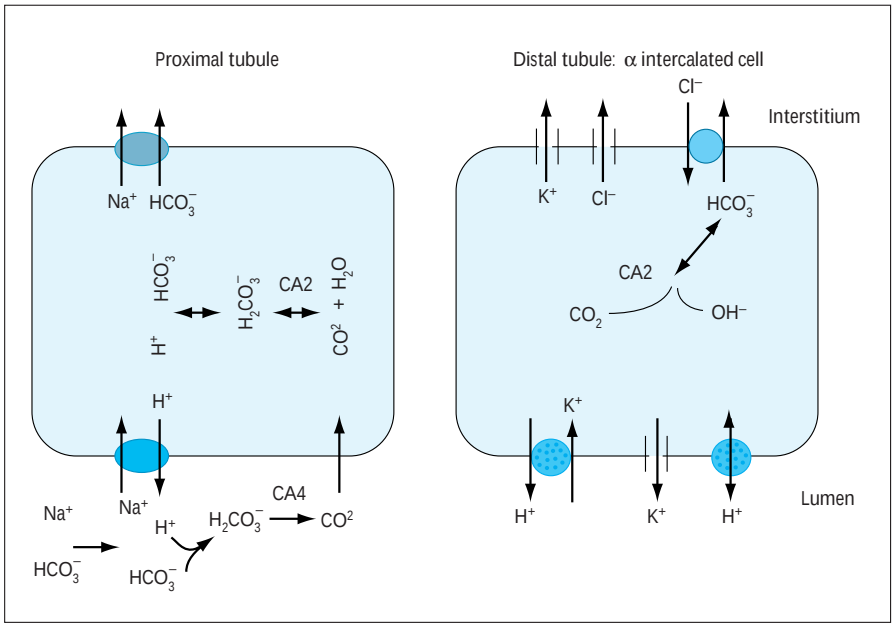

FIGURE 12-11

Carbonic anhydrase II deficiency. Carbonic anhydrase II deficiency is an autosomal recessive disorder characterized by renal tubular acidosis (RTA), with both proximal and distal components, osteopetrosis, and cerebral calcification. Carbonic anhydrase catalyzes the reversible hydration of carbon dioxide (CO_2), and thereby accelerates the conversion of carbon dioxide and water to hydrogen ions (H^+) and bicarbonate (HCO^-_3) [21]. A least two isoenzymes of carbonic anhydrase are expressed in the kidney and play critical roles in urinary acidification. In the proximal tubule, bicarbonate reabsorption is accomplished by the combined action of both luminal carbonic anhydrase type IV (CA4) and cytosolic carbonic anhydrase type II (CA2), the luminal sodium-hydrogen exchanger, and the basolateral sodium-bicarbonate exchanger. Impaired bicarbonate reabsorption in the proximal tubule is the underlying defect in type II or proximal RTA. In the distal nephron, carbonic anhydrase type II is expressed in the intercalated cells of the cortical collecting duct. There carbonic anhydrase type II plays a critical role in catalyzing the condensation of hydroxy ions, generated by the proton-translocating H^+-adenosine triphosphatase (H^+ ATPase), with carbon dioxide to form bicarbonate. In carbonic anhydrase type II deficiency, the increase in intracellular pH impairs the activity of the proton-translocating H-ATPase. Carbonic anhydrase inhibitors (*eg*, acetazolamide) act as weak diuretics by blocking bicarbonate reabsorption. Cl^-—chloride ion; H_2CO_3—carbonic acid; K^+—potassium ion; Na^+—sodium ion.

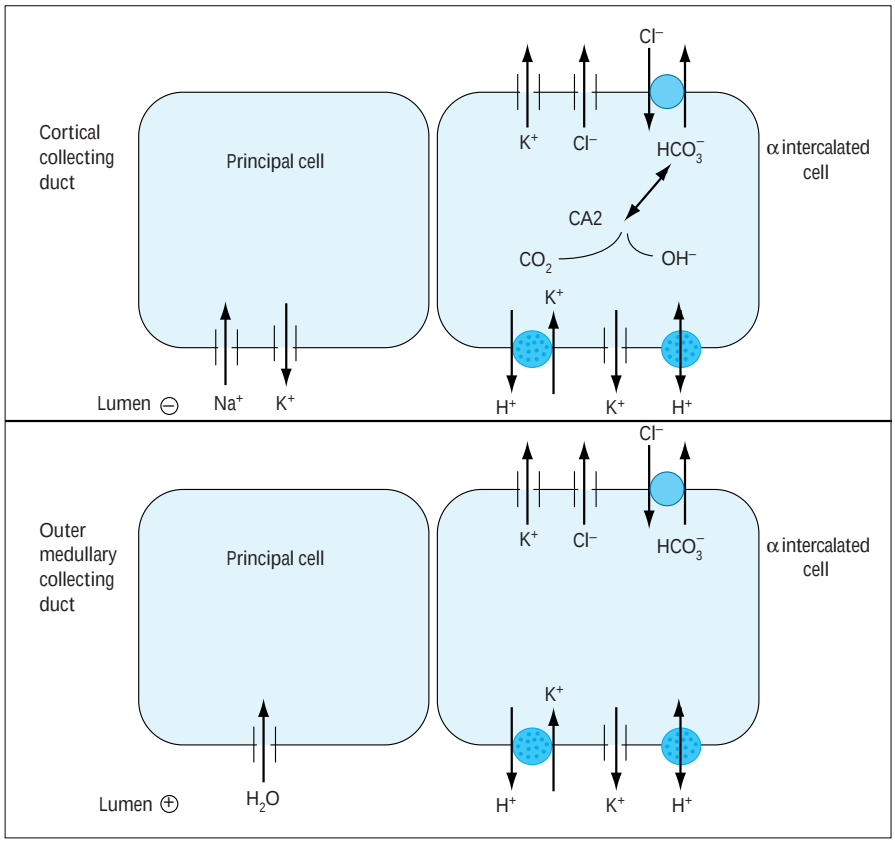

FIGURE 12-12

Distal renal tubular acidosis (RTA). The collecting duct is the principal site of distal tubule acidification, where the final 5% to 10% of the filtered bicarbonate load is reabsorbed and the hydrogen ions (H^+) generated from dietary protein catabolism are secreted. The distal nephron is composed of several distinct segments, *eg*, the connecting tubule, cortical collecting duct, and medullary collecting duct. The tubular epithelia within these segments are composed of two cell types: principal cells that transport sodium, potassium, and water; and intercalated cells that secrete hydrogen ions and bicarbonate (HCO^-_3) [22].

Urinary acidification in the distal nephron depends on several factors: an impermeant luminal membrane capable of sustaining large pH gradients; a lumen-negative potential difference in the cortical collecting duct that supports both hydrogen and potassium ion (K^+) secretion; and secretion of hydrogen ions by the intercalated cells of the cortical and medullary collecting ducts at a rate sufficient to regenerate the bicarbonate consumed by metabolic protons [22]. Abnormalities in any of these processes could result in a distal acidification defect.

Recent studies in families with isolated autosomal dominant distal RTA have identified defects in the basolateral chloride-bicarbonate exchanger, AE1 [23,24]. Defects in various components of the H^+-adenosine triphosphatase (H^+ ATPase) and subunits of the H^+-K^+ ATPase ($H^+\backslash K^+$ ATPase) also have been proposed as the basis for other hereditary forms of distal RTA. CA2—cytosolic carbonic anhydrase type II; Cl^-—chloride ion; CO_2—carbon dioxide; Na^+—sodium ion; OH^-—hydroxy ions.

Bartter-like Syndromes

CLINICAL FEATURES DISTINGUISHING BARTTER-LIKE SYNDROMES

Feature	Classic Bartter's syndrome	Gitelman's syndrome	Antenatal Bartter's syndrome
Age at presentation	Infancy, early childhood	Childhood, adolescence	In utero, infancy
Prematurity, polyhydramnios	+/-	-	++
Delayed growth	++	-	+++
Delayed cognitive development	+/-	-	+
Polyuria, polydipsia	++	+	+++
Tetany	Rare	++	-
Serum magnesium	Low in 20%	Low in about 100%	Low-normal to normal
Urinary calcium excretion	Normal to high	Low	Very high
Nephrocalcinosis	+/-	-	++
Urine prostaglandin excretion	High	Normal	Very high
Clinical response to indomethacin	+/-	-	Often life-saving

From Guay-Woodford [25]; with permission.

FIGURE 12-13

Familial hypokalemic, hypochloremic metabolic alkalosis, or Bartter's syndrome, is not a single disorder but rather a set of closely related disorders. These Bartter-like syndromes share many of the same physiologic derangements but differ with regard to the age of onset, presenting symptoms, magnitude of urinary potassium and prostaglandin excretion, and extent of urinary calcium excretion. At least three clinical phenotypes have been distinguished: classic Bartter's syndrome, the antenatal hypercalciuric variant (also called *hyperprostaglandin E syndrome*), and hypocalciuric-hypomagnesemic Gitelman's syndrome [25].

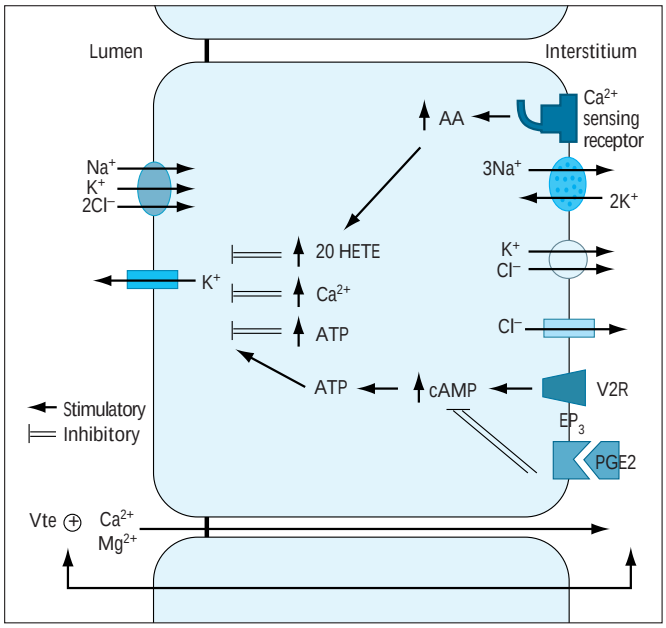

FIGURE 12-14

Transport systems involved in transepithelial sodium-chloride transport in the thick ascending limb (TAL). Clinical data suggest that the primary defect in the antenatal and classic Bartter syndrome variants involves impaired sodium chloride transport in the TAL. Under normal physiologic conditions, sodium chloride is transported across the apical membrane by way of the bumetanide-sensitive sodium-potassium-2chloride (Na-K-2Cl) cotransporter (NKCC2). This electroneutral transporter is driven by the low intracellular sodium and chloride concentrations generated by the sodium-potassium pump and the basolateral chloride channels and potassium-chloride cotransporter. In addition, apical potassium recycling by way of the low-conductance potassium channel (ROMK) ensures the efficient functioning of the Na-K-2Cl cotransporter. The activity of the ROMK channel, in turn, is regulated by a number of cell messengers, *eg*, calcium (Ca^{2+}) and adenosine triphosphate (ATP), as well as by the calcium-sensing receptor (CaR), prostaglandin EP_3 receptor, and vasopressin receptor (V2R) by way of cAMP-dependent pathways and arachidonic acid (AA) metabolites, *eg*, 20-hydroxy-eicosatetraenoic acid (20-HETE). The positive transluminal voltage (Vte) drives the paracellular reabsorption of calcium ions and magnesium ions (Mg^{2+}) [25]. cAMP—cyclic adenosine monophosphate; PGE2—prostaglandin E2; PKA—protein kinase A.

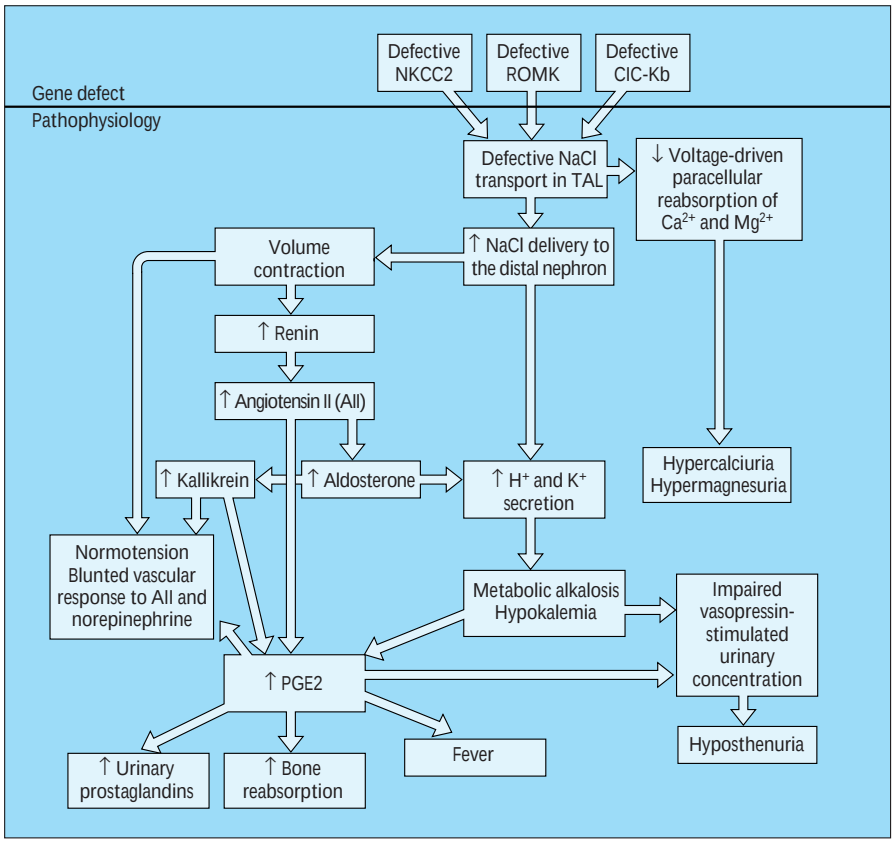

FIGURE 12-15

Proposed pathogenic model for the antenatal and classic variants of Bartter's syndrome. Genetic studies have identified mutations in the genes encoding the bumetanide-sensitive sodium-potassium-2chloride cotransporter (NKCC2), luminal ATP–regulated potassium channel (ROMK), and kidney-specific chloride channel (ClC-K2). These findings support the theory of a primary defect in thick ascending limb (TAL) sodium-chloride (Na-Cl) reabsorption in, at least, subsets of patients with the antenatal or classic variants of Bartter's syndrome. In the proposed model the potential interrelationships of the complex set of pathophysiologic phenomena are illustrated. The resulting clinical manifestations are highlighted in boxes [25]. Ca^{2+}—calcium ion; H^+—hydrogen ion; K^+—potassium ion; Mg^{2+}—magnesium ion; PGE2—prostaglandin E2.

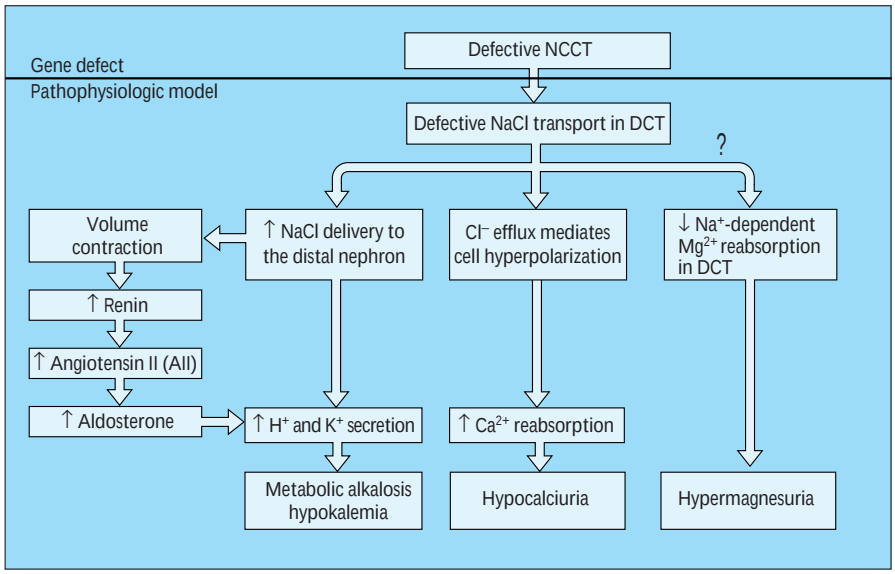

FIGURE 12-16

Proposed pathogenic model for Gitelman's syndrome. The electrolyte disturbances evident in Gitelman's syndrome also are observed with administration of thiazide diuretics, which inhibit the sodium-chloride (Na-Cl) cotransporter in the distal convoluted tubule (DCT). In families with Gitelman's syndrome, genetic studies have identified defects in the gene encoding the thiazide-sensitive cotransporter (NCCT) protein. The proposed pathogenic model is predicated on loss of function of the NCCT protein and, thus, most closely applies to those patients who inherit Gitelman's syndrome as an autosomal recessive trait. Given that the physiologic features of this syndrome are virtually indistinguishable in familial and sporadic cases, it may be reasonable to propose the same pathogenesis for all patients with Gitelman's syndrome. However, it is important to caution that evidence for NCCT mutations in sporadic cases has not yet been established [25]. Ca^{2+}—calcium ion; Cl^-—chloride ion; H^+—hydrogen ion; K^+—potassium ion; Mg^{2+}—magnesium ion; Na^+—sodium ion.

Pseudohypoparathyroidism

CLINICAL SUBTYPES OF PSEUDOHYPOPARATHYROIDISM

Disorder	Pathophysiology	Skeletal anomalies	Associated endocrinopathies
Pseudohypoparathyroidism type Ia	Defect in guanine nucleotide—binding protein	Yes	Yes
Pseudohypoparathyroidism type Ib	Resistance to parathyroid hormone, normal guanine nucleotide—binding protein activity ? Defect in parathyroid hormone receptor	No	No

FIGURE 12-17

Pseudohypoparathyroidism applies to a heterogeneous group of hereditary disorders whose common feature is resistance to parathyroid hormone (PTH). Affected patients are hypocalcemic and hyperphosphatemic, despite elevated plasma PTH levels. Hypocalcemia and hyperphophatemia result from the combined effects of defective PTH-mediated calcium reabsorption in the distal convoluted tubule and reduced formation of 1,25-dihydroxy-vitamin D_3. The latter leads to defects in renal phosphate excretion, calcium mobilization from bone, and gastrointestinal calcium reabsorption. Differences in clinical features and urinary cyclic adenosine monophosphate response to infused PTH provide the basis for distinguishing three distinct subtypes of pseudohypoparathyroidism (type Ia, type Ib, and type II) [26].

Pseudohypoparathyroidism type Ia (Albright's hereditary osteodystrophy) is associated with a myriad of physical abnormalities and resistance to multiple adenylate cyclase–coupled hormones, most notably thyrotropin and gonadotropin [27]. The molecular defect in a guanine nucleotide–binding protein (Gs) blocks the coupling of PTH and other hormone receptors to adenylate cyclase. The molecular defect has not been identified in type Ib, although specific resistance to PTH suggests a defect in the PTH receptor. Oral supplementation with 1,25 dihydroxy-vitamin D_3 and, if necessary, oral calcium, is used to correct the hypocalcemia and minimize PTH-induced bone disease [26]. Pseudohypoparathroidism type II may be an acquired disease.

Disorders of Aldosterone-Regulated Transport

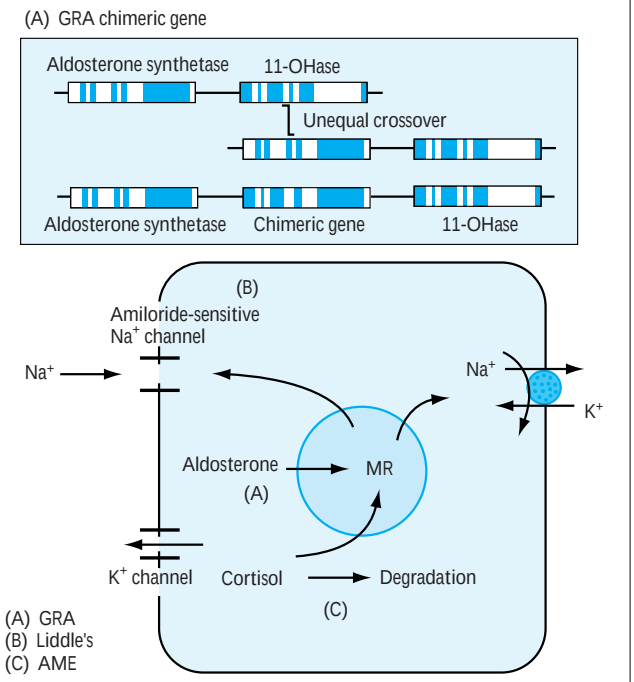

FIGURE 12-18

Aldosterone-regulated transport in the cortical collecting duct and defects causing low-renin hypertension. The mineralocorticoid aldosterone regulates electrolyte excretion and intravascular volume by way of its action in the principal cells of the cortical collecting duct. The binding of aldosterone to its nuclear receptor (MR) leads directly or indirectly to increased activity of the apical sodium (Na) channel and the basolateral sodium-potassium adenosine triphosphatase (Na-K ATPase). Sodium moves from the lumen into the cell and down its electrochemical gradient, thus generating a lumen-negative transepithelial voltage that drives potassium secretion from the principal cells and hydrogen secretion from the intercalated cells. The type I mineralocorticoid receptor (MR) is nonspecific and can bind both aldosterone and cortisol, but not cortisone. The selective receptor specificity for aldosterone is mediated by the kidney isoform of the enzyme, 11-β-hydroxysteroid dehydrogenase, which oxidizes intracellular cortisol to its metabolite cortisone.

Three hypertensive syndromes, glucocorticoid-remedial aldosteronism (GRA), Liddle's syndrome, and apparent mineralocorticoid excess (AME), share a common clinical phenotype that is characterized by normal physical examinations, hypokalemia, and very low plasma renin activity. The molecular defect in GRA derives from an unequal crossover event between two adjacent genes encoding 11-β-hydroxylase and aldosterone synthase (A). The resulting chimeric gene duplication fuses the regulatory elements of 11-β-hydroxylase and the coding sequence of aldosterone synthase. Consequently, aldosterone is ectopically synthesized in the adrenal zona fasciculata and its synthesis regulated by adrenocorticotropic hormone rather than its physiologically normal secretagogue, angiotensin II [28]. Activating mutations in the β and γ regulatory subunits of the epithelial sodium channel (B) are responsible for Liddle's syndrome [29]. Deficiency of the kidney type 2 isozyme of 11-β-hydroxysteroid dehydrogenase (C) can render type I MR responsive to cortisol and produce the syndrome of apparent mineralocorticoid excess [30]. Inhibitors of this enzyme (*eg,* licorice) also can produce an acquired form of apparent mineralocorticoid excess. Medical management of these disorders focuses on dietary sodium restriction, blocking the sodium channel with the potassium-sparing diuretics triamterene and amiloride, downregulating the ectopic aldosterone synthesis with glucocorticoids (GRA), or blocking the MR using the competitive antagonist spironolactone (GRA and AME).

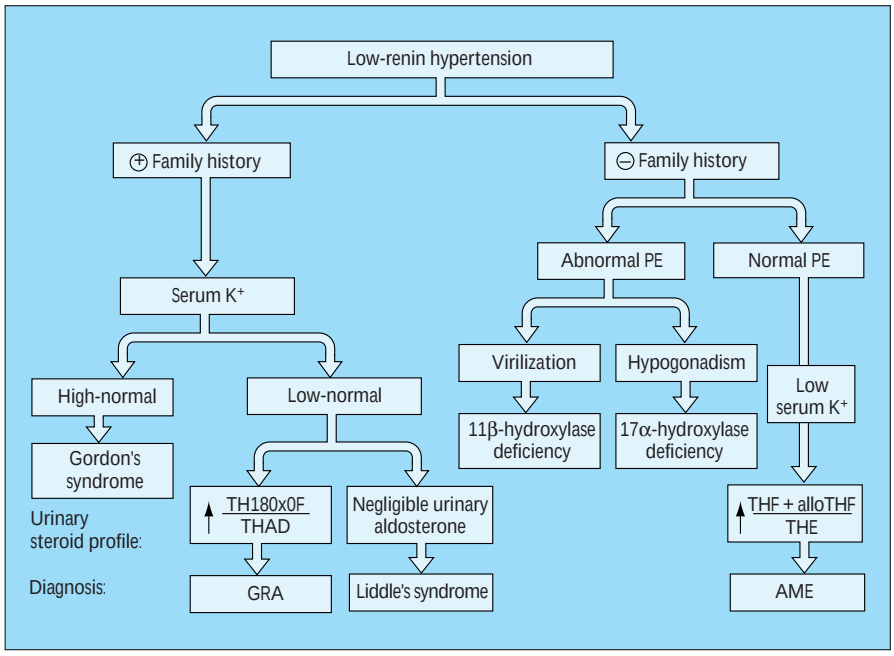

FIGURE 12-19

Algorithm for evaluating patients with low-renin hypertension. Glucocorticoid-remedial aldosteronism (GRA), Liddle's syndrome, and apparent mineralocorticoid excess (AME) can be distinguished from one another by characteristic urinary steroid profiles [31]. K^+—potassium ion; PE—physical examination; TH18oxoF/THAD—ratio of urinary 18-oxotetrahydrocortisol (TH18oxoF) to urinary tetrahydroaldosterone (normal: 0–0.4; GRA patients: >1); THF + allo-THF/THE—ratio of the combined urinary tetrahydrocortisol and allotetrahydrocortisol to urinary tetrahydrocortisone (normal: <1.3; AME patients: 5–10-fold higher).

CLINICAL SUBTYPES OF PSEUDOHYPOALDOSTERONISM

Disorder	Clinical features	Treatment
Pseudohypoaldosteronism type I		
Autosomal recessive	Dehydration, severe neonatal salt wasting, hyperkalemia, metabolic acidosis	Sodium chloride supplementation
	Elevated plasma renin activity	Ion-binding resin; dialysis
	Severity of electrolyte abnormalities may diminish after infancy	
Autosomal dominant	Mild salt wasting	
Pseudohypoaldosteronism type II (Gordon's syndrome)	Hypertension, hyperkalemia, mild hyperchloremic metabolic acidosis	Thiazide diuretics
	Undetectable plasma renin activity	

FIGURE 12-20

Mineralocorticoid resistance with hyperkalemia (pseudohypoaldosteronism) includes at least three clinical subtypes, two of which are hereditary disorders. Pseudohypoaldosteronism type I (PHA1) is characterized by severe neonatal salt wasting, hyperkalemia, and metabolic acidosis. The diagnosis is supported by elevated plasma renin and plasma aldosterone concentrations. Life-saving interventions include aggressive sodium chloride supplementation and treatment with ion-binding resins or dialysis to reduce the hyperkalemia. This autosomal recessive form of PHA1 results from inactivating mutations in the α or β subunits of the epithelial sodium channel [32]. A milder form of PHA1 with autosomal dominant inheritance also has been described; however, the molecular defect remains unexplained [33]. Adolescents or adults with hyperkalemic, hyperchloremic metabolic acidosis, low-normal renin and aldosterone levels, and hypertension have been recently described and classified as having pseudohypoaldosteronism type II (PHA2) or Gordon's syndrome [34]. Phenotypically, this disorder is the mirror image of Gitelman's syndrome; however, the thiazide-sensitive cotransporter (NCCT) has been excluded as a candidate gene [35].

Nephrogenic Diabetes Insipidus

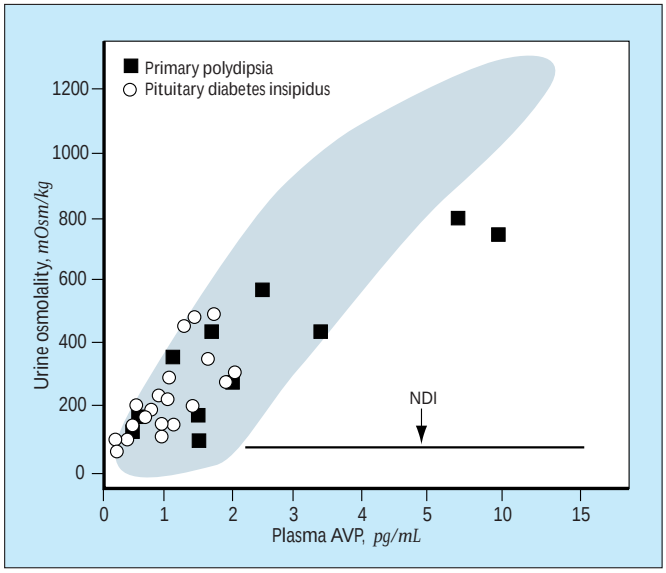

FIGURE 12-21

The relationship between urine osmolality and plasma arginine vasopressin (AVP). Nephrogenic diabetes insipidus (NDI) is characterized by renal tubular unresponsiveness to the antidiuretic hormone AVP or its antidiuretic analogue 1-desamino-8-D-arginine vasopressin (DDAVP). In both the congenital and acquired forms of this disorder the clinical picture is dominated by polyuria, polydipsia, and hyposthenuria despite often elevated AVP levels [17]. (*From* Robertson *et al*. [36]; with permission.)

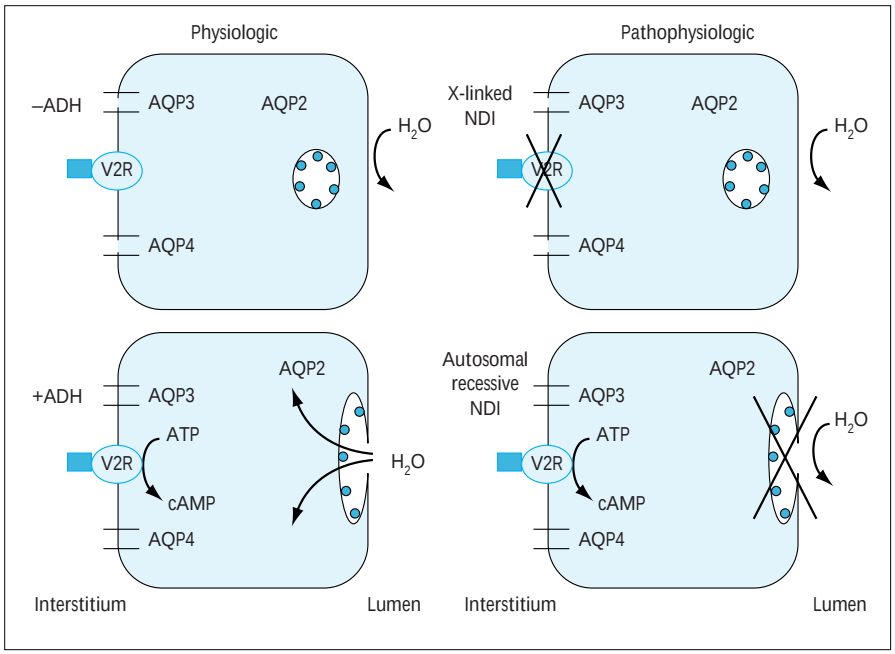

FIGURE 12-22

Pathogenic model for nephrogenic diabetes insipidus (NDI). The principle cell of the inner medullary collecting duct is the site where fine tuning of the final urinary composition and volume occurs. As shown, the binding of arginine vasopressin (AVP) to the vasopressin V2 receptor (V2R) stimulates a series of cyclic adenosine monophosphate–(cAMP) mediated events that results in the fusion of cytoplasmic vesicles carrying water channel proteins (aquaporin-2 [AQP2]), with the apical membrane, thereby increasing the water permeability of this membrane. Water exits the cell through the basolateral water channels AQP3 and AQP4. In the absence of AVP, water channels are retrieved into cytoplasmic vesicles and the water permeability of the apical membrane returns to its baseline low rate [37].

Genetic studies have identified mutations in two proteins involved in this water transport process, the V2 receptor and AQP2 water channels. Most patients (>90%) inherit NDI as an X-linked recessive trait. In these patients, defects in the V2 receptor have been identified. In the remaining patients, the disease is transmitted as either an autosomal recessive or autosomal dominant trait involving mutations in the AQP2 gene [38,39]. ADH— antidiuretic hormone; ATP—adenosine triphosphate.

Urolithiases

INHERITED CAUSES OF UROLITHIASES

Disorder	Stone characteristics	Treatment
Cystinuria	Cystine	High fluid intake, urinary alkalization Sulfhydryl-containing drugs
Dent's disease	Calcium-containing	High fluid intake, urinary alkalization
X-linked recessive nephrolithiasis	Calcium-containing	High fluid intake, urinary alkalization
X-linked recessive hypophosphatemic rickets	Calcium-containing	High fluid intake, urinary alkalization
Hereditary renal hypouricemia	Uric acid, calcium oxalate	High fluid intake, urinary alkalization Allopurinol
Hypoxanthine-guanine phosphoribosyltransferase deficiency	Uric acid	High fluid intake, urinary alkalization Allopurinol
Xanthinuria	Xanthine	High fluid intake, dietary purine restriction
Primary hyperoxaluria	Calcium oxalate	High fluid intake, dietary oxalate restriction Magnesium oxide, inorganic phosphates

FIGURE 12-23

Urolithiases are a common urinary tract abnormality, afflicting 12% of men and 5% of women in North America and Europe [40]. Renal stone formation is most commonly associated with hypercalciuria. Perhaps in as many as 45% of these patients, there seems to be a familial predisposition. In comparison, a group of relatively rare disorders exists, each of which is transmitted as a Mendelian trait and causes a variety of different crystal nephropathies. The most common of these disorders is cystinuria, which involves defective cystine and dibasic amino acid transport in the proximal tubule. Cystinuria is the leading single gene cause of inheritable urolithiasis in both children and adults [41,42]. Three Mendelian disorders, Dent's disease, X-linked recessive nephrolithiasis, and X-linked recessive hypophosphatemic rickets cause hypercalciuric urolithiasis. These disorders involve a functional loss of the renal chloride channel ClC-5 [43]. The common molecular basis for these three inherited kidney stone diseases has led to speculation that ClC-5 also may be involved in other renal tubular disorders associated with kidney stones. Hereditary renal hypouricemia is an inborn error of renal tubular transport that appears to involve urate reabsorption in the proximal tubule [16].

In addition to renal transport deficiencies, defects in metabolic enzymes also can cause urolithiases. Inherited defects in the purine salvage enzymes hypoxanthine-guanine phosphoribosyltransferase (HPRT) and adenine phosphoribosyltransferase (APRT) or in the catabolic enzyme xanthine dehydrogenase (XDH) all can lead to stone formation [44]. Finally, defective enzymes in the oxalate metabolic pathway result in hyperoxaluria, oxalate stone formation, and consequent loss of renal function [45].

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