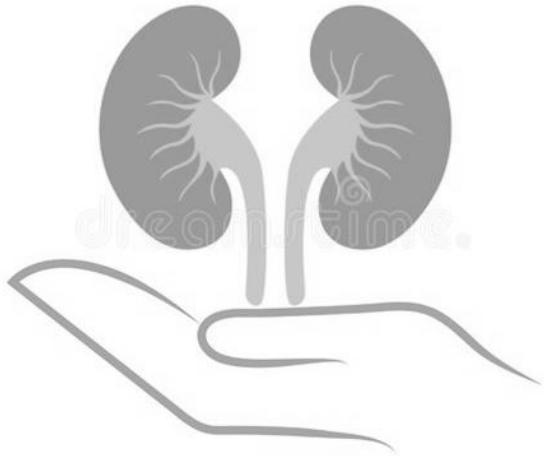
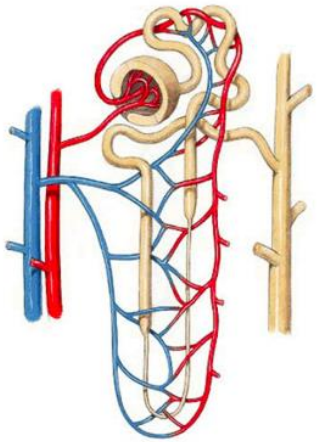


Renal Tubular Disorders

by: Anas Alahmad ,Sara AInafisi,Nouf ALnafisi

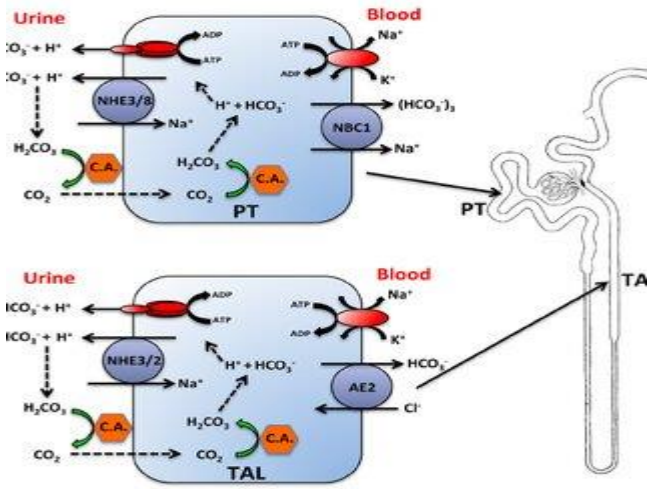
Outlines

1



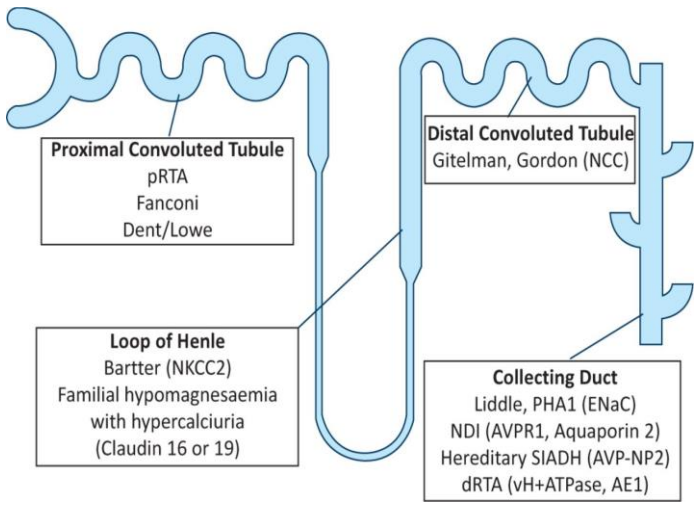
Overview of renal tubular anatomy and function

2



Urine acidification

3



Renal tubular disorders:

1. Renal tubular acidosis.
2. Fanconi syndrome and cystinosis
3. Barrter syndrome.
4. Gittelmann & Liddle Syndromes.
5. Nephrogenic DI.

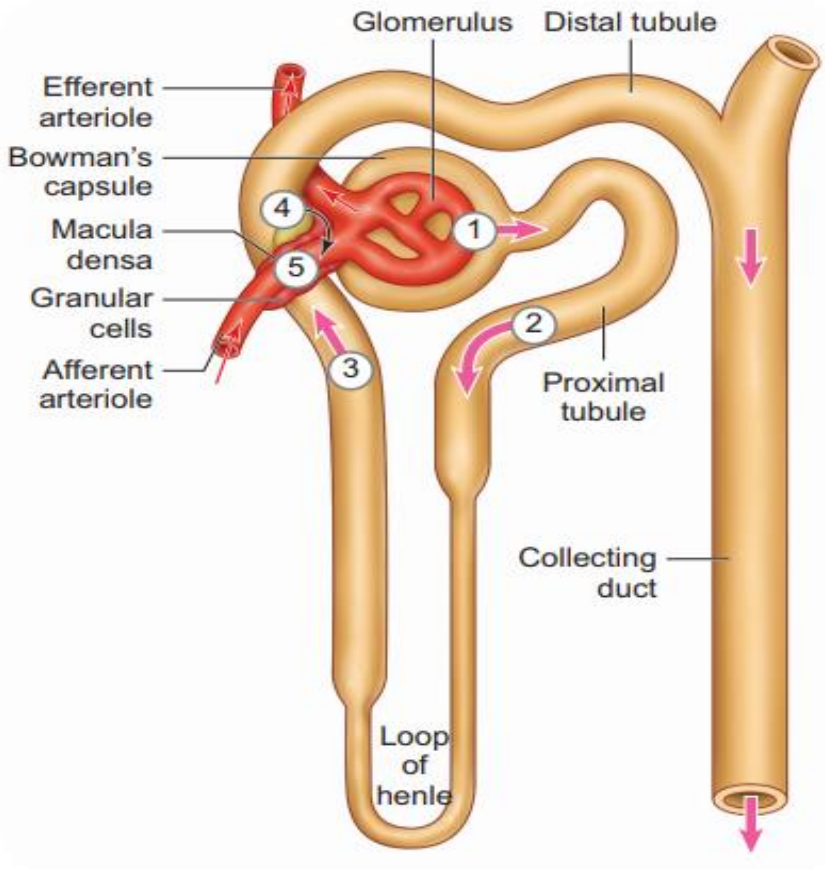
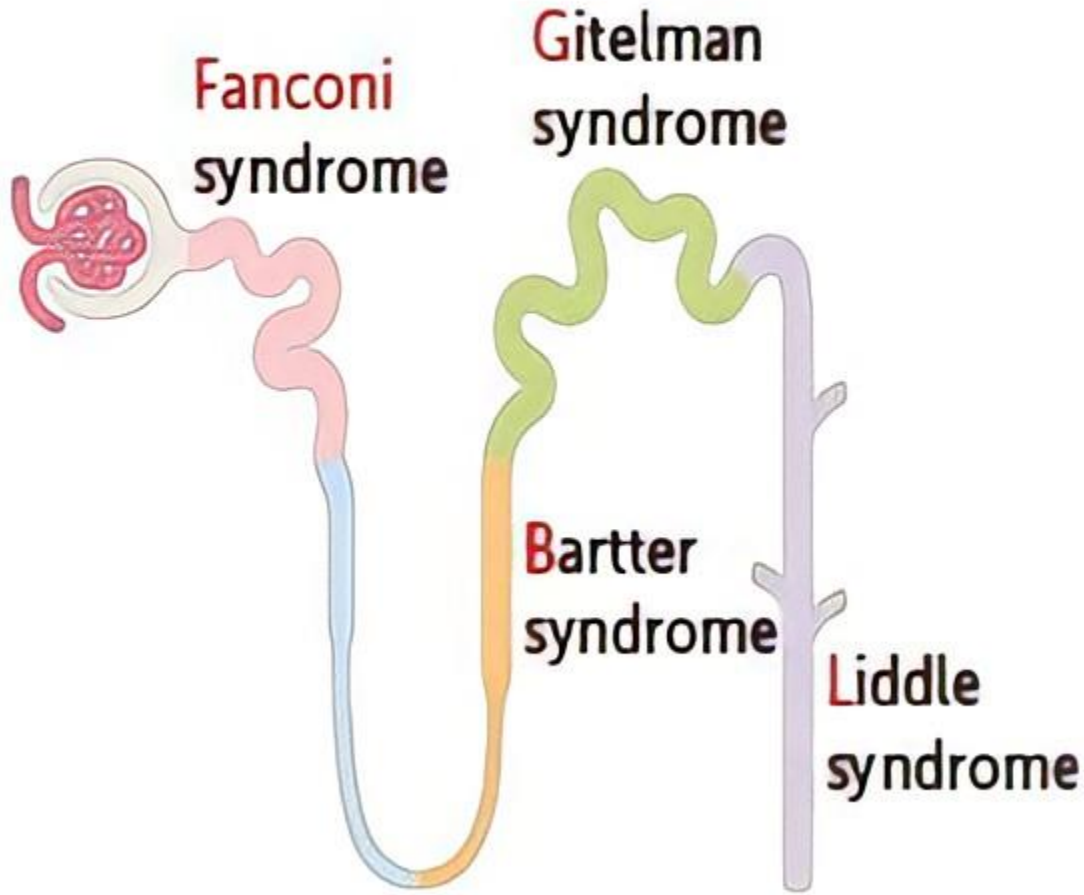
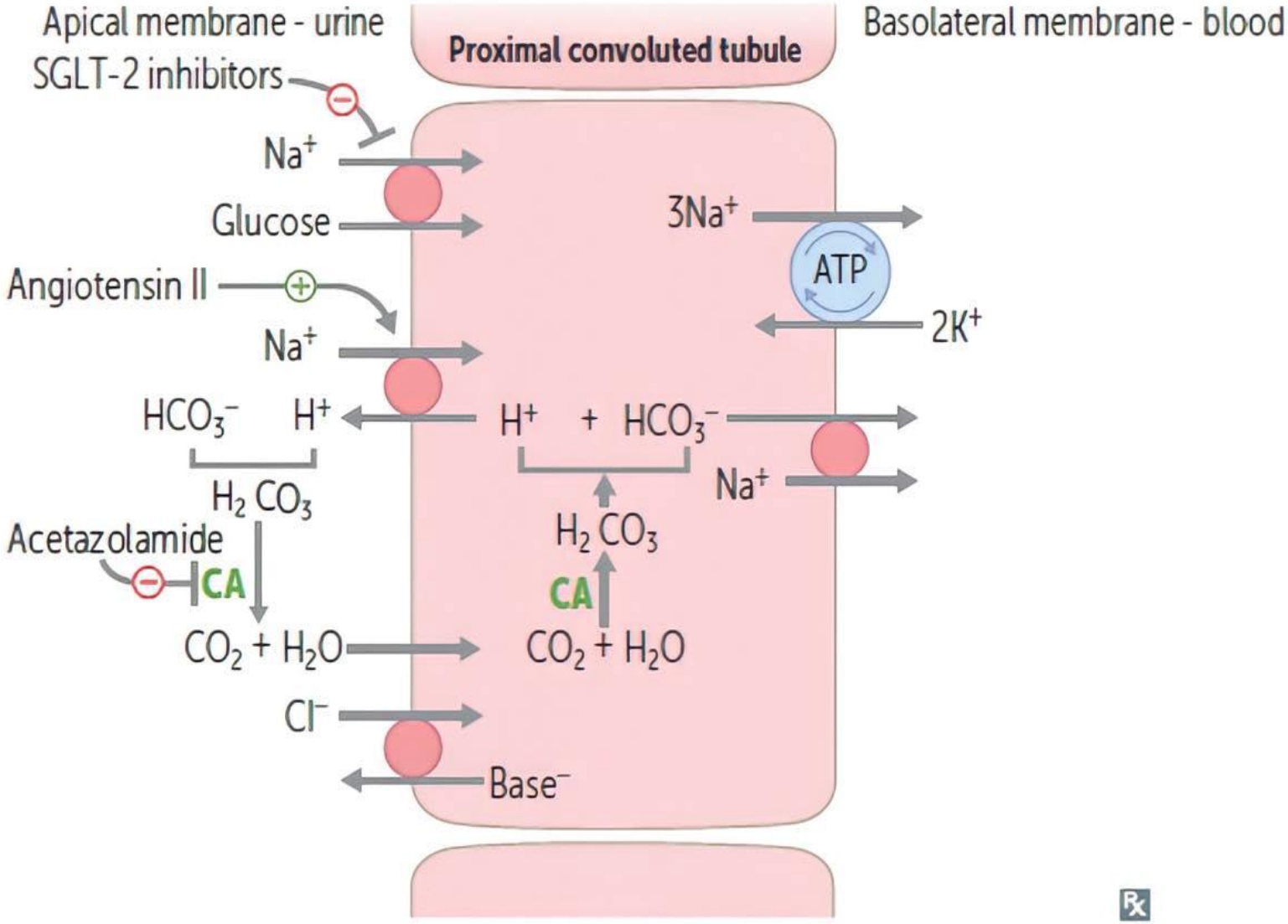


Figure 8.4 Structure of a Nephrons




Apical membrane - urine
Proximal convoluted tubule
Basolateral membrane - blood
SGLT-2 inhibitors
Na+
Glucose
Angiotensin II
Na+
HCO3− H+
H2 CO3
Acetazolamide
CA
CO2 + H2O
Cl−
Base−
3Na+
ATP
2K+
H+ + HCO3−
Na+
H2 CO3
CA
CO2 + H2O

EARLY proximal convoluted tubule

- Isotonic reabsorption
- reabsorbs Na+ and H2O with HCO3 - , glucose, amino acids, phosphate, and lactate.
- Na+ is reabsorbed by cotransport with glucose, amino acids, phosphate, and lactate. These cotransport processes account for the reabsorption of all the filtered glucose and amino acids.
- Generates and secretes NH3, which enables the kidney to secrete more H+.
- PTH—inhibits Na+/phosphate contrasport, and thus increases phosphate excretion.
- Na+ is also reabsorbed by **countertransport** via Na+ /H+ exchange, which is linked directly to the reabsorption of filtered HCO3-.
- 65-80 % of Na+ reabsorbed.

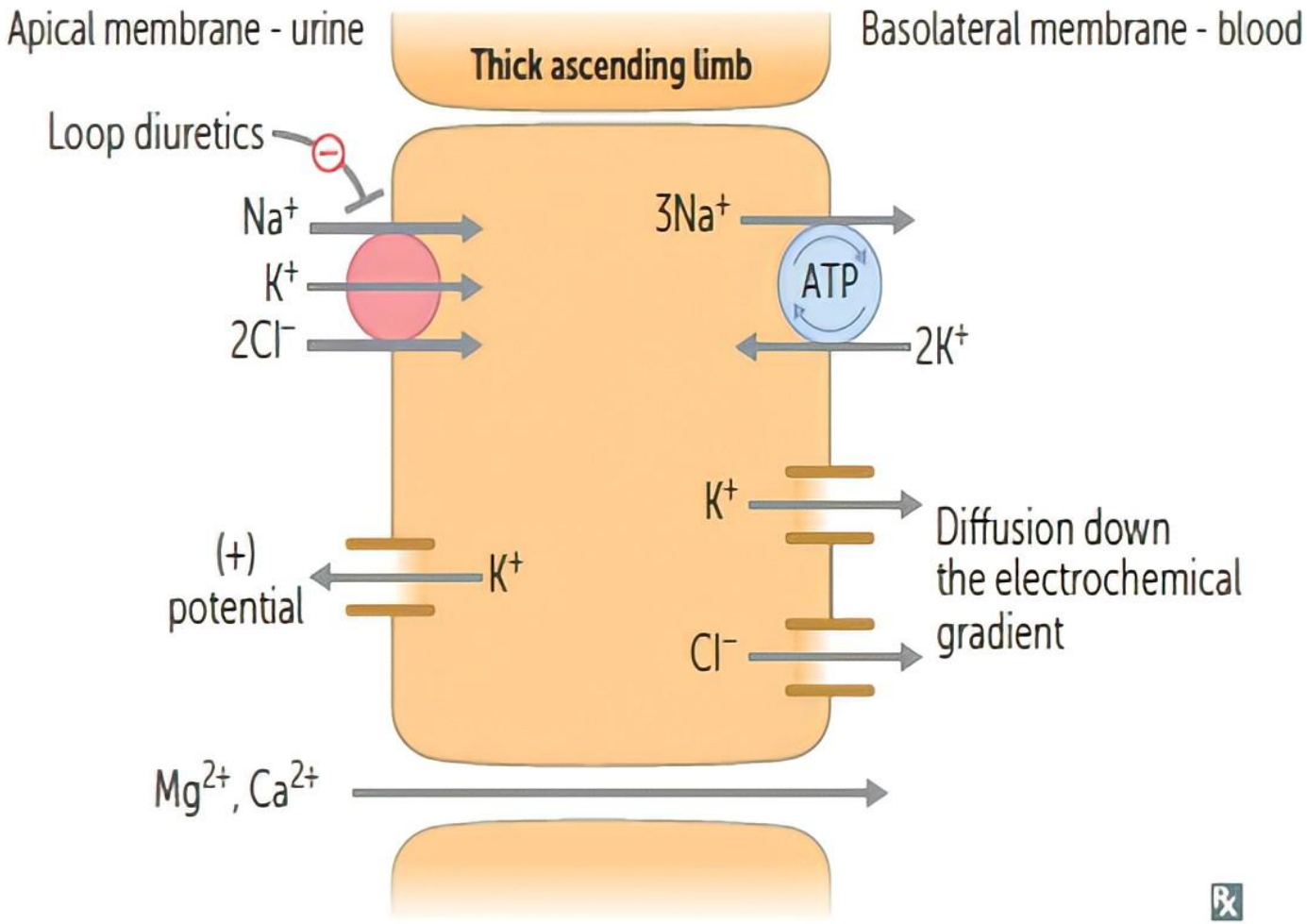
LATE proximal convoluted tubule

- Filtered glucose, amino acids, and HCO3- have already been completely removed from the tubular fluid by reabsorption in the early proximal tubule.

- In the late proximal tubule, Na+ is reabsorbed with Cl-, either trans-cellularly, or paracellularly.

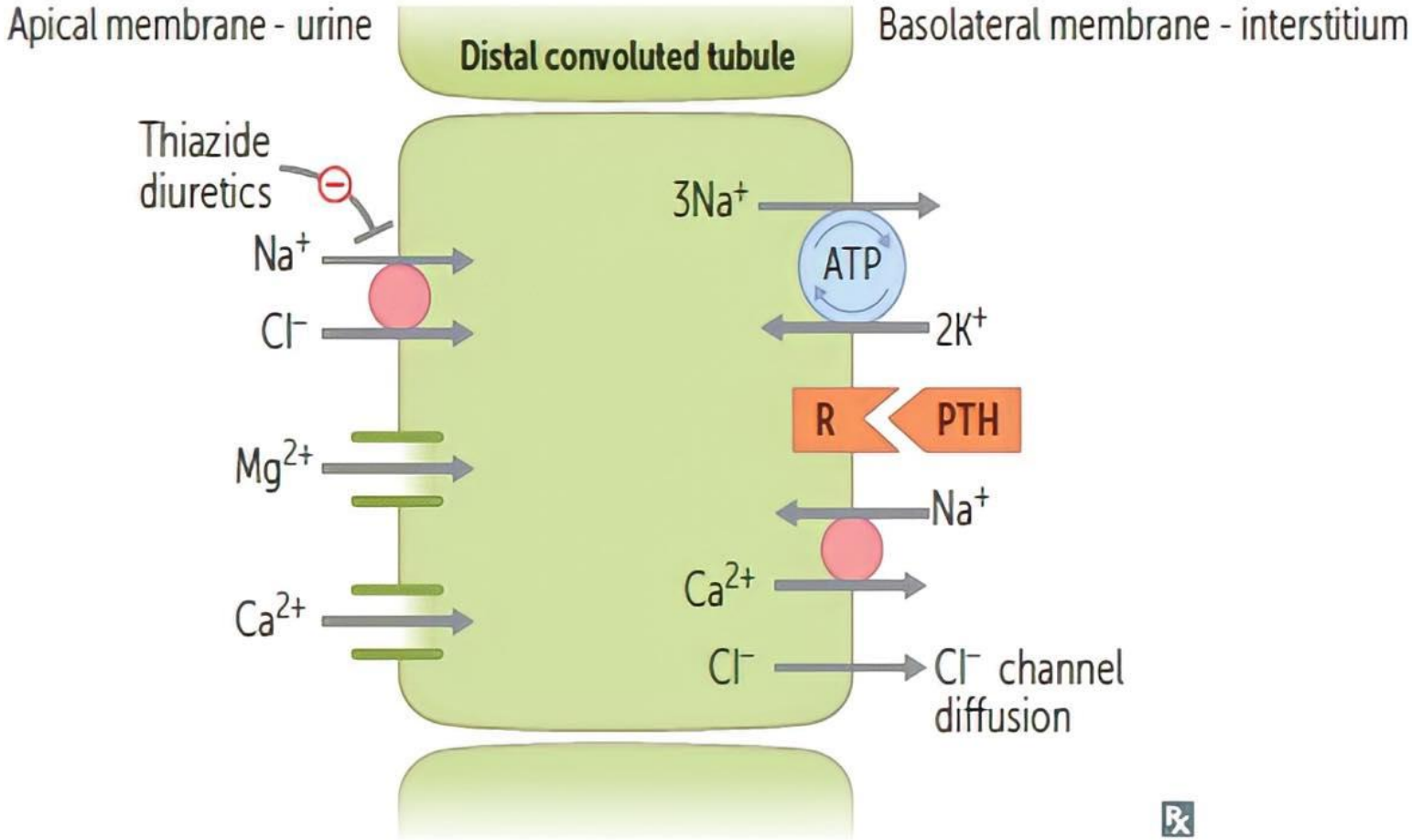
Thin descending loop of Henle

- passively reabsorbs H2O via medullary hypertonicity (impermeable to Na+). Concentrating segment. Makes urine hypertonic.


Apical membrane - urine
Thick ascending limb
Basolateral membrane - blood
Loop diuretics
Na+
K+
2Cl−
3Na+
ATP
2K+
K+
Diffusion down
the electrochemical
gradient
(+)
potential
K+
Cl−
Mg2+, Ca2+

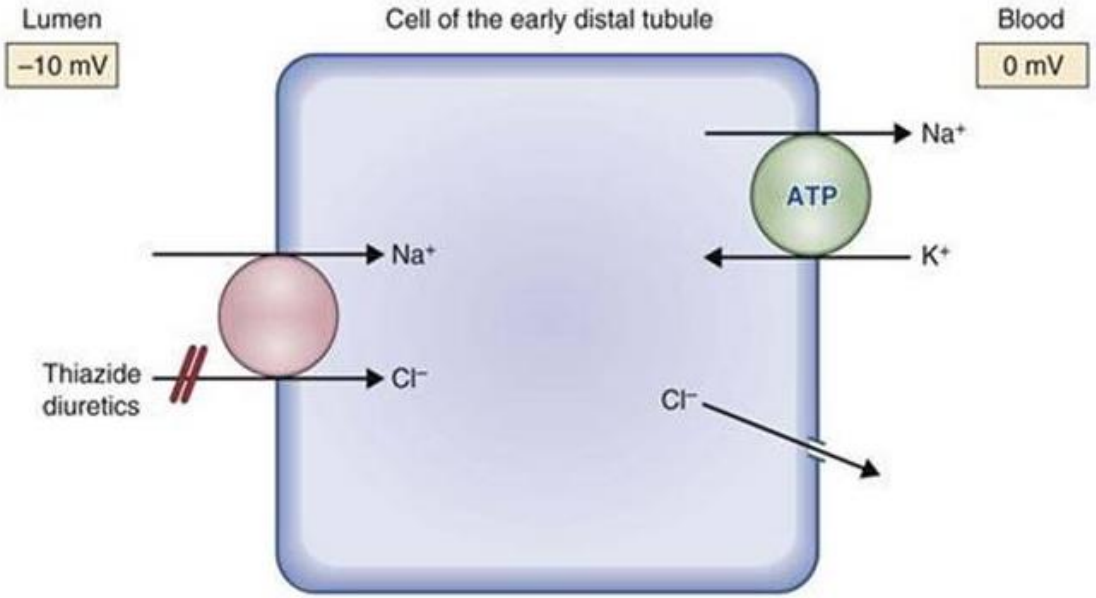
Thick Ascending loop of Henle

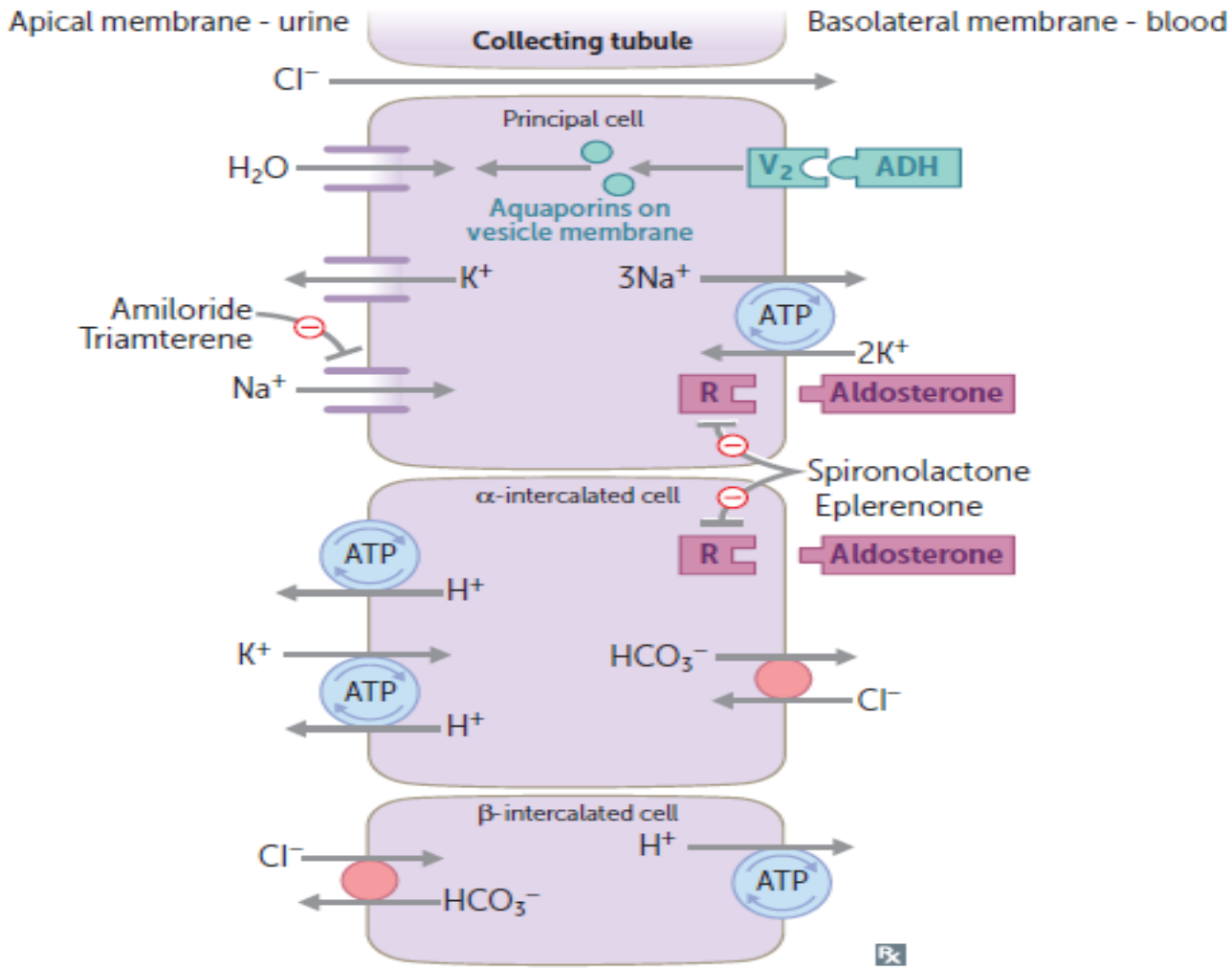
- reabsorbs 10-20% of the filtered Na+.
- Contains a Na+ –K+ –2Cl- cotransporter in the luminal membrane.
- Is impermeable to water, thus called the diluting segment.
- Indirectly induces paracellular reabsorption of Mg2+ and Ca2+ through positive lumen potential generated by K+ back leak.
- Is the site of action for loop diuretics.


Apical membrane - urine
Distal convoluted tubule
Basolateral membrane - interstitium
Thiazide diuretics
Na+
Cl−
Mg2+
Ca2+
3Na+
ATP
2K+
R
PTH
Na+
Ca2+
Cl−
Cl− channel diffusion

Early Distal convoluted tubule

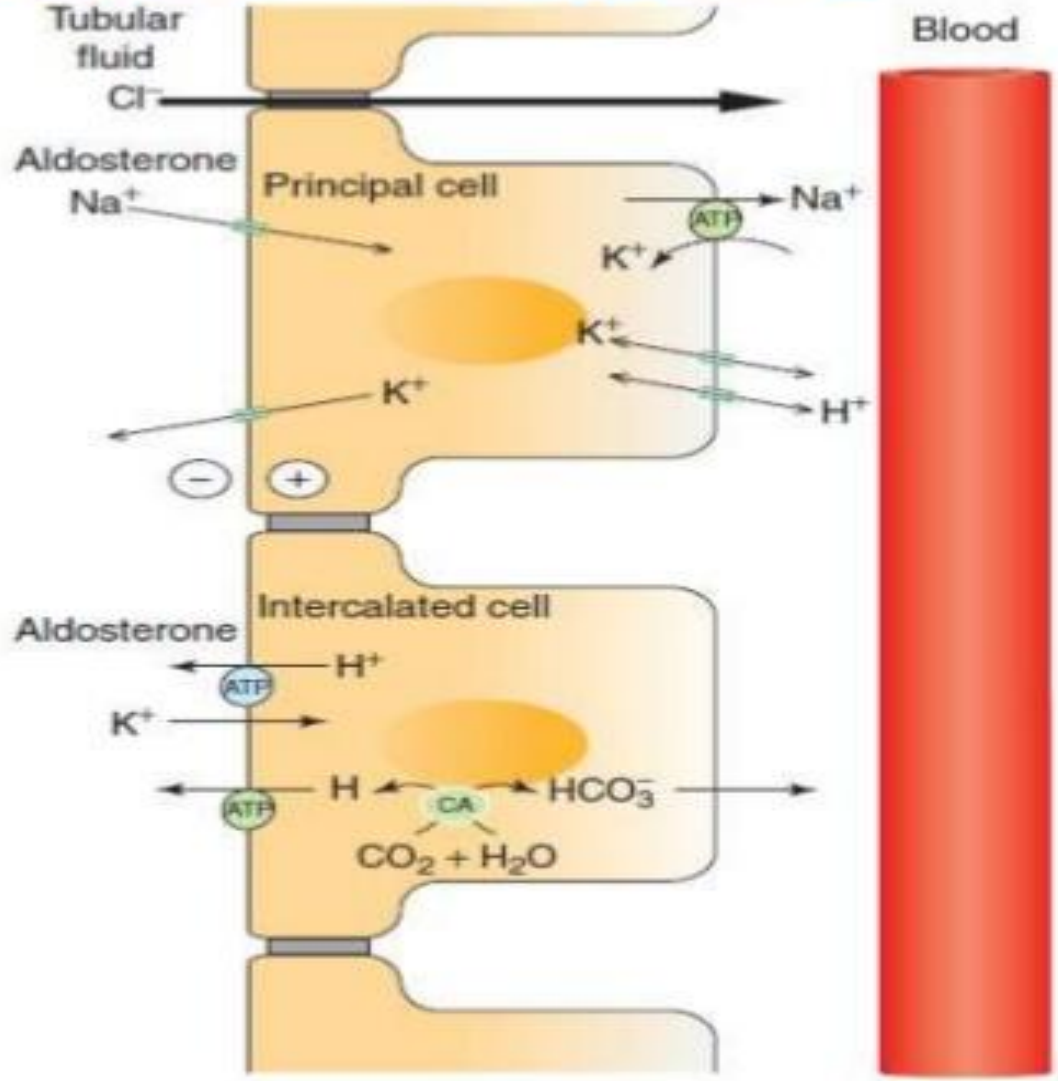
- reabsorbs NaCl by a Na+ –Cl- cotransporter.
- is impermeable to water, as is the thick ascending limb. Thus, reabsorption of NaCl occurs without water, which further dilutes the tubular fluid. It is called the cortical diluting segment.
- Reabsorb 5-10% of filtered Na+.
- PTH increases Ca+/Na+ exchange, and thus increases Ca+ reabsorption.
- Is the site of action of thiazides diuretics.




Apical membrane - urine
Collecting tubule
Basolateral membrane - blood
Cl⁻
Principal cell
H₂O
V₂
ADH
Aquaporins on vesicle membrane
K⁺
3Na⁺
Amiloride
Triamterene
ATP
2K⁺
Na⁺
R
Aldosterone
Spironolactone
Eplerenone
α-intercalated cell
ATP
R
Aldosterone
H⁺
K⁺
HCO₃⁻
ATP
Cl⁻
H⁺
β-intercalated cell
Cl⁻
H⁺
ATP
HCO₃⁻

Late distal tubules & collecting duct

- **Two types of cells …**
- **1) principle cells : specialized for K+ secretion**
- **2) intercalated cells: specialized for K+ absorption & H+ secretion**



Principal cells

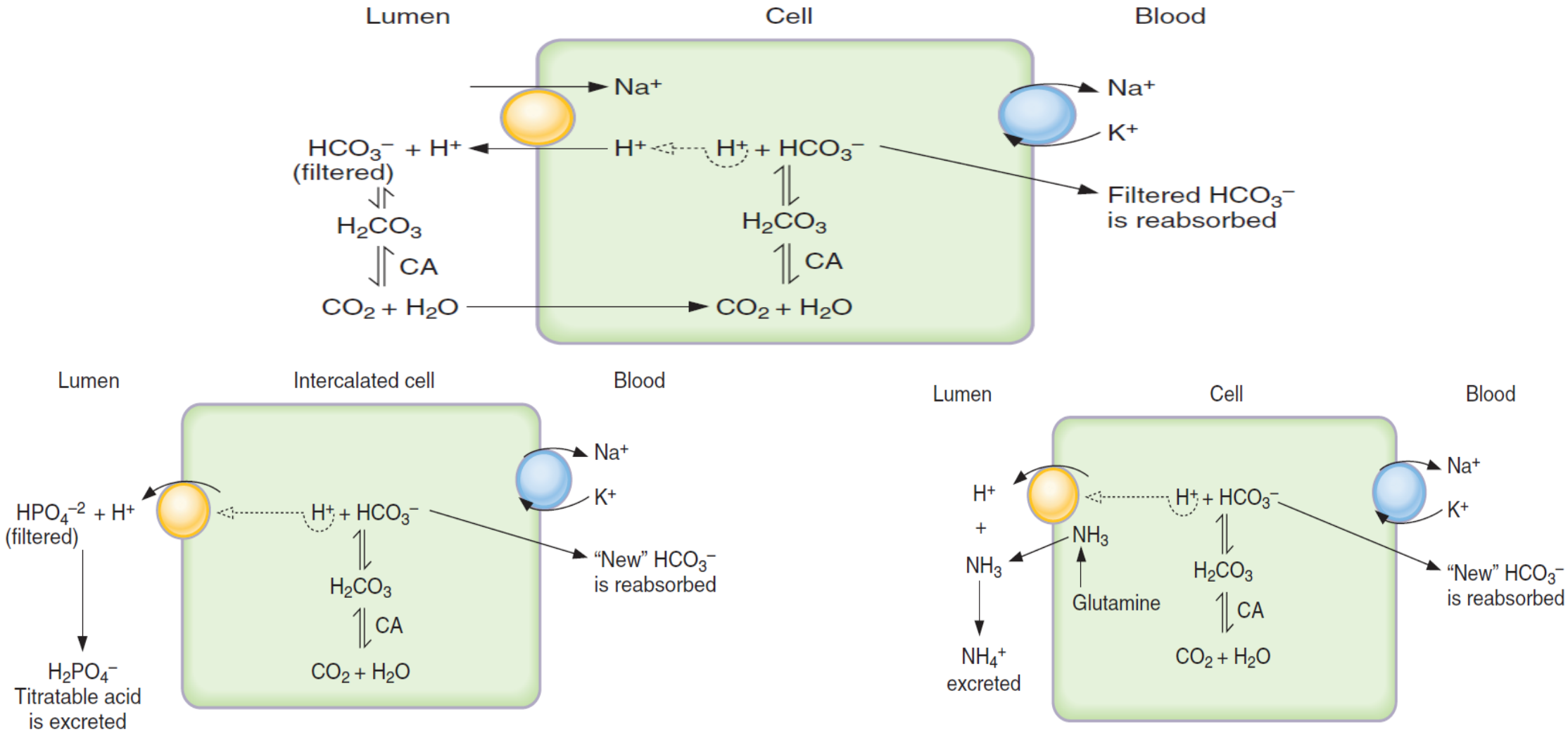
- Reabsorb Na+ and H2O
- Secrete K+.
- Aldosterone increases Na+ reabsorption and increases K+ secretion.
- Antidiuretic hormone (ADH) increases H2O permeability by directing the insertion of H2O channels (aquaporin) in the luminal membrane. In the absence of ADH, the principal cells are virtually impermeable to water
- Site of action of potassium sparing agents.

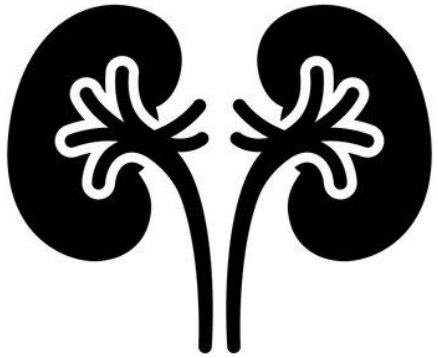
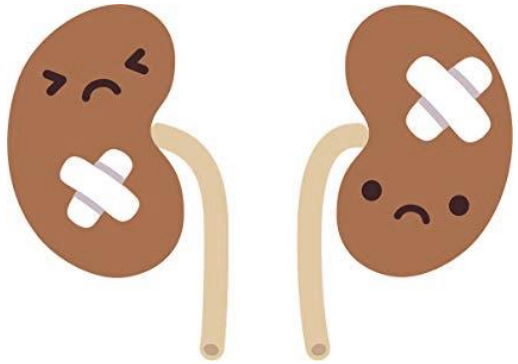
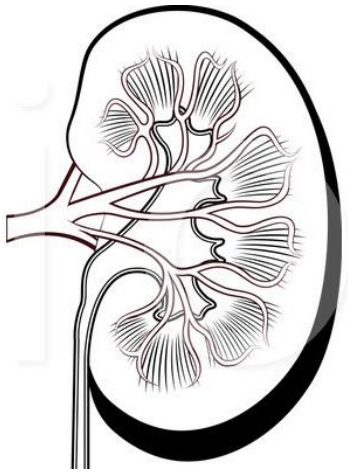
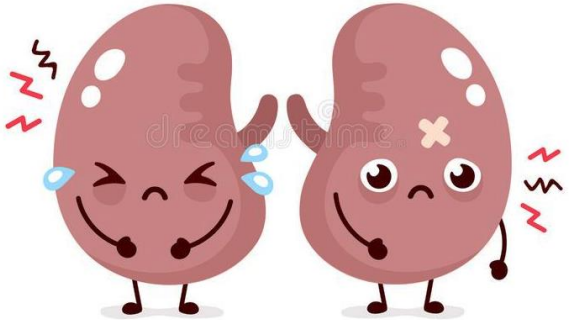
α-Intercalated cells

- Secrete H+ by an H+ -adenosine triphosphatase (ATPase), which is stimulated by aldosterone.
- Reabsorb K+ by an H+,K+ -ATPase

Normal urine acidification

- The renal acid-base homeostasis divided into two processes:
- (*1*) reabsorption of filtered HCO_3^- and generation of new HCO_3^-
- (*2*) excretion of fixed acids(H+) through the titration of urinary buffers and the excretion of ammonium.


Lumen
Cell
Blood
Na+
HCO3− + H+
(filtered)
H2CO3
CA
CO2 + H2O
H+
H+ + HCO3−
H2CO3
CA
CO2 + H2O
Na+
K+
Filtered HCO3−
is reabsorbed
Lumen
Intercalated cell
Blood
HPO4−2 + H+
(filtered)
H2PO4−
Titratable acid
is excreted
H+ + HCO3−
H2CO3
CA
CO2 + H2O
Na+
K+
"New" HCO3−
is reabsorbed
Lumen
Cell
Blood
H+
+
NH3
NH4+
excreted
NH3
Glutamine
H+ + HCO3−
H2CO3
CA
CO2 + H2O
Na+
K+
"New" HCO3−
is reabsorbed

Renal Tubular Acidosis

- is a clinical syndrome of disordered renal acidification in which the kidney fails to maintain a normal plasma concentration of bicarbonate despite a relatively well-preserved glomerular filtration rate in the setting of a normal rate of acid production from diet and metabolism.

- This syndrome is characterized by a *hyperchloremic metabolic acidosis ,bicarbonaturia*, *decreased production of titratable acids* and *ammonium* with, usually, an *elevated urinary pH*.

Types of Renal tubular acidosis(RTA)

- **Type I** Distal RTA: defective proton (H+) secretion.

- **Type II** Proximal RTA: defective HCO3 reabsorption.

Type III ➔ is extremely rare, has features of type 1 + 2

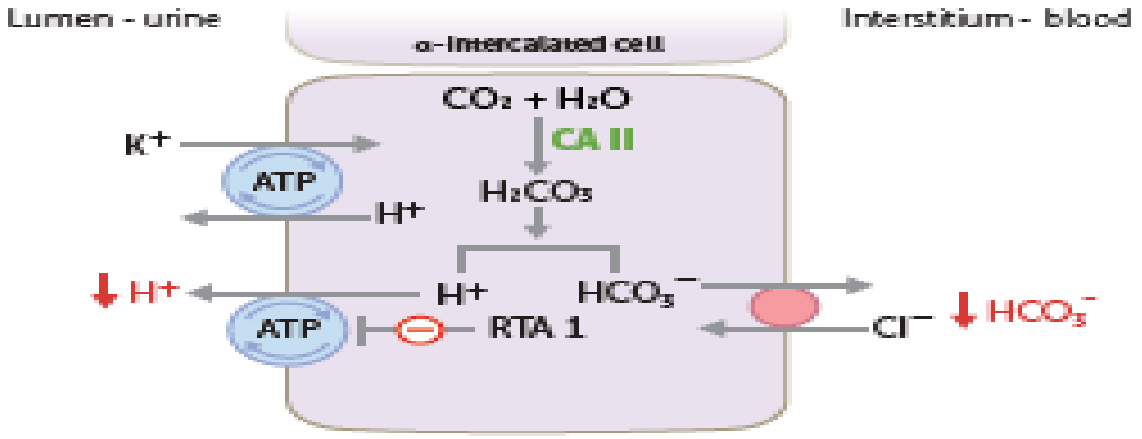
- **Type IV** Distal hyperkalemic RTA: hypoaldosteronism.

All three types are associated with a hyperchloremic normal anion gap acidosis

Type I Distal RTA

- Distal RTA results from Inability of α-intercalated cells to secrete H+ So no new HCO3 is generated results in metabolic acidosis .

In the absence of alkali therapy, progressive hydrogen ion retention leads to a fall in plasma bicarbonate concentration that is accompanied by an **abnormally high urine pH.**



CAUSES OF DISTAL RTA I

1. **Primary**
- Sporadic
- Inherited

2. **Secondary**
- Intrinsic renal
- Urologic
- Toxins or medications

PRIMARY INHERITED CAUSES OF DISTAL RTA I

Inherited renal diseases	Inherited syndromes associated with type I renal tubular acidosis
• Autosomal dominant late presentation • Autosomal recessive presentation at infancy	• Marfan syndrome • Wilson syndrome • Ehlers-Danlos syndrome • Familial hypercalciuria

SECONDARY CAUSES OF DISTAL RTA I

Intrinsic Renal	Urologic	Toxins or medications
• Interstitial nephritis • Pyelonephritis • Sickle cell nephropathy • Lupus nephritis • Nephrocalcinosis	• Obstructive uropathy • Vesicoureteral reflux	• Amphotericin B • Lithium • Cisplatin

Distal RTA features

- Non-anion gap metabolic acidosis.
- Urinary pH > 5.5 ➔ differentiates rta 1 from other types
- Hypokalemia
- Hyperchloremia
- Hypercalciuria
- Hypocitraturia
- Bone disease

- The clinical manifestations of distal RTA vary depending upon the underlying etiology.

➢ The recessive genetic forms present in infancy.

➢ The dominant form later in life.

➢ Acquired distal RTA may occur at any age based upon the timing of renal tubular injury

Clinical manifestation

Due to loss of calcium salts from bones	• **Failure to Growth/ due to electrolyte imbalance similar to other rta** • **Rickets**
symptoms of severe acidosis or hypokalemia	• **Polyuria similar to other rta** • **Polydypsia similar to other rta** • **Weakness/fatigue**
Due to hypercalciuria+hyporcitruria	• **Nephrolithiasis** • **Nephrocalcinosis**

Management

The goals of RTA therapy are to improve growth, correct metabolic bone disease, prevent nephrolithiasis and nephrocalcinosis, and control any underlying disease process. Alkali therapy (potassium citrate or sodium bicarbonate): This is required for all forms of RTA, with the goal of a normal plasma HCO3 level.

-Patients with distal RTA generally require only 2 to 3 mEq of alkali/kg/day. However, infants may also experience some increased urinary bicarbonate wasting and require up to 10 mEq/kg per day.

Administration of alkali

- This is usually approximately 2-3 mEq/kg/d and can be administered in any form, although the preferred form is as potassium citrate.
- Correction of acidosis usually corrects the hypokalemia, but K^+ supplements may be necessary.

Type IV Distal hyperkalemic RTA

- It is uncommon in children and is usually due to either aldosterone deficiency or tubular resistance to the action of aldosterone, called pseudo-hypoaldosteronism (mineralocorticoid deficiency).

- hypoaldosteronism is typically characterized by hyperkalemia and mild acidosis (serum bicarbonate above 17 mEq/L) leads to subnormal net acid excretion due to very low rates of NH_4^+ excretion.

- Unlike adults, in whom the most common causes for a lack of response to aldosterone are kidney damage due to diabetic nephropathy or chronic interstitial nephritis.

- hypoaldosteronism in children is more likely to be **due to drugs that impair aldosterone release or function.**

-These include heparin, non-steroidal anti-inflammatory agents, angiotensin inhibitors, trimethoprim, calcineurin inhibitors (cyclosporine and tacrolimus), and potassium sparing diuretics (eg, spironolactone).

- Other clinical features in children with hypoaldosteronism may include failure to thrive and hyponatremia because of sodium loss.
- The different causes of hypoaldosteronism can be differentiated by measurement of plasma renin activity (PRA), serum aldosterone, and serum cortisol.

- Hyperkalaemia distinguishes this form from types I and II.
- There are five subtypes of type IV RTA but the predominant feature is aldosterone deficiency or unresponsiveness.
- One form in children occurs with obstructive uropathy and renal insufficiency.
- This causes a defect leads to hyporeninemia with secondary hypoaldosteronism.
- Children with this form of RTA may present with failure to thrive.

Management

- They need chronic treatment for hyperkalemia with sodium-potassium exchange resin (Kayexalate).

- Fludrocortisone

- restricting potassium intake
- avoid dehydration
- using diuretics that increase potassium loss and stop potassium sparing drug

Proximal Type (RTA II)

- Proximal RTA is caused by a Defect in proximal tubule absorption of bicarbonate
- The main contrast between this type and type 1 is the alpha intercalated cells in collecting tubules can acidify the urine and which decrease the urine PH<5.5 ,but this secretion can’t over come the increased secretion of bicarbonate which will cause Non-anion gap metabolic acidosis
- Proximal RTA may present either as an isolated tubular defect or as a component of a generalized proximal tubular disorder called the Fanconi syndrome

Proximal Type (RTA II)/2

- Primary:
  - Isolated:
  - Sporadic
  - Autosomal dominant
  - Autosomal recessive
  - Fanconi syndrome

Proximal Type (RTA II)/3

- Secondary:
  - Multiple myeloma
  - Amyloidosis
  - Paroxysmal nocturnal hemoglobinuria
  - Toxins

clinical manifestation

Patients with isolated, sporadic, or inherited pRTA present with growth failure in the 1st yr of life.

Patients with primary Fanconi syndrome have additional symptoms, secondary to phosphate wasting, such as rickets

Those with systemic diseases present with additional signs and symptoms specific to their underlying disease

clinical manifestation

- Depending on the nature of the underlying disorder, laboratory evidence of chronic renal insufficiency, including elevated serum creatinine, may be present.
- Urinalysis in patients with isolated proximal RTA is generally unremarkable. The urine pH is acidic (<5.5) because distal acidification mechanisms are intact in these patients.
- Urinary indices in patients with Fanconi syndrome demonstrate varying degrees of phosphaturia, aminoaciduria, glycosuria, uricosuria, and elevated urinary sodium or potassium.

Approach to RTA

- History &Physical examination:
  - History: A detailed history asking about :
  - Growth and development(Failure to thrive)
  - Recent or recurrent diarrheal illnesses
  - And a family history of mental retardation and ocular abnormalities (AR)
  - End-stage renal disease,

Approach to RTA/2

- Physical examination:
  - Determine growth parameters and volume status
  - Look for any dysmorphic features suggesting an underlying syndrome

Approach to rta/3

- Lab Findings:
  - Serum electrolytes, blood urea nitrogen, calcium, phosphorus, creatinine, and pH should be obtained by venous puncture.
  - Confirm the presence of a normal anion gap metabolic acidosis and rule out other causes of bicarbonate loss such as diarrhea
  - Values of anion gap <12 demonstrate the absence of an anion gap. Values of >20 indicate the presence of an anion gap(>20 ➔ its not RTA). If such an anion gap is found, then other diagnoses (lactic acidosis, inborn errors of metabolism ingested toxins)is investigated

Approach to rta/4

- If the lab results was:
  - Hyperkalemic acidosis is consistent with type IV RTA
  - Hypokalemic and urine pH <5.5 in the presence of acidosis suggests pRTA
  - Hypokalemic whereas patients with distal RTA typically have a urine pH >6.0.
- A urinalysis should also be obtained to determine the presence of glycosuria, proteinuria, or hematuria, suggesting more global tubular damage or dysfunction.
- Random or 24 hr urine calcium and creatinine measurements will identify hypercalciuria.
- Renal ultrasonography should be performed to identify underlying structural abnormalities

***The most common cause of non ionic gap acidosis if diarhea, in diarhea if we give fluids➔ good response.

TABLE 13-7. CLINICAL AND LABORATORY MANIFESTATIONS OF VARIOUS RENAL TUBULAR ACIDOSES

	Type 1 (Classic, Distal)	Type 2 (Proximal)	Type 4 (Aldosterone Deficiency)
Growth failure	+++	++	+++
Serum potassium	Normal or low	Normal or low	High
Nephrocalcinosis	Frequent	Rare	Rare
Low citrate excretion	+++	±	±
Fractional excretion of filtered HCO_3 at normal serum HCO_3 levels	<5%	5%-10%	<10%
Daily alkali treatment (mEq/kg)	1-3	5-20	1-3
Daily potassium requirement	Decreases with correction	Increases with correction	
Urine pH	>5.5	<5.5	<5.5
Presence of other tubular defects	Rare	Common	Rare

TABLE 24-4 Types of Renal Tubular Acidosis

	Distal type 1	Proximal type II	Type IV
Urine anion gap	Positive	Negative	Positive
Urine ammonia	Low	Appropriately high	Low
Plasma potassium	Low	Low	High
Urine pH (when acidotic)	>6	<6	<6
Defect	Abnormal H^+ pump	Abnormal HCO_3 transport	Low distal sodium transport, low aldosterone
Treatment	Bicarbonate	Investigate and treat underlying disease	Fludrocortisone (Florinef), surgery
Examples	Amphotericin, nephrocalcinosis	Fanconi syndrome (e.g., cystinosis), heavy metal poisoning, drugs (e.g., ifosfamide), primary hyperparathyroidism	Obstructive uropathy, chronic dehydration

Treatment

- The mainstay of therapy in all forms of RTA is bicarbonate replacement.
- Patients with pRTA often require large quantities of bicarbonate, up to 20 mEq/kg/24 hr, in the form of sodium bicarbonate or sodium citrate solution
- The base requirement for distal RTAs is generally in the range of 2-4 mEq/kg/24 hr, although patients' requirements can vary.
- Patients with distal RTA should be monitored for the development of hypercalciuria.
- Symptomatic hypercalciuria (recurrent episodes of gross hematuria), nephrocalcinosis, or nephrolithiasis can require thiazide diuretics to decrease urine calcium excretion
- Patients with type IV RTA can require chronic treatment for hyperkalemia with sodium-potassium exchange resin (Kayexalate).

Prognosis

- Prognosis of RTA depends to a large part on the nature of any exist- ing underlying disease :
  - Patients with treated isolated proximal or distal RTA generally demonstrate improvement in growth, provided serum bicarbonate levels can be maintained in the normal range
  - Patients with systemic illness and Fanconi syndrome can have ongoing morbidity with growth failure, rickets, and signs and symptoms related to their underlying disease.

Fanconi Syndrome (Renal Fanconi)

- Fanconi Syndrome is a generalized proximal tubular defect that results in excess amounts of glucose, bicarbonate, phosphates ,uric acid, potassium, and certain amino acids being excreted in the urine.
- The genetic causes of Fanconi syndrome can be primary or secondary to systemic diseases

Fanconi Syndrome

- Primary Fanconi syndrome is caused by a missense mutation in Na phosphate cotransporter (NaPi-II) of the proximal tubular apical membrane
- The secondary causes of Fanconi syndrome include:
- Inherited cystinosis(Most common)
- Galactosemia
- Hereditary fructose intolerance,
- Tyrosinemia,
- Lowe syndrome
- Alport syndrome,
- Wilson disease

CLINICAL PRESENTATION

- Due to the decreased ability of the reabsorb, probably the patient will be presented with polyuria and polydepisa in addition to the signs of dehydration
- Phosphaturia: the trademark of the fanconi syndrome is reduction in phosphate level and phosphate reabsorption which will lead to bone disease like malacia and rickets
- RTA due to decreased absorption of $HCO3^-$

CLINICAL PRESENTAION/2

A. Potassium and sodium wasting which can lead to hyotension and headaches in addition to muscle weakness due to the hypokalemia.
B. Amino aciduria due to the inability to reabsorb some amino acids
C. Proteinuria: Low molecular weight proteins usually found
D. But the most important presentation is Failure to thrive which is caused by the multiple metabolic abnormalities present in this condition(acidosis and disturbances in mineral and vitamin D metabolism).

Fanconi syndrome And metabolic disorders

- Cystinosis :
  - Rare AR
  - Caused by mutations in the CTNS gene, located on chromosome 17, that codes for cystinosin, the lysosomal membrane-specific transporter for cystine.
- Abnormal accumulation of the amino acid Cystine in the lysosomes, eventually leading to intracellular crystal formation throughout the body
- Intracellular cystine profoundly disturbs cellular oxidative metabolism and glutathione status, leading to altered mitochondrial energy metabolism, autophagy, and apoptosis.
- Its the most common cause of Fanconi syndrome in pediatric age group

Clinical pattern of cystinosis

- Infantile or nephropathic cystinosis :
- More severe type , present in the first 2 years of life
- Characterized by the presence of large amounts of cystine in all cells, including the kidneys.
- Children with Cystinosis usually have a fair complexion and blond hair.
- The first symptoms are polyuria and polydipsia, followed by episodes of dehydration, anorexia, and failure to thrive. The metabolic and renal features are detectable after the first few months of life

- Photophobia, which is caused by the deposition of cystine crystals in the cornea, usually appears in children aged 3- 6 years. Retinopathy is a later finding.
- Cystinosis ends up with chronic renal failure if it left untreated

- Benign, or adult, cystinosis is characterized by the deposition of relatively low amounts of cystine in the cornea and bone marrow. The kidneys are spared, and the renal manifestations are absent.

Treatment of cystinosis

- Give the pt Cystamine to decrease intralysosomal cystine accumulation
- In the absence of treatment, the disease leads to chronic renal failure by the end of the first decade of life
- Dialysis and transplantation can be successfully performed in these children.

Patients Always progress to renal failure.

Approach

- History & Physical Examination:
- History:
- Polyuria &Polydipsia(signs of dehydration)
- Failure to Thrive(multiple metabolic abnormalities present in this condition)
- Bone abnormalities(phosphaturia & calcinuria)
- Muscle weakness(hypokalemia)
- Exposure to drugs or heavy metals (lead) or specific drugs
- Family history of renal disease or kidney transplant
- Consinguity between parents
- If the patient have other genetic disorders

- Physical examination:
  - signs of dehydration(dry skin and pallor)
  - Bone abnormality due to rickets(bowing of legs, craniotabes)
  - Hepatomegaly seen in Galactosemia, Tyrosinemia and cystinosis
  - Cystine deposit on the cornea

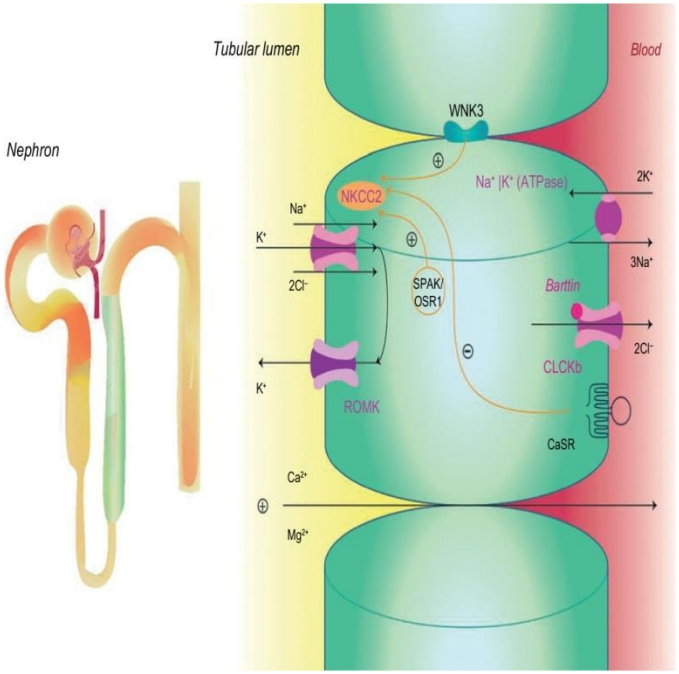
  - Lab findings:
  - Serum electrolytes and blood gas:
  - Hypophosphatemia,
  - Hypouricemia
  - Hyponatremia, Hypokalemia .
  - Metabolic acidosis .
  - Urine analysis:
  - Increased secretion of Glucose, Uric acid , Phosphate , Amino acids , Citrate, Calcium , K and proteins.
  - Measuring enzyme levels can help in ruling out specific disorder like Cystinosis
  - Checking drug levels or heavy metal levels in blood or urine can help in finding the acquired cause of Fanconi syndrome.
  - On CXR you may see rachitic rosary sign on the patient costochondral junction

Treatment

- The only accurate way to treat Fanconi syndrome is indirectly by the treatment of the cause of the syndrome
- General measures include avoidance of dehydration and replacement of lost electrolytes including potassium, phosphate, bicarbonate and vitamin D (prefered in active form)
- If a medication causes the condition or if heavy metal poisoning is suspected, it strongly recommended to avoid or eliminate the harmful substance.
- Kidney transplant if renal failure occur

Bartter Syndrome

- is an **autosomal recessive** disease characterized by a defect in the thick ascending limb of the loop of Henle, which results in low potassium levels (hypokalemia), increased blood pH (alkalosis), and normal to low blood pressure.



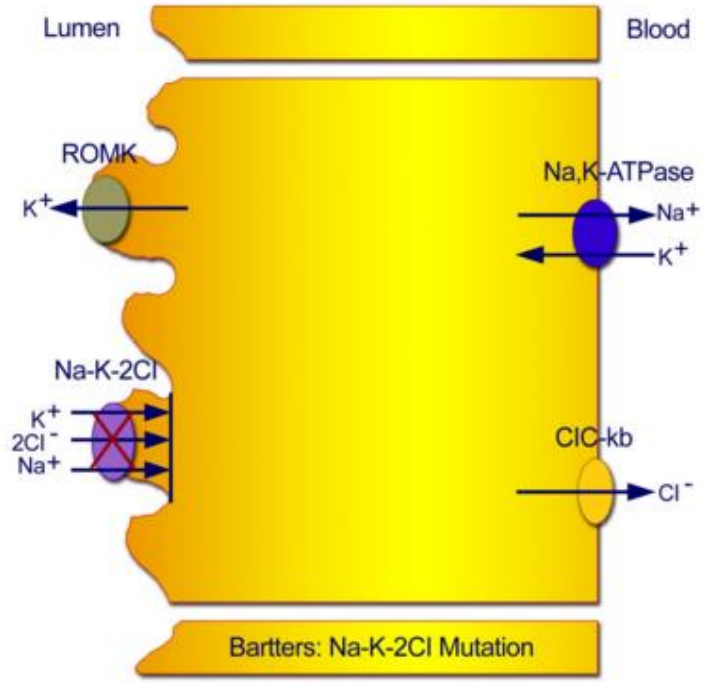
Pathophysiology

- The loss of sodium and chloride, with resultant volume contraction, stimulates the renin–angiotensin II–aldosterone axis.
- Aldosterone promotes sodium uptake and potassium secretion, exacerbating the hypokalemia.
- It also stimulates hydrogen ion secretion distally, worsening the metabolic alkalosis.
- Hypokalemia stimulates prostaglandin synthesis, which further activates the renin–angiotensin II–aldosterone axis.

- In addition, **the paracellular reabsorption** of both **calcium and magnesium** in the thick ascending limb requires the electrochemical gradient created by sodium chloride transport in this tubule segment , Thus, abnormal sodium chloride transport in the thick ascending limb increases renal calcium and magnesium excretion.
- As a result, urinary calcium excretion is normal or increased, and hypomagnesemia often develops (usually mild).

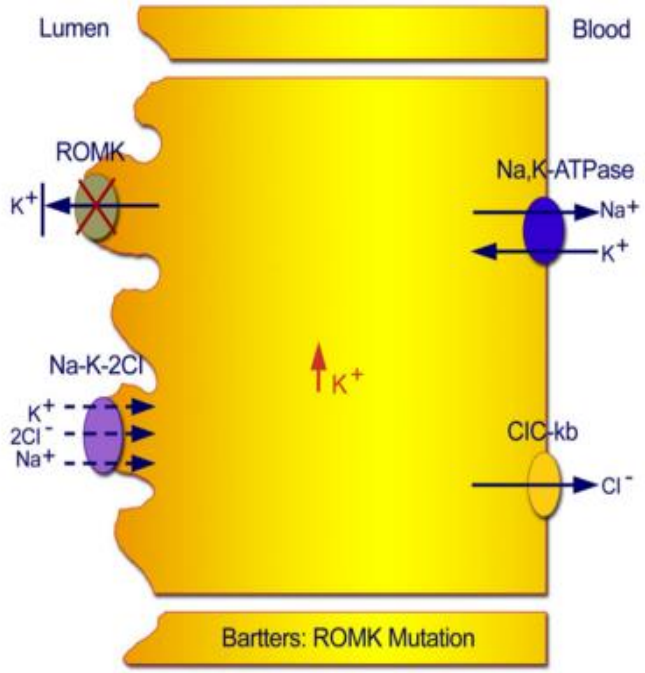
Type I Bartter syndrome

Type I neonatal Bartter syndrome. Mutations in the sodium chloride/potassium chloride cotransporter gene result in defective reabsorption of sodium, chloride, and potassium.



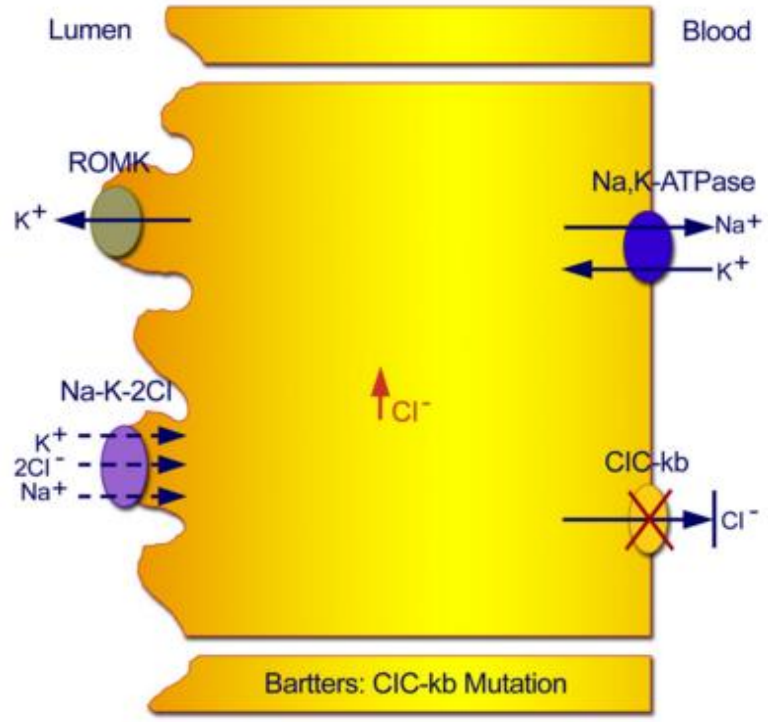
Type II Bartter syndrome

Type II neonatal Bartter syndrome. Mutations in the ROMK gene result in an inability to recycle potassium from the cell back into the tubular lumen, with resultant inhibition of the sodium chloride/potassium chloride cotransporter.



Type III Bartter syndrome (classic type)

Classic Bartter syndrome. Mutations in the ClC-kb chloride channel lead to an inability of chloride to exit the cell, with resultant inhibition of the sodium chloride/potassium chloride cotransporter.



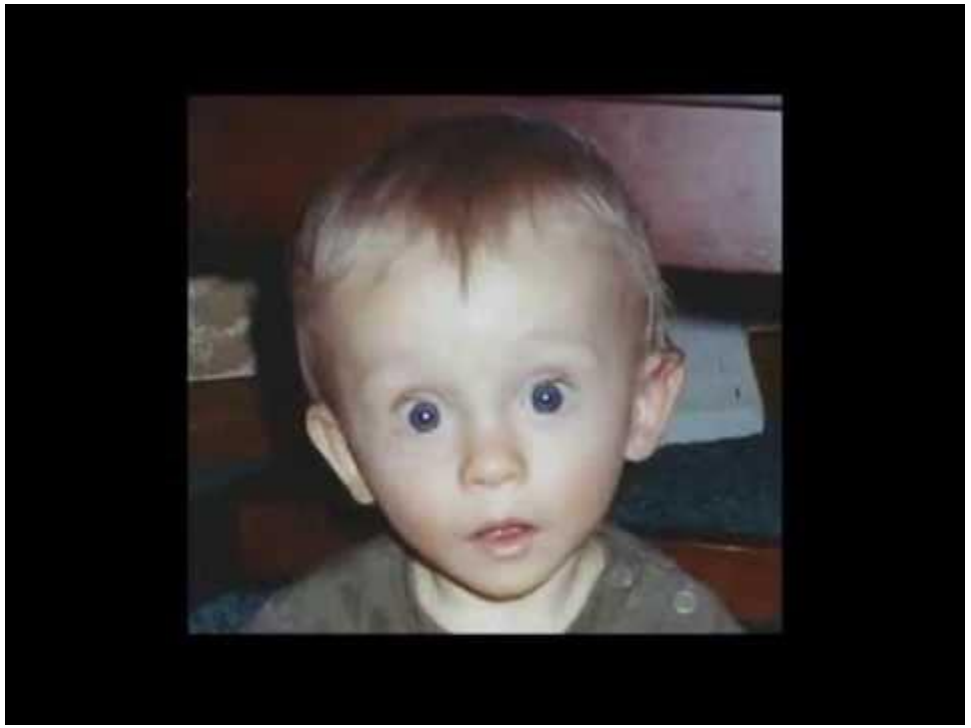
Type IV

- have defects that involve both the ClC-Ka and ClC-Kb and cause severe disease, generally with **antenatal presentation** and **congenital hearing problem** because These two chloride channels are critical for normal ion transport in the inner ear and are vital to establish normal endocochlear potential differences .
- Patients with type IV Bartter syndrome develop nephrocalcinosis less commonly than those with other Bartter subtypes. **However, they more often develop progressive kidney dysfunction.**

Clinical presentation

- Polyuria
- Polydipsia
- Constipation
- Salt craving
- Failure to thrive
- nonspecific fatigue,
- dizziness
- A history of maternal polyhydramnios with or without prematurity may be elicited

- Dysmorphic features :
  - Triangular face
  - Large eyes with strabismus
  - Drooping mouth
  - Protruding ears



Diagnosis

- The diagnosis is usually made based on clinical presentation and laboratory findings.
- The diagnosis in the neonate or infant is suggested by severe hypokalemia, usually <2.5 mmol/L, with metabolic alkalosis.
- Hypercalciuria is typical; hypomagnesemia is seen in a minority of patients .

Treatment

- Preventing dehydration
- Maintaining nutritional status
- Correcting hypokalemia (High dose potassium supplementation)
- Indomethacin (prostaglandin inhibitors)
- Infants and young children may require sodium supplementation as well

K+ is very low and doesn’t improve

Pts. Have adaptation with low k+ and doesn’t improve with ttt.

Gitelman syndrome

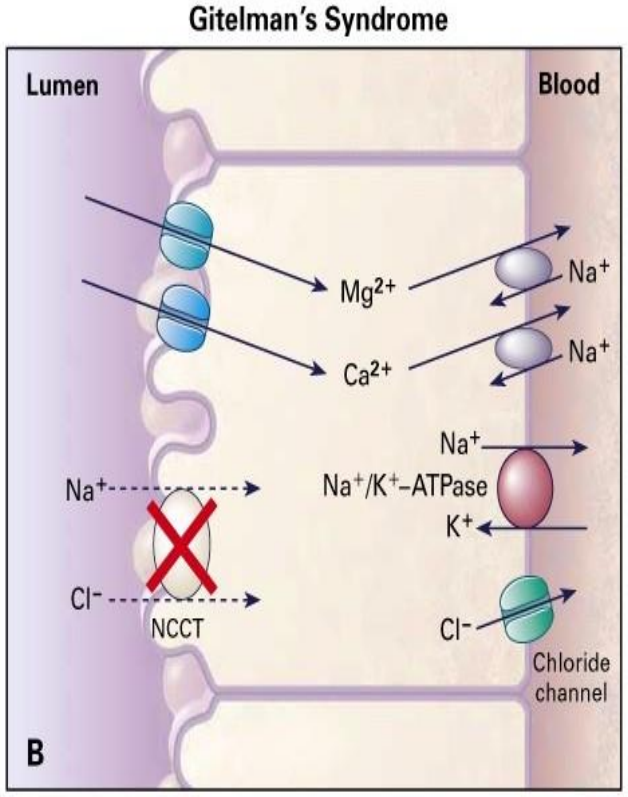
- **Gitelman syndrome** (often called a “Bartter syndrome variant”) is a rare **autosomal recessive** cause of hypokalemic metabolic alkalosis,

with distinct features of **hypocalciuria** and **hypomagnesemia.** Patients

with Gitelman syndrome typically present in late childhood or early adulthood .

- The biochemical features of Gitelman syndrome resemble those of chronic use of thiazide diuretics. Thiazides act on the sodium chloride cotransporter NCCT, present in the distal convoluted tubule.

- Genetic mutations along the sodium chloride cotransporter , lead to inadequate transport of multiple electrolytes along this channel such as sodium ,chloride ,calcium , magnesium, and potassium.



Clinical presentation

❖Asymptomatic

❖Symptomatic :

- Cramps of the arms and legs, due hypokalemia and hypomagnesemia
- History of Muscle weakness, spasms, and cramps
- Fatigue, which may be severe
- polyuria and nocturia
- electrolyte imbalances, irregular heartbeats (cardiac arrhythmias)

Adult presentation ==> so no failure to thrive.

Diagnosis

The diagnosis of Gitelman syndrome is suggested in an adolescent or adult presenting with :

- hypokalemic metabolic alkalosis
- hypomagnesemia
- hypocalciuria.

❑ Molecular genetic testing can confirm a diagnosis of Gitelman syndrome.

Treatment

- Therapy is directed at correcting hypokalemia and hypomagnesemia

with **supplemental potassium and magnesium.**

- Sodium supplementation or treatment with prostaglandin inhibitors is generally not necessary because patients typically do not have episodes of volume depletion or elevated prostaglandin E excretion

Liddle Syndrome

Diagnosis ???

Liddle's Syndrome

Hypertension (due to volume expansion as well as excessive sodium retention)

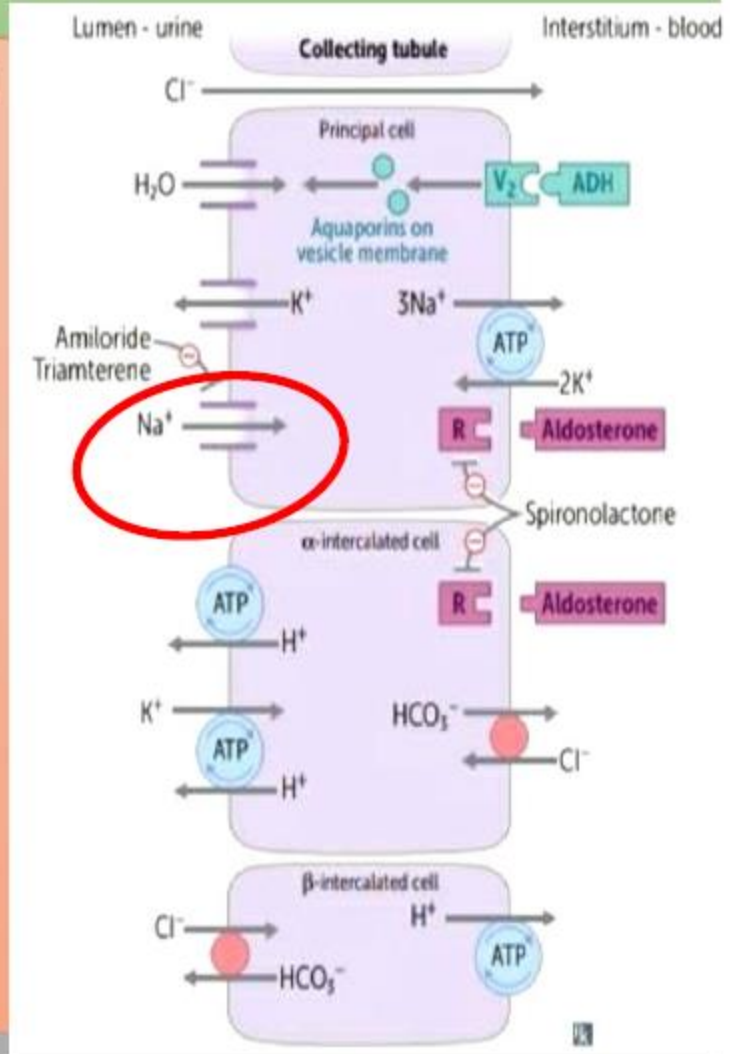
Hypernatremia

Hypokalemia

Alkalosis

Decrease renin

Decrease aldosterone



Liddle's syndrome= Hypokalemia + Hypertension

- **Liddle syndrome** is an **autosomal dominant** disorder
- that results from a mutation of the distal nephron sodium channel that is normally upregulated by aldosterone.
- Patients have the characteristics of hyperaldosteronism, hypertension, hypokalemia, and alkalosis—but low serum aldosterone levels.

- Mutation in **beta** or **gamma** subunits of the epithelial sodium channel (ENaC) leads to an **increased activity** of this channel, **independent of aldosterone activity**.

- Liddle Syndrome is primarily characterized by **severe, early-onset RESISTANT hypertension➔ in infancy, requiring 2-3 medications**
- Affected people have **hypokalemia** and **metabolic alkalosis.**
- Symptoms of **hypokalemia** can include weakness, fatigue, muscle pain (myalgia), constipation or heart palpitations.

- **In most cases, the condition becomes apparent at a young age but some affected people are not diagnosed until adulthood .**

Lab findings

- Hypokalemia
- Aldosterone and renin levels are suppressed but all steroid hormone levels are normal.
- Urine tests to identify low levels of sodium and aldosterone
- Genetic testing to look for a (mutations)
  in the SCNN1B or SCNN1G gene

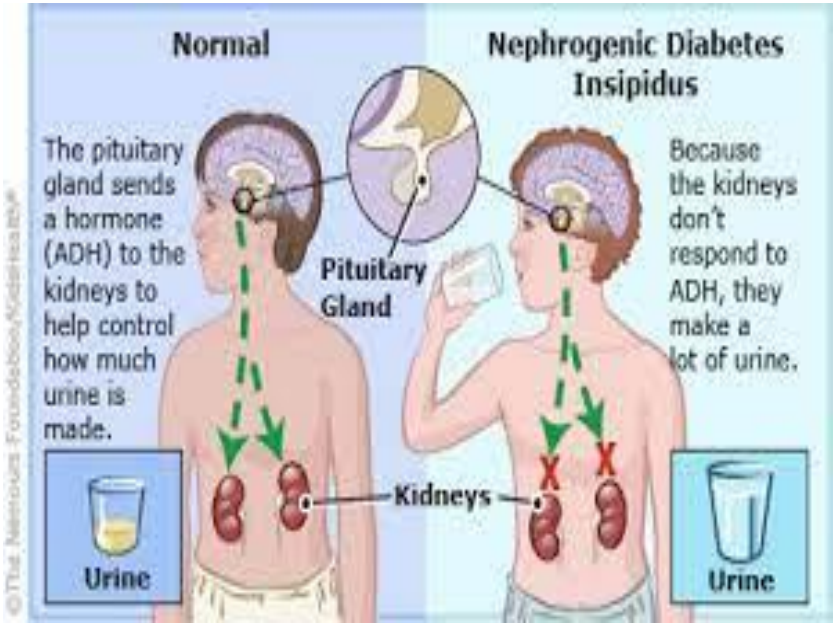
Treatment by

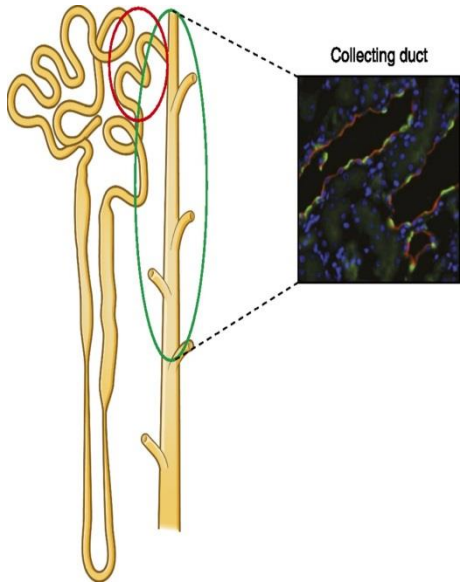
- Low salt diet
- Potassium supplements
- Sodium channel blockers :

❑Amiloride is prescribed daily with a dose ranges from 5 to 20 mg.

❑ Triamterene, another potassium-sparing diuretic, similar to amiloride can also be used to manage this syndrome

Nephrogenic Diabetes Insipidus





Nephrogenic Diabetes Insipidus:

Where the collecting ducts in the kidney don't respond to ADH in blood stream.

- Nephrogenic diabetes insipidus (NDI) **can be a rare congenital or, more commonly, acquired disorder**
- **characterized by an inability to concentrate urine, even in the presence of antidiuretic hormone (ADH).**

- The most common pattern of inheritance in congenital NDI is

as **an X-linked** disorder.

- 10% of cases of congenital NDI are inherited as **autosomal dominant** or **recessive** disorders.

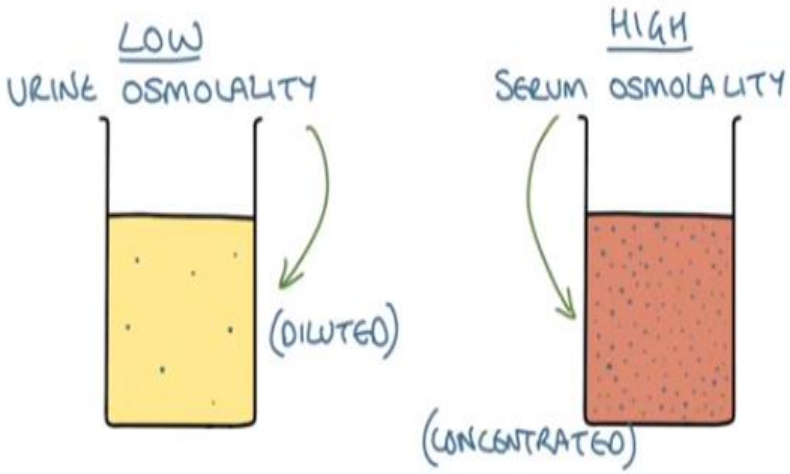
- **It can be caused by:**
- Drugs, particularly ***lithium*** used in ***bipolar affective disorder***
- Mutations in the **AVP R2** gene on **X-chromosome** that codes for the ADH receptor
- Intrinsic kidney disease
- Electrolyte disturbance (hypokalaemia and hypercalcaemia)

Clinical manifestations

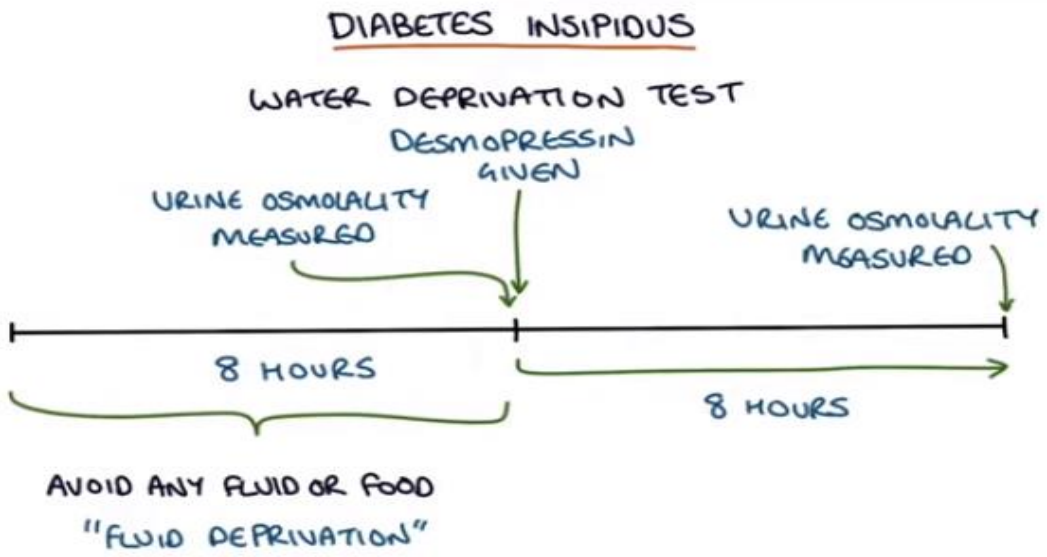
- Massive polyuria
- Hypernatremia ; because there is a too much water loss
- Decreased appetite and poor food intake➔ the pt. Is not interested in food, the pt. only needs water➔ leading to Failure to thrive (FTT) .
- Irritability and crying
- Constipation and poor weight gain are also seen
- Enuresis :intermittent urinary incontinence during sleep in a child ; caused by large urine volume
- patients can also have developmental delay and mental retardation.

Investigations

- Low urine osmolality
- High serum osmolality
- Water deprivation test

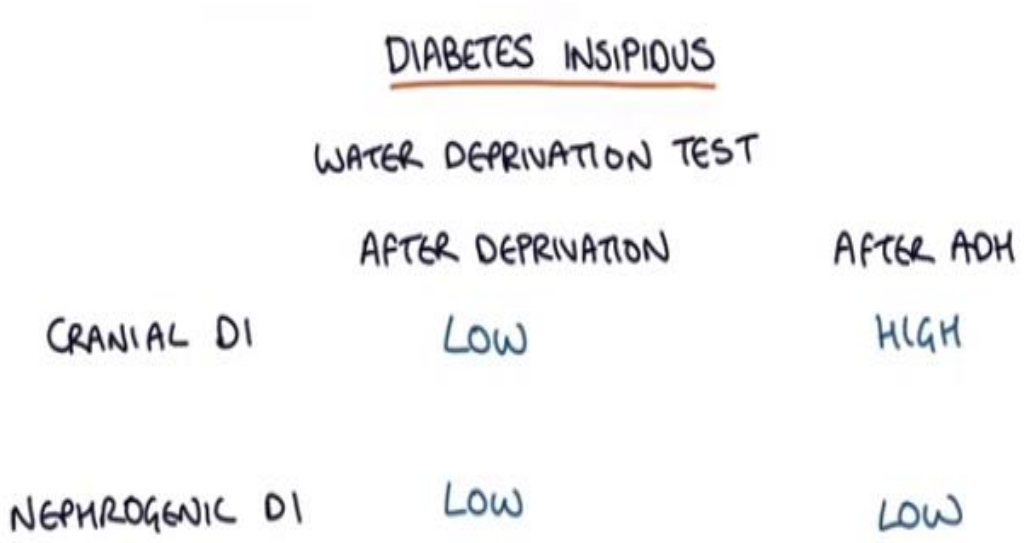


Water Deprivation



- The ***water deprivation test*** is also known as ***desmopressin stimulation test***. This is the test of choice for diagnosing ***diabetes insipidus***.
- **Method :**

Initially the patient should avoid taking in any fluids for 8 hours. This is referred to as ***fluid deprivation***. Then, ***urine osmolality*** is measured and ***synthetic ADH*** (***desmopressin***) is administered. 8 hours later ***urine osmolality*** is measured again.



- In ***nephrogenic diabetes insipidus*** the patient is unable to respond to ADH. They are diluting their urine with the excessive water secretion by the kidneys. Therefore the ***urine osmolality*** will be low initially and remain low even after the synthetic ADH is given.

Depprevation test is very risky, needs an advanced center to preform the test in, because we aggravate

TREATMENT

- maintenance of adequate fluid intake and access to free water
- minimizing urine output by limiting solute load with a low-osmolar and low-sodium diet
- administering of medications directed at decreasing urine output

- For infants, human milk
- formula, such as Similac PM 60/40, is preferred.
- Most infants with congenital NDI require gastrostomy or nasogastric feedings to ensure adequate fluid administration throughout the day and night.

- Thiazide diuretics (2-3 mg/kg/24 hr of hydrochlorothiazide) effectively induce sodium loss and stimulate proximal tubule reabsorption of water. (paradoxical phenomena)
- Potassium-sparing diuretics, in particular, amiloride (0.3 mg/kg/24 hr in 3 divided doses), are often indicated.
- indomethacin (2 mg/kg/24 hr), in Patients who have an inadequate response to diuretics alone

Thank You