Renal Tubular Acidosis

By

Prof. Amr Sarhan

Mansoura University

Renal Tubular Acidosis

- Renal tubular acidosis (RTA) is not a single disease, rather it is a biochemical state with clinical consequences that occurs during the course of many tubular disorders (inherited or acquired).
- RTA is characterized by normal anion gap metabolic acidosis, usually associated with normal or near normal glomerular filtration rate.
- In medical practice, RTA is a *tough* subject.

Tough Subject

- Diagnosis of RTA does not depend on clinical assessment, rather it depends mainly on laboratory assessment.
- Laboratory assessment is important not only for diagnosis but also for dose adjustment during treatment and patient's follow up
- Laboratory assessment in RTA is problematic …. ***Why?***

Problems of Lab. Assessment

- Normal values of ***urinary contents*** (water, electrolytes, minerals and pH) have a wide range. In addition, these values are diet and age dependent.

- Proper assessment of ***urinary contents*** needs:
  - 24h urine collection
  - Challenging tests (water deprivation test,…)
  - Fractional excretion (sodium, K …)
  - Creatinine ratio (Ca/creatinine ratio,…)

Problems of Lab. Assessment

- Lab assessment is not available in many places, in addition ***reference values*** is not standardized, it depends on many factors:
  - Type of sample (plasma, serum, whole blood…arterial, venous, mixed …)
  - Time of sample (morning, evening,..)
  - Method used
- Diagnosis by ***molecular genetics techniques*** is not usually available

Problems of Lab. Assessment

- There are multiple ***units for measurement*** (mg/dl, mEq/L, mmol/L, mOsm/kg/H_2O, specific gravity, osmolality, pH, serum and urine anion gap, osmolar gap, fractional excretion, creatinine ratio,…..etc.) So, interpretation is not simple, it needs good experience .

Important Subject

- It is not uncommon
- Serious
  - Acute life threatening conditions

    Potassium .....Heart
    Sodium .....Brain
    Calcium .....Fits
    Metabolic acidosis

  - Chronic morbidity

    FTT, growth retardation ...
    Bone disease (osteopenia, rickets, ...)
    Renal diseases (nephrocalcinosis, nephrolithiasis,...)

Important Subject

- Response to treatment of isolated RTA is reasonable, provided that serum bicarbonate level is maintained within normal range
- Methods of treatment are usually available, simple and affordable

Important Subject

So,

All pediatricians should be aware of pathophysiology of this subject, when to suspect, how to diagnose and how to manage RTA

Objectives

- Pathophysiology
- Pathogenesis
- When do you suspect RTA?
- Diagnostic work up
- General lines of treatment

Pathophysiology

Function of Kidney

- **The main function of the kidney is *urine formation*, by urine formation the kidney**
  - ***Regulate water, electrolytes and acid base balance.***
  - ***Excrete non-volatile waste products.***

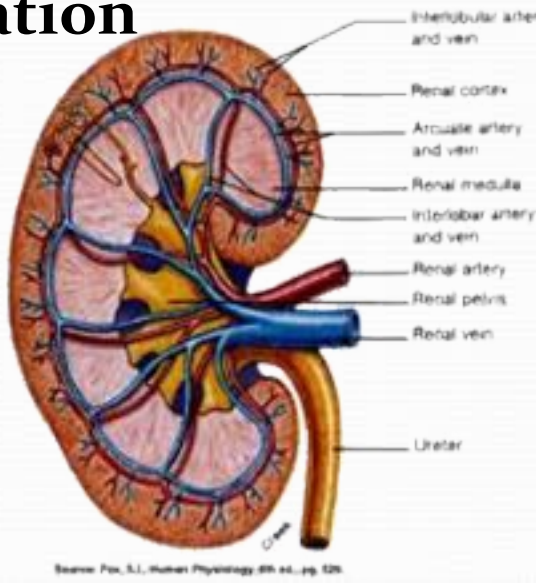
- **Other functions include:**
  - ***Erythropoietin secretion.***
  - ***Regulation of blood pressure through renin.***
  - ***Activation of Vit. D***

How do the kidneys form urine?

- Renal blood flow
- Glomerular filtration
- Tubular function (mainly reabsorption)

Renal Blood Flow

- Renal blood flow = 20-25% total cardiac output
- In adult, it is more than one liter /min
- About 90% of RBF supplies cortex of kidney
- RBF is subjected to restricted autoregulation
- Plasma renal flow = 700ml/min



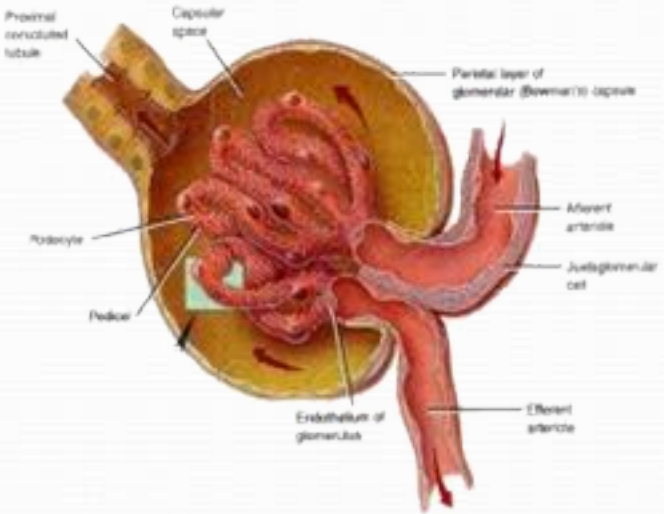
Glomerular Filtration

- **Initial step of urine formation occurs in the glomeruli.**
- **Glomerular filtrate (GF) is formed by filtration across the glomerular membrane an ultrafiltrate identical to plasma minus its protein.**
- **Driving force is pressure gradient between both intracapillary blood pressure and Bowman's space pressure**
- **In adults**

GFR /min = 125ml/min

GFR /hour = 7.5 L/h

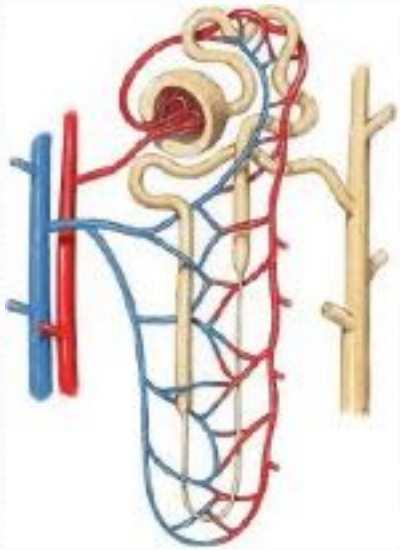
GFR /day = 180 L/day



Tubular Function

- GF from the Bowman's capsule enters renal tubules, where 98 - 99% of GF is *reabsorbed* and only 1 - 2% is excreted as urine.

- The volume (water content) of urine, its pH and electrolyte contents reflect the state of the body regarding these constitutes

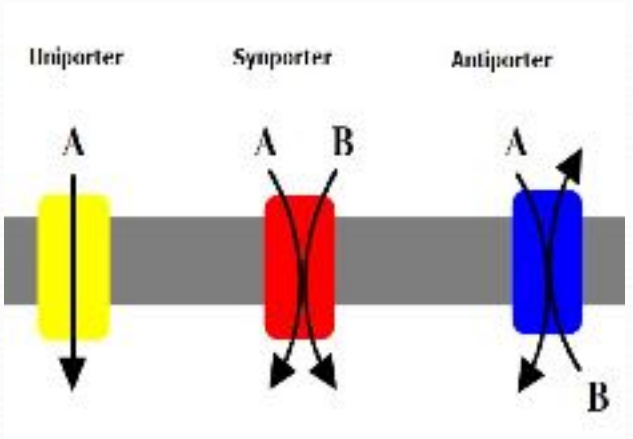


Tubular Function

- **Reabsorption** is the main function of renal tubules, although there is a limited *excretory* tubular function

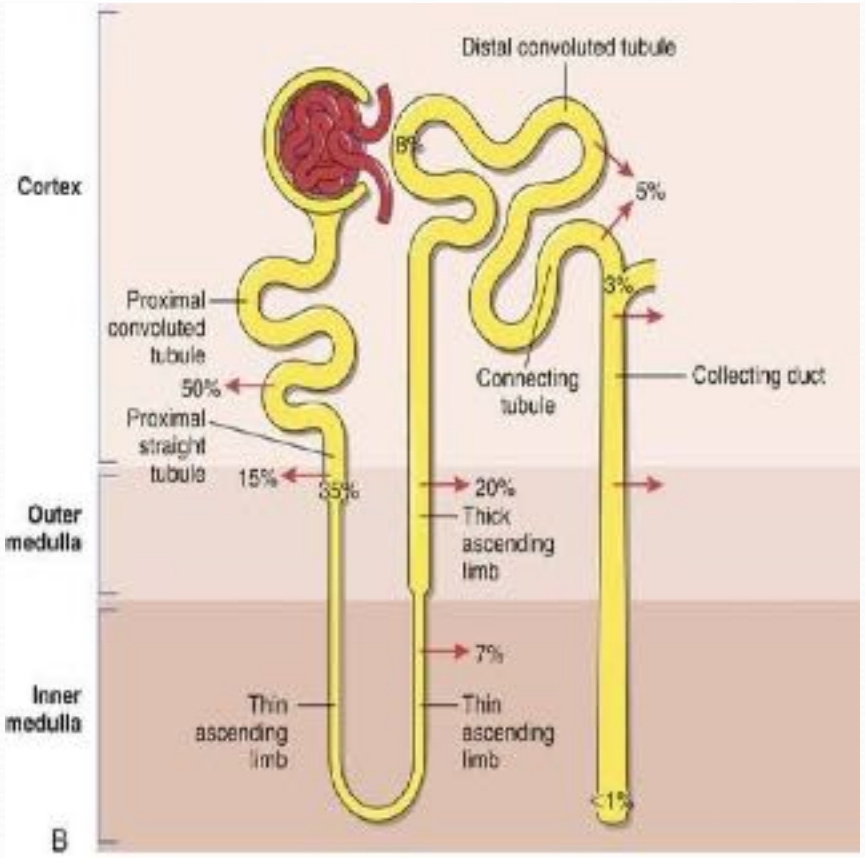
- Solutes reabsorption is an active and controlled process. In certain sites, it is under hormonal control *(ADH, aldosterone, ANP ….)*

- Solutes are transported across cell membrane through: *ionic channels, pumps, transport proteins (carrier proteins)*



Tubular Structure

- Proximal tubules
- Loop of Henle
- Distal tubules
- Collecting ducts
  - Segments
    - Connecting ducts
    - Cortical collecting ducts
    - Medullary collecting ducts
  - Cells
    - Principal cells
    - Intercalated cells



Pathogenesis of RTA

Daily $[H]^+$Load

- **Production :**

  Under normal physiological condition, metabolism of standard Western diet produces a daily hydrogen ions equal to:

  - ***1-2 mEq/kg/24h …….. adults***
  - ***2-3 mEq/kg/24h …….. children***

- **Sources :**

  - ***Protein metabolism***
  - ***Incomplete metabolism of fats and carbohydrates***
  - ***Intestinal secretion of bicarbonate***

Control of $[H]^+$Load

- **$[H^+]$ are buffered to maintain acid- base homeostasis by:**
  - **Dilution with tissue fluids**
    Intracellular and extracellular fluids
  - **Buffering system:**
    Bicarbonate (strong base + weak acid)
    Non-bicarbonate (proteins, phosphates and bones)
  - **Lung → immediate control**
    Immediate effect by removal of CO_2 and maintain Pco_2
  - **kidney → remote control**

Role of Kidney

- **Reclaiming of all filtered HCO_3 at:**
  - **Proximal tubules (90%)**
  - **Loop of Henle and collecting ducts (10%)**

- **Excretion of {H+} at the collecting ducts, {H+} then combine with:**
  - **Remaining filtered HCO_3**
  - **Urinary buffers :**

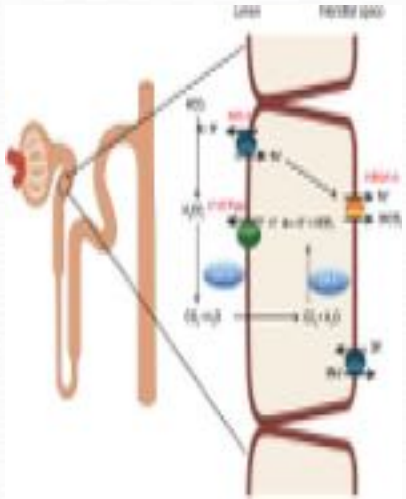
    {H+} + NH_3 (ammonia) → NH_4 (ammonium ion)

    {H+} + HPO_4 → H_2PO_4 (dihydrogen phosphate ion)

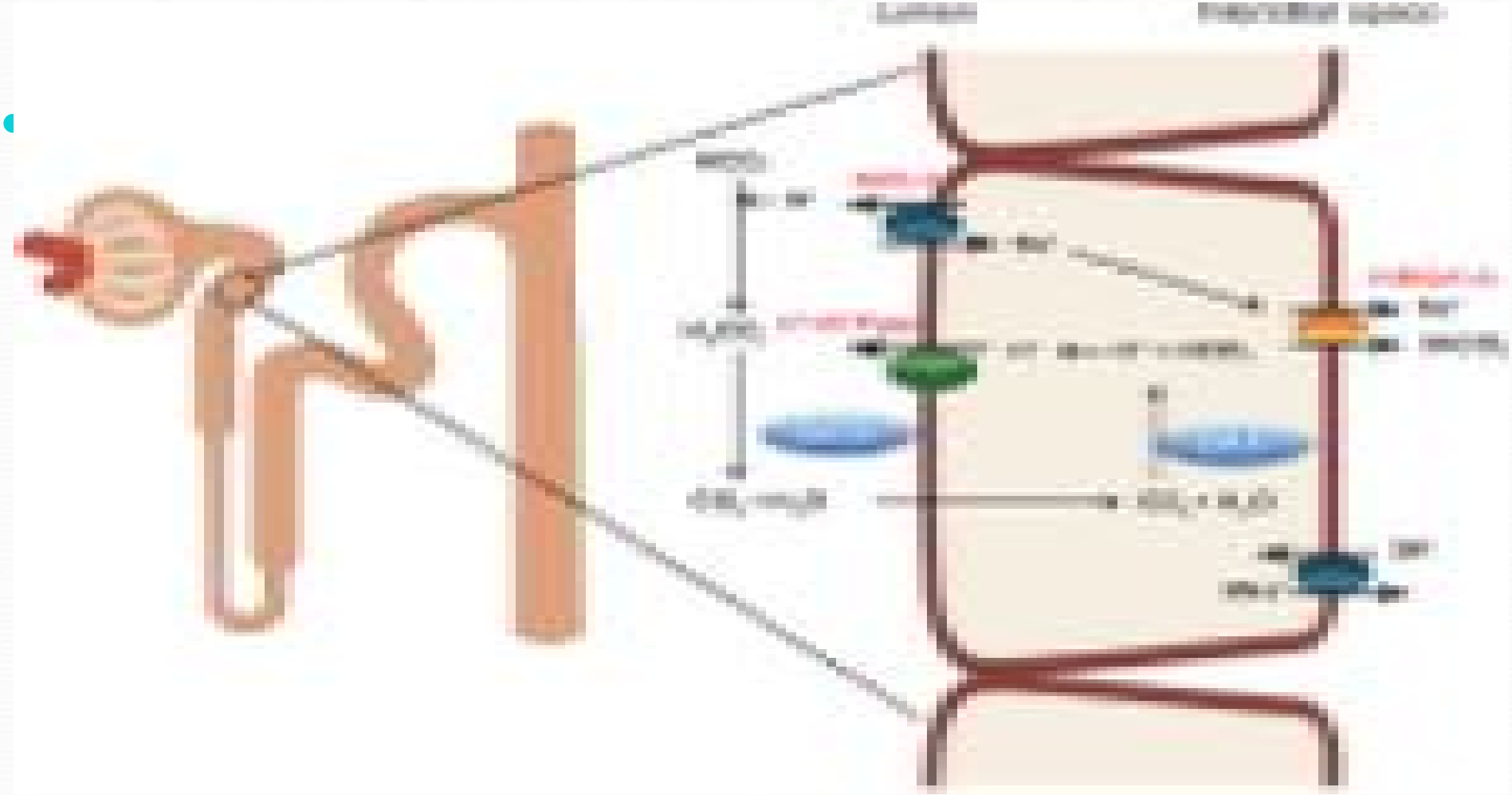
- **Generation of HCO_3**
  - **Glutamic acid → NH_3 + HCO_3**

Reabsorption of Filtered HCO3

- **At the level of proximal tubules**
  - About 90% of filtered bicarbonate is absorbed in PRT.
  - Other solutes (glucose, P, amino acid, low molecular weight protein ….) are absorbed by sodium co-transporters
  - It is an active and controlled process
  - The driving force is NaKATPase



Reabsorption of Filtered HCO3



Proximal RTA (type II)

- **Etiology**

1-Isolated dysfunction due to

Mutation of the gene encoding $Na3HCO_3$ co-transporter

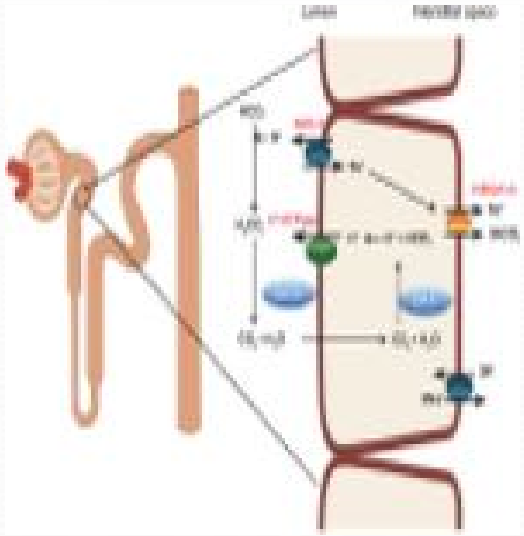
2- Global dysfunction (Fanconi syndrome) due to:

- Inherited syndromes

  Cystinosis, glactosemia, Wilson disease, hereditary fructose intolerance, tyrosinemia, lowe syndrome ….

- Acquired

  Drugs, heavy metals, kwashiorkor, intrinsic renal disease ….



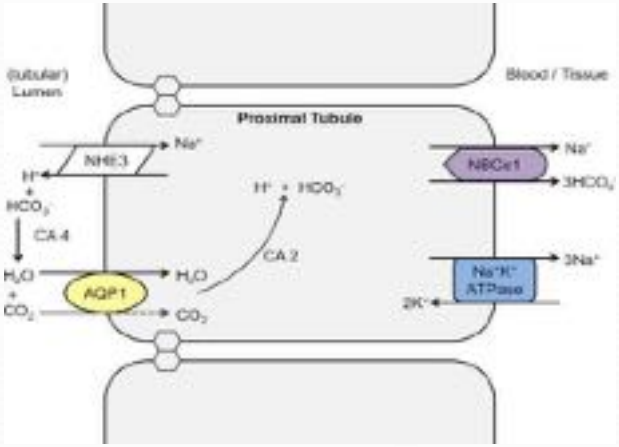
Proximal RTA (type II)

- **Mechanism**

  1- ***Isolated***

  Failure of bicarb. reabsorption at PRT leads to urinary loss of bicarb. and metabolic acidosis. This occurs due to:

  Mutation of gene encoding Na3HCO3 co-transporter



Proximal RTA (type II)

- **Mechanism**

2-Global

Inherited or acquired Fanconi syndrome leads to cell cytopathy of proximal tubules with subsequent

Disruption of energy production …. NaKATPase

Diminished activity of sodium co-transporters

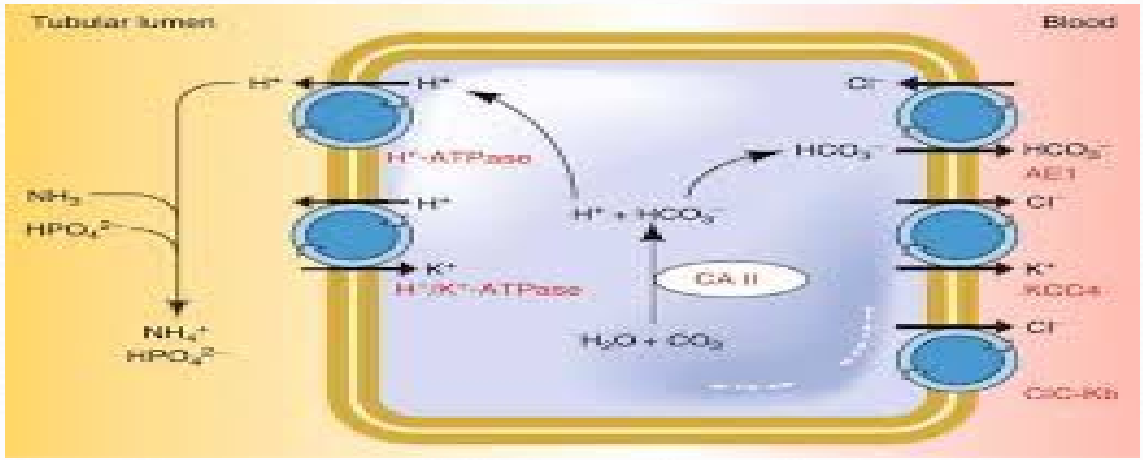
Disruption of endocytic pathway (*Megalin/Cubilin)*

Defective apoptosis

The end result is failure of bicarb. and other solutes reabsorption (glucose, amino acids, P, low molecular weight proteins …)

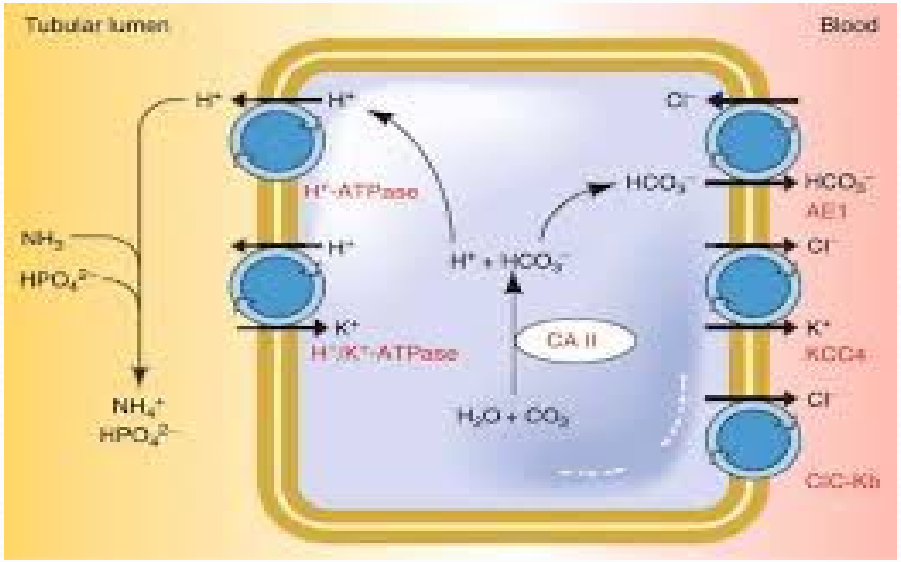
Collecting Ducts

- **Function of intercalated cells**
  - ***Excretion of {H+} with subsequent***
    - Reclaiming the remaining filtered bicarbonate
    - Combining with urinary buffers:
      - *Ammonia (NH_3)*
      - *Monohydrogen phosphate (HPO_4)*
  - ***Generation of HCO_3***
- **Defects in this function leads to distal RTA**



Distal RTA (type I)

❖ Etiology of distal RTA



1-Isolated

Mutation of gene encoding

{H+} ATPase (proton pump)

HCO_3/Cl exchanger

2-Secondary

Intrinsic renal disease (interstitial nephritis, pyelonephritis, LN …)

Urologic (obstructive uropathy, VUR, ….)

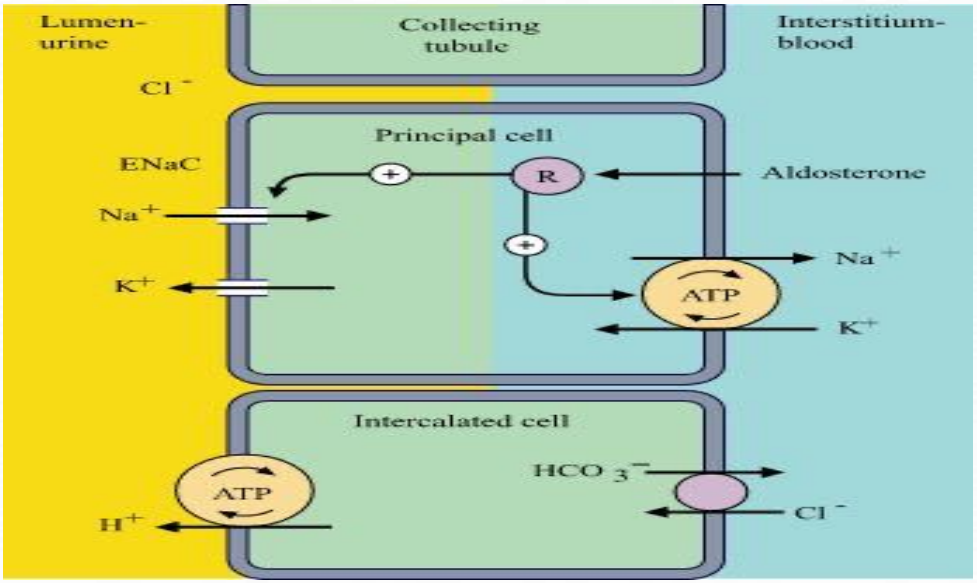
Drugs (Cisplatin, amphotericin B …..)

Collecting Ducts

- **Function of principal cells**

  Final adjustment of sodium and water reabsorption under control of aldosterone and ADH

- **Defect of aldosterone function leads to hyperkalemic RTA (type IV)**



Hyperkalemic RTA (type IV)

❖Etiology

1. Primary

   Impaired aldosterone production

   Impaired renal response to aldosterone

   Mutation of gene encoding aldosterone receptor

   Mutation of gene encoding ENaC

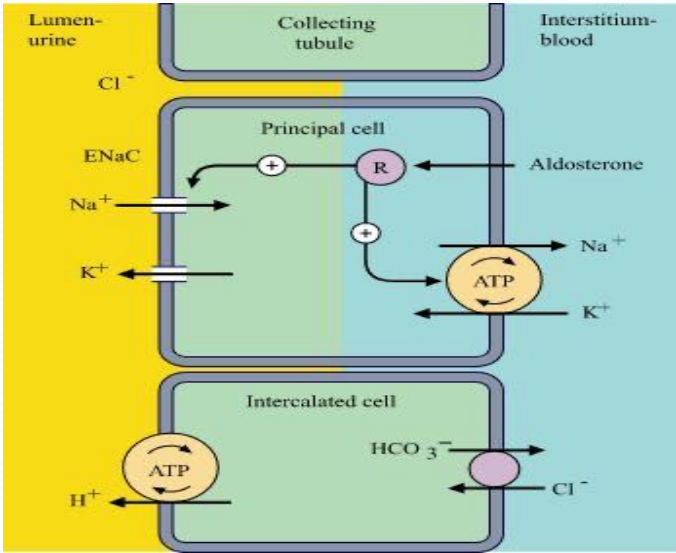
2. Secondary

   Urologic

   Intrinsic renal

   Drugs

   Systemic diseases



When do you Suspect RTA?

When do you suspect RTA?

- **Polyuria and polydipsia**
- **Failure to thrive**
- **Pyrexia of unknown origin (PUO)**
- **Rickets … not matched with vit. D deficiency**
- **History of:**
  - Polyhydramnios, prematurity
  - Family history of similar condition
  - +ve consanguinity,
  - Drug intake

When do you suspect RTA?

- **Dysmorphic features:**
  - Eye, ear, CNS, skeletal system, hair
- **GIT manifestations:**
  - Nausea, vomiting, constipation
- **Nephrocalcinosis**
- **Recurrent attacks of dehydration with mild to moderate gastroenteritis**

Diagnostic Work up

Diagnostic Work up

- Diagnostic work up of suspected cases includes:

  1-Diagnosis of RTA

  2-Diagnosis of RTA subtypes

  3-Etiological diagnosis

  4-Complications and associated conditions

1-Diagnosis of RTA

- First step is ***diagnosis of metabolic acidosis***
- It is done by measuring arterial blood gases

  ABGs of metabolic acidosis should have:

  - *low pH ..... < 7.35*
  - *low HCO_3 ..... < 20 mmol/L*
  - *low Pco_2 ..... < 35 mmHg*

- If there is appropriate respiratory compensation

$$Pco_2 = 1.5 \times \{HCO_3\} + 8 \pm 2$$

1-Diagnosis of RTA

- Second step is ***diagnosis of normal anion gap***
- Anion gap equals

serum (Na + K) - serum (Cl + HCO3)

(140+4) – (104+25) = 15

- Upper limit of normal anion gap is …. < 18 : < 14

1-Diagnosis of RTA

- Third step is

Exclusion of diarrhea

Normal or near normal GFR

Gold standard of RTA diagnosis

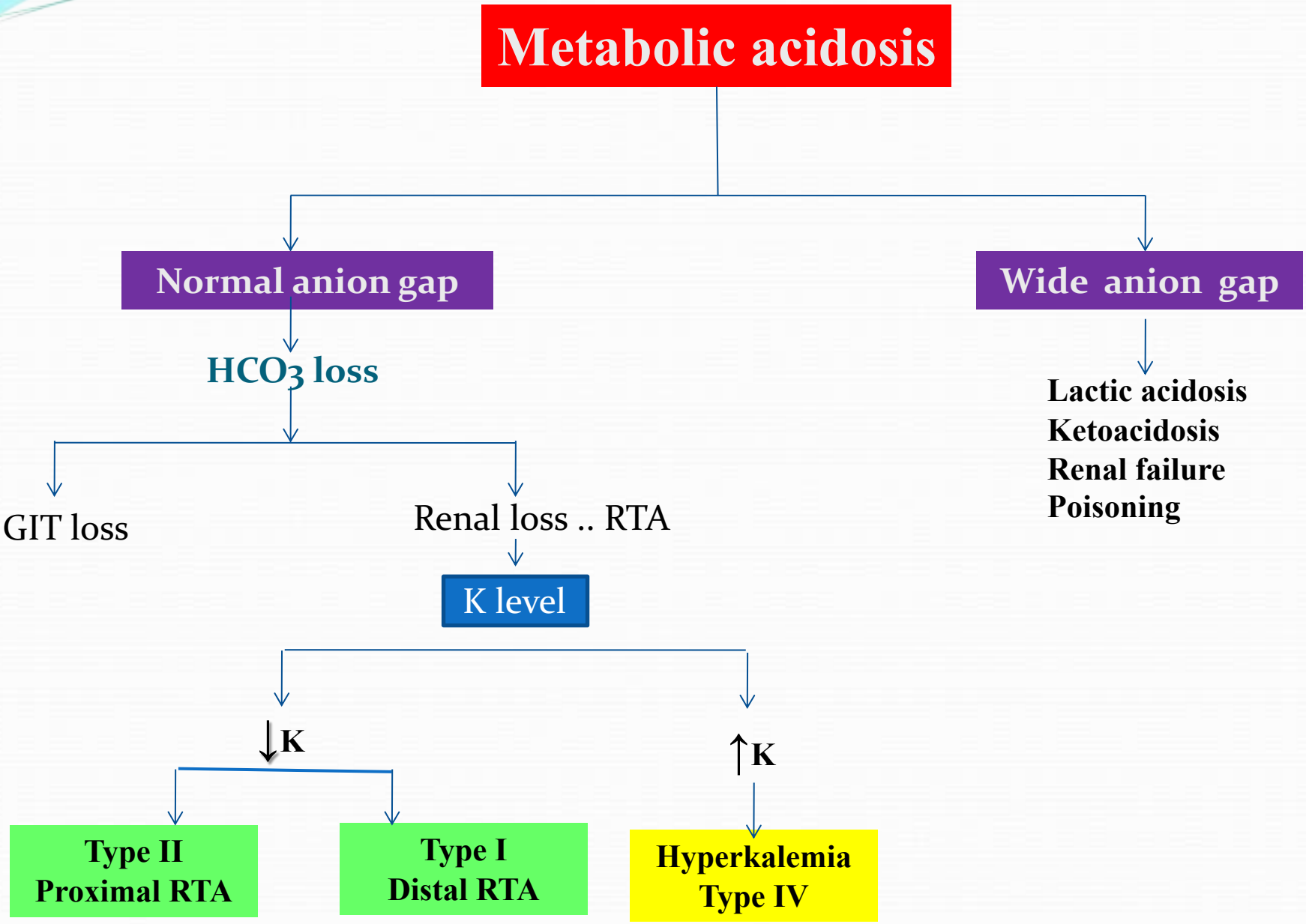
- Normal anion gap metabolic acidosis with normal or near normal GFR without diarrhea are the gold standard of RTA diagnosis.

2-Diagnosis of RTA Subtypes

- Diagnosis of RTA subtypes is done by measuring serum potassium level

  Hypokalemia ……type I or type II

  Hyperkalemia …. type VI


Metabolic acidosis
Normal anion gap
Wide anion gap
HCO3 loss
Lactic acidosis
Ketoacidosis
Renal failure
Poisoning
GIT loss
Renal loss .. RTA
K level
↓K
↑K
Type II
Proximal RTA
Type I
Distal RTA
Hyperkalemia
Type IV

2-Differentiation Between Type I & II

- **Urine analysis**

  Other solutes loss ***glucosuria, phosphaturia, aminoaciduria*** **….**

  Urine pH < 5.5

  Urinary anion gap

  Urinary citrates

- **Ultra sound**

  Nephrocalcinosis, renal stones …

- **X-ray bone**

  Rachitic changes ..

Proximal RTA (type II)

Criteria

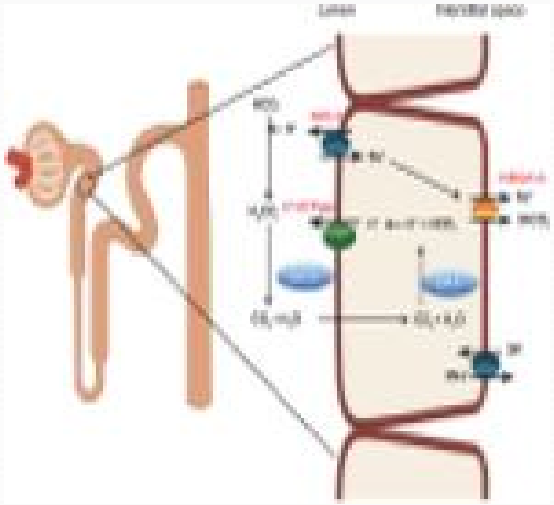
Urine pH may be < 5.5

Other tubular losses

No nephrocalcinosis

Normal urinary citrate

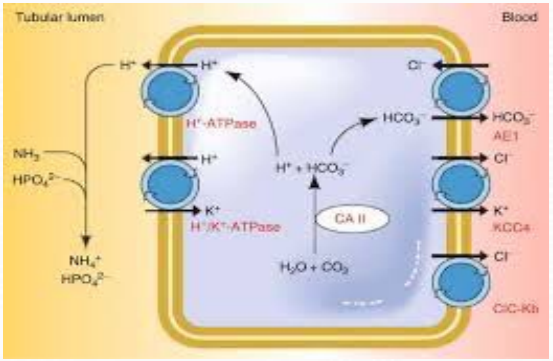
Negative urinary anion gap



- Urinary anion gap = $(NH_4) + Na + K = Cl$

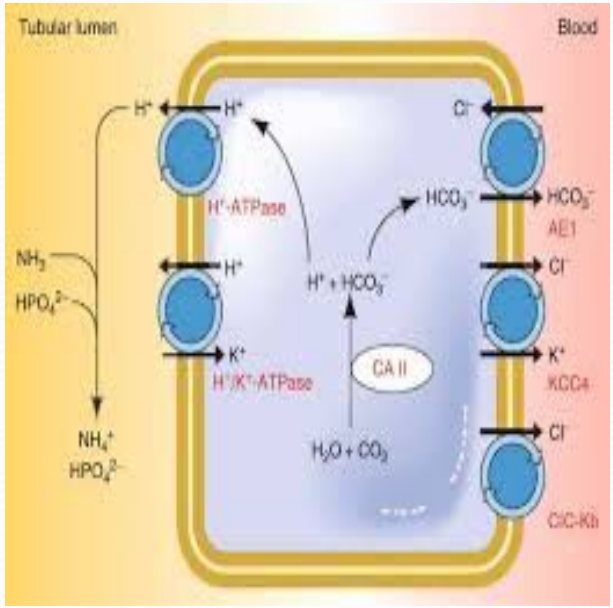
  $Na + K - Cl$

Na + K < Cl -ve anion gap … NH4



Distal RTA (Type I)

- Criteria
  - Urine pH ***is never*** < 5.5
  - No other tubular disfunction
  - Nephrocalcinosis
  - Low urinary citrate
  - Positive urinary anion gap



- Urinary anion gap

Na + K > Cl +ve anion gap .. no NH_4

Hyperkalemic RTA (type IV)

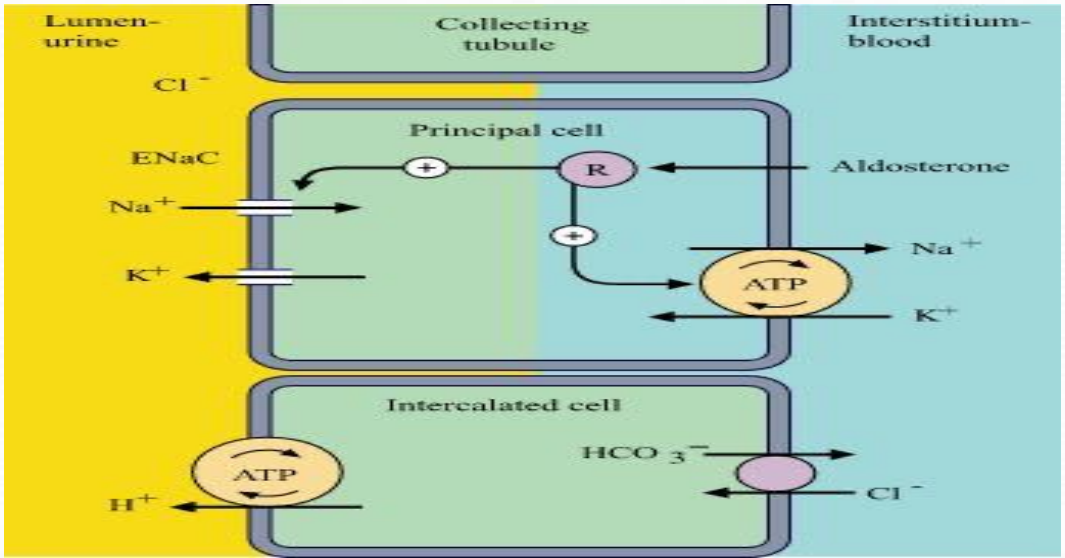
Renal tubular acidosis with hyperkalemia occurs due to:

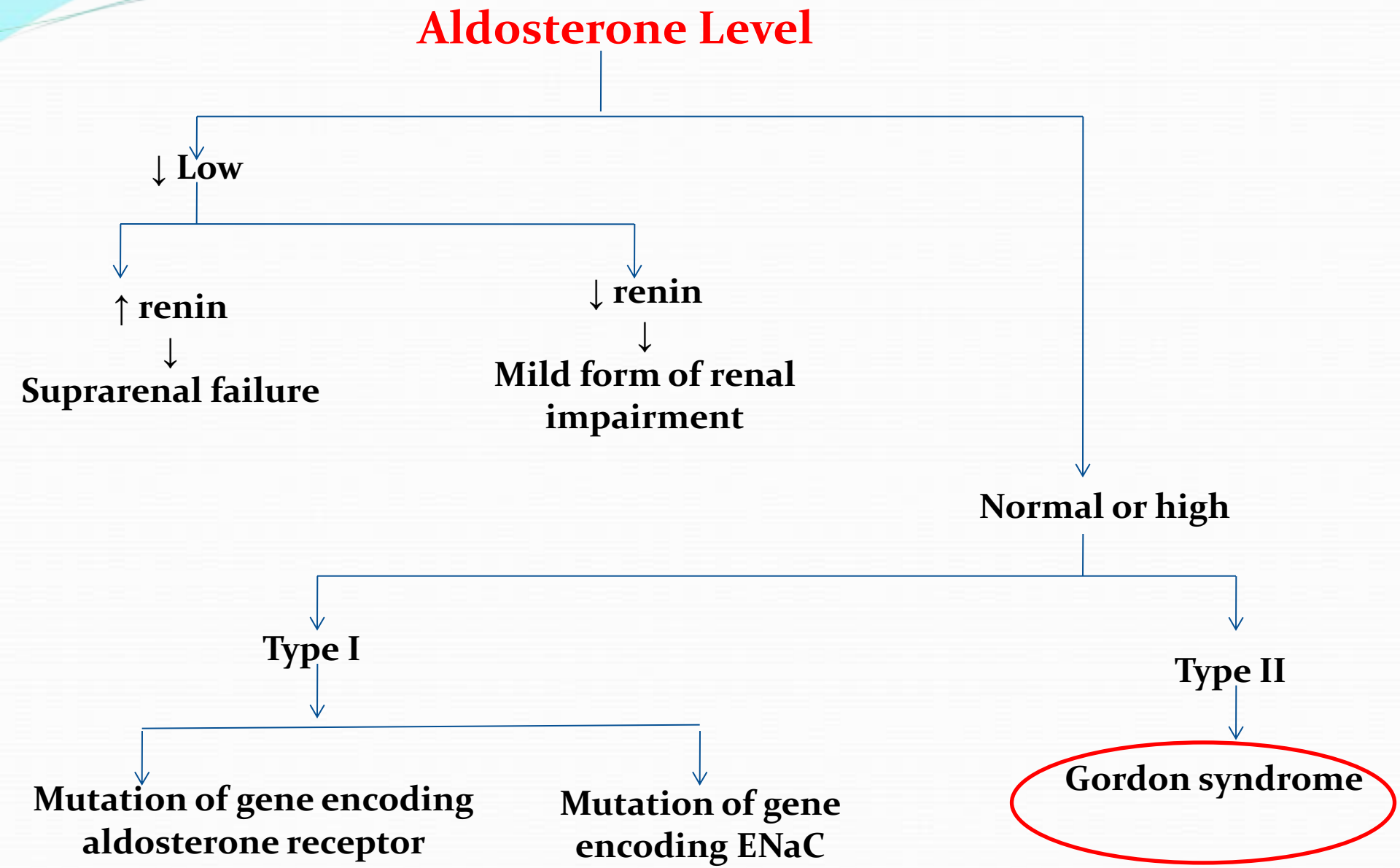
Impaired aldosterone production

Impaired renal response to aldosterone :

Mutation of gene encoding aldosterone receptor

Mutation of gene encoding ENaC




Aldosterone Level
↓ Low
↑ renin
Suprarenal failure
↓ renin
Mild form of renal impairment
Normal or high
Type I
Mutation of gene encoding aldosterone receptor
Mutation of gene encoding ENaC
Type II
Gordon syndrome

3-Etiological Diagnosis

- After diagnosis of RTA and it's subtypes, the next step is to proceed to:

  Etiological diagnosis

  Isolated vs global

  Primary vs secondary

  Inherited vs acquired

  It needs further investigations (molecular genetics, enzyme assay, radiological assessment ….)

4-Complications and Associated Conditions

- Great attention is essential to:
  - *Growth and development*
  - *Bone diseases*
  - *Dysmorphic features*
  - *History of drug intake*
  - *Systemic diseases*
  - *Renal function*
  - *Nephrocalcinosis*

General Lines of Treatment

General Lines of Treatment

- Correction of primary genetic defect is not yet feasible
- Secondary forms of RTA can be treatment
- Replacement therapy
- Treatment of associated conditions

Replacement Therapy

❑ Base therapy

- **Sodium bicarbonate**

  Solution 8.4% …… each 1ml …. 1mmol of bicarb.

  Tablets 650 mg …... each tab. … 8mmol of bicarb.

- **Sodium citrate**

  Bicitra …... each 1ml ….1mEq of bicarbonate (Na)

  Polycitra ... each 1ml …. 2mEq of bicarbonate (Na & K)

- **Does :**

  Type I ….. 3-4mEq/Kg/24h

  Type II …..up to 18mEq/Kg/24h

Replacement Therapy

- **Potassium therapy**
  - **Forms**
    - **Potassium chloride**
    - **Potassium citrate**
    - **Potassium phosphate**
  - **Dose: 1-2mEq/Kg/24h**

- **Phosphate supplement**

Treatment of Associated Conditions

- **In type I RTA, *Symptomatic hypercalciuria* (nephrocalsinosis, hematuria, nephrolithiasis) is treated by thiazide**

- **In type II RTA, *Rickets* is treated by phosphate supplement and vitamin D**

- **In type IV RTA, Hyperkalemia is treated by potassium- binding resins**

  Calcium poly styrene sulfonate …. Sorbisteirt
  Sodium poly styrene sulfonate ….. kayexalate

Conclusions

- Renal tubular acidosis is not a single disease, rather it is biochemical state with clinical consequences that occurs during the course of many tubular disorders (inherited or acquired)

- RTA is characterized by normal anion gap metabolic acidosis with normal or near normal GFR

- The pathogenesis of RTA is due to defect in renal excretion of hydrogen ions (type I), defect in reabsorption of bicarb. (type II) or both

Conclusions

- There are 4 main types: proximal RTA (type II), distal RTA (type I), hyperkalemic (type VI), and combined proximal and distal (type III)
- Diagnosis depends mainly on high level of clinical suspicion, followed by proper lab assessment and diagnostic algorithm
- General lines of treatment include mainly replacement therapy, treatment of secondary causes and associated conditions.

Questions ?

Question No 1

- In distal RTA, where is the site of tubular injury?

A- proximal tubules

B- loop of Henle

C- distal tubules

D- collecting ducts

Question No 2

- Which of the following is associated with nephrocalcinosis?

A- RTA type I
B- RTA type II
C- RTA type III
D- RTA type IV

Question No 3

- Which of the following is associated with proximal RTA ?

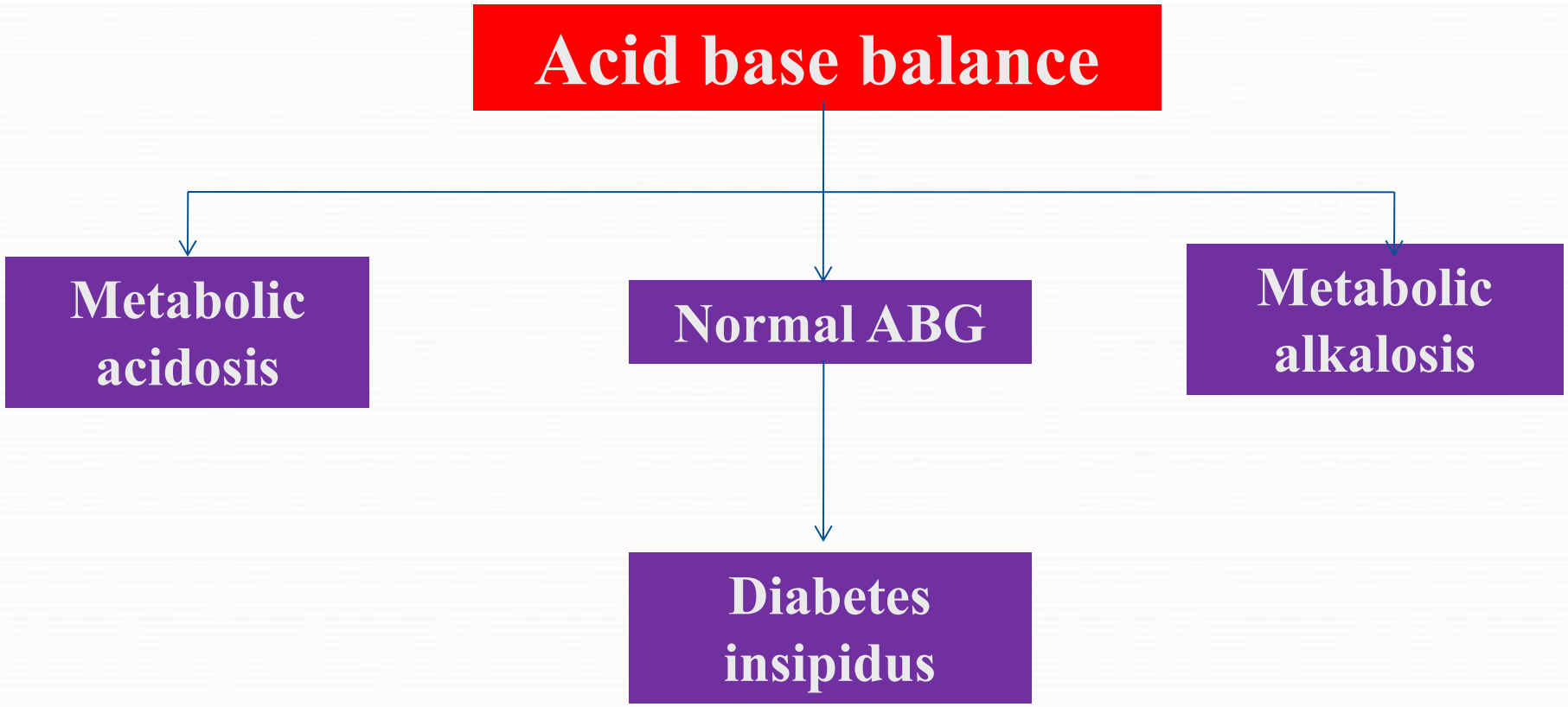
A- positive urinary anion gap

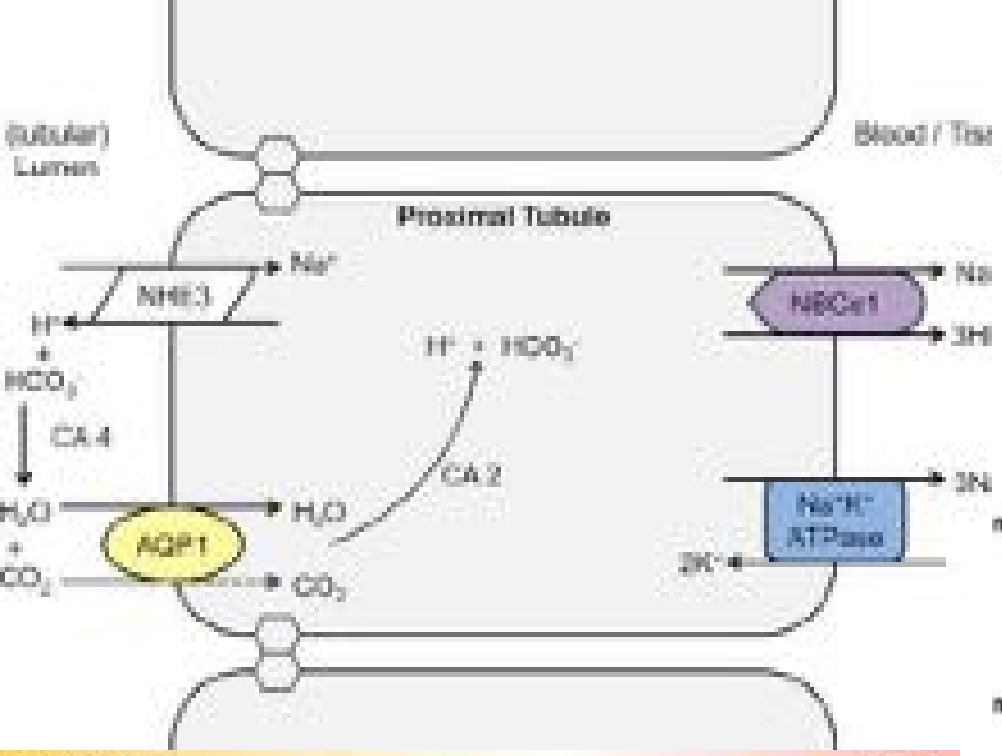
B- urine pH less than 5.5

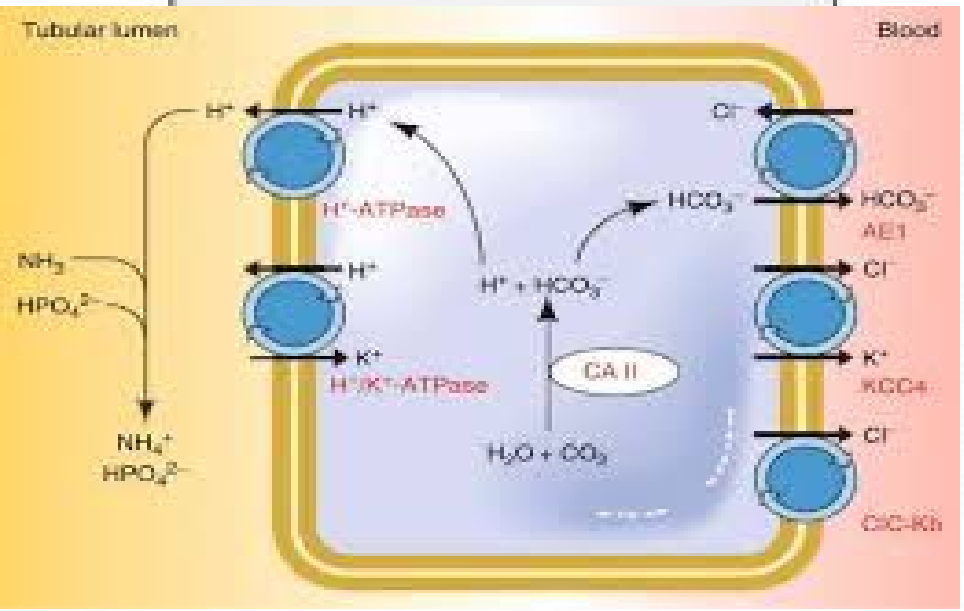
C- low urinary citrates

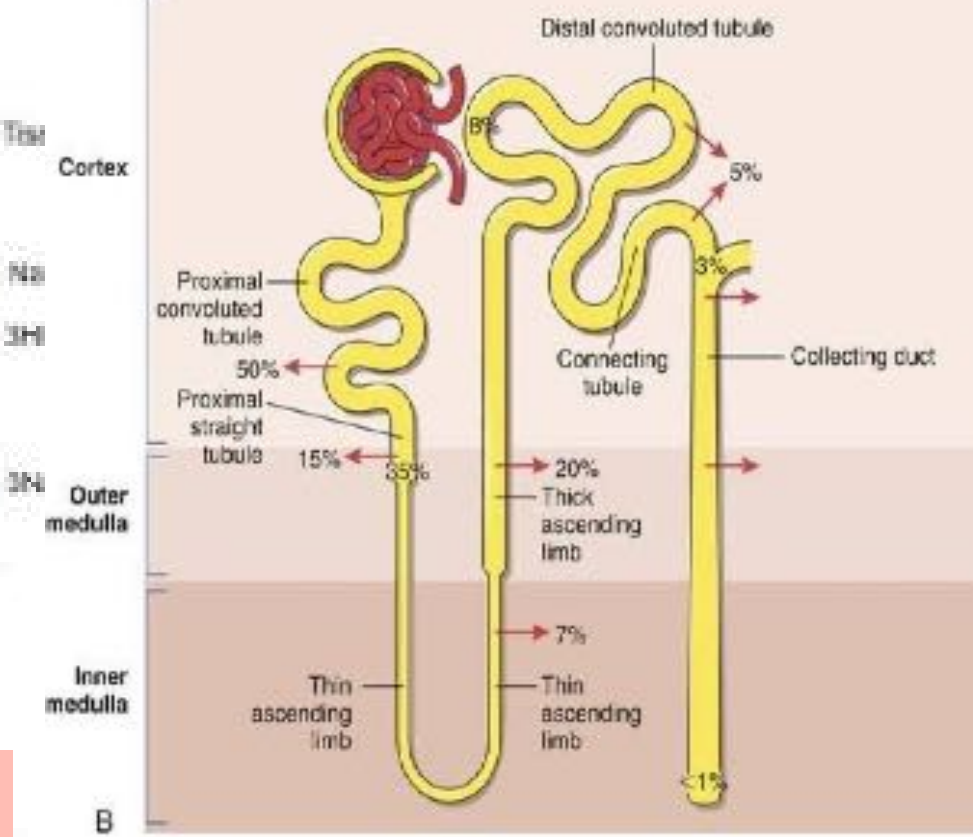
D- hyperkalemia

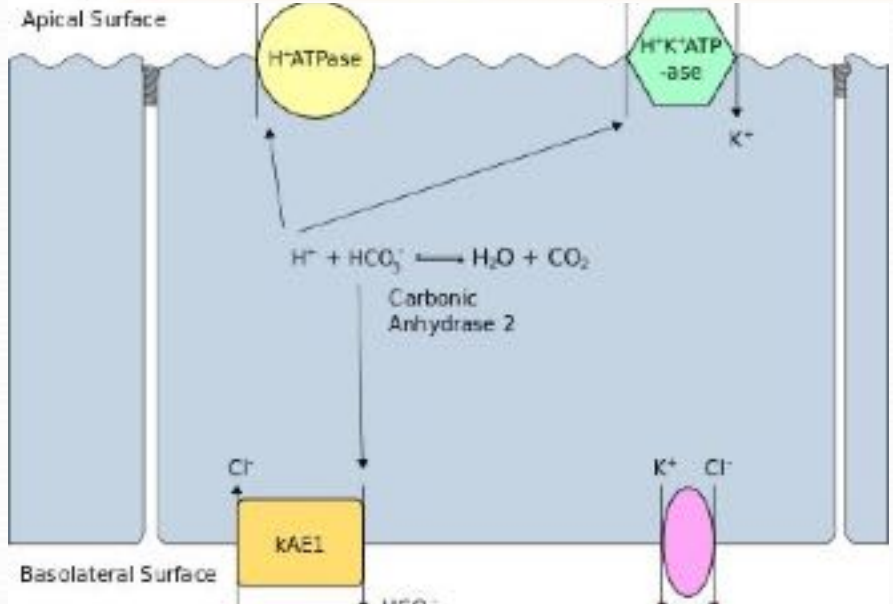
Thank You

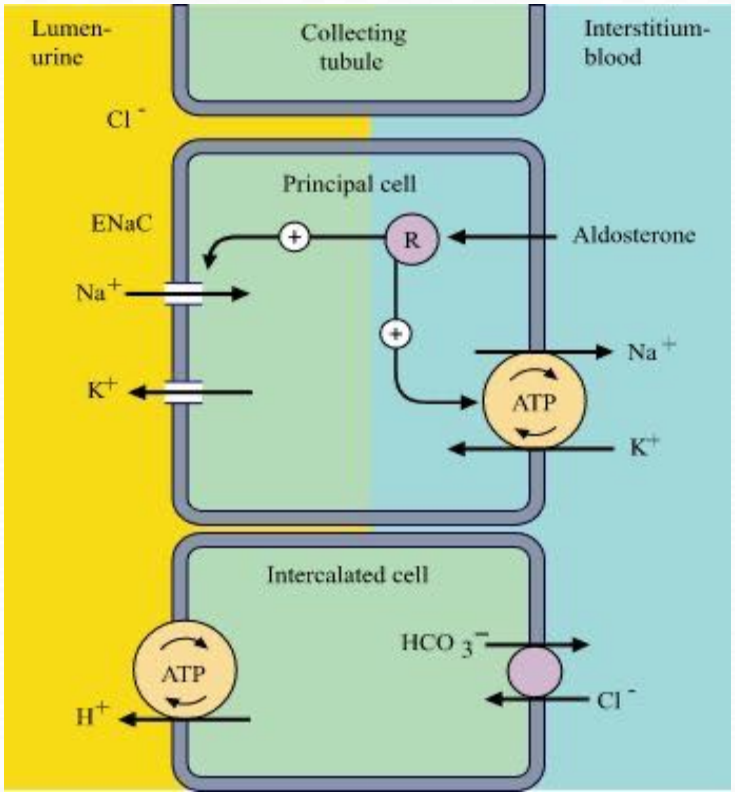

Acid base balance
Metabolic acidosis
Normal ABG
Metabolic alkalosis
Diabetes insipidus

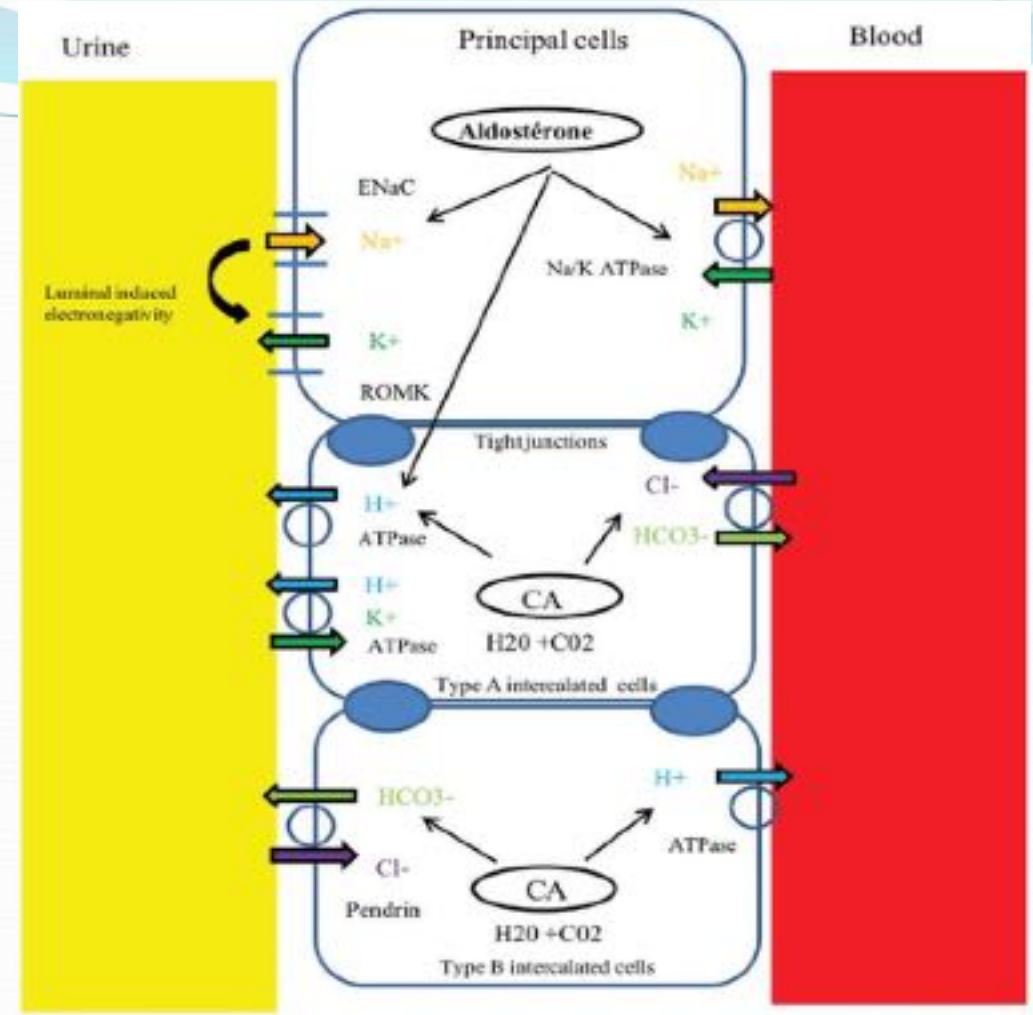

(tubular)
Lumen
Proximal Tubule
NHE3
NBCe1
CA 4
CA 2
AQP1
Na⁺/K⁺
ATPase

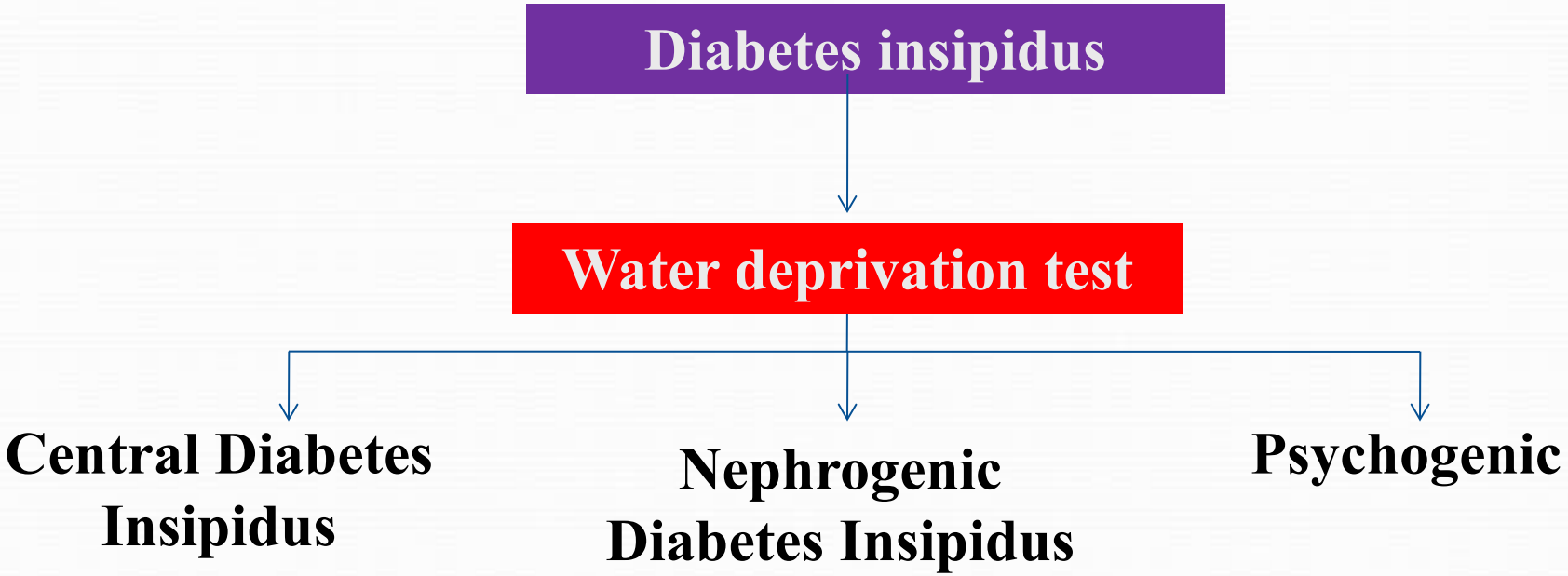

Tubular lumen
Blood
H⁺-ATPase
H⁺/K⁺-ATPase
CA II
AE1
KCC4
ClC-Kb

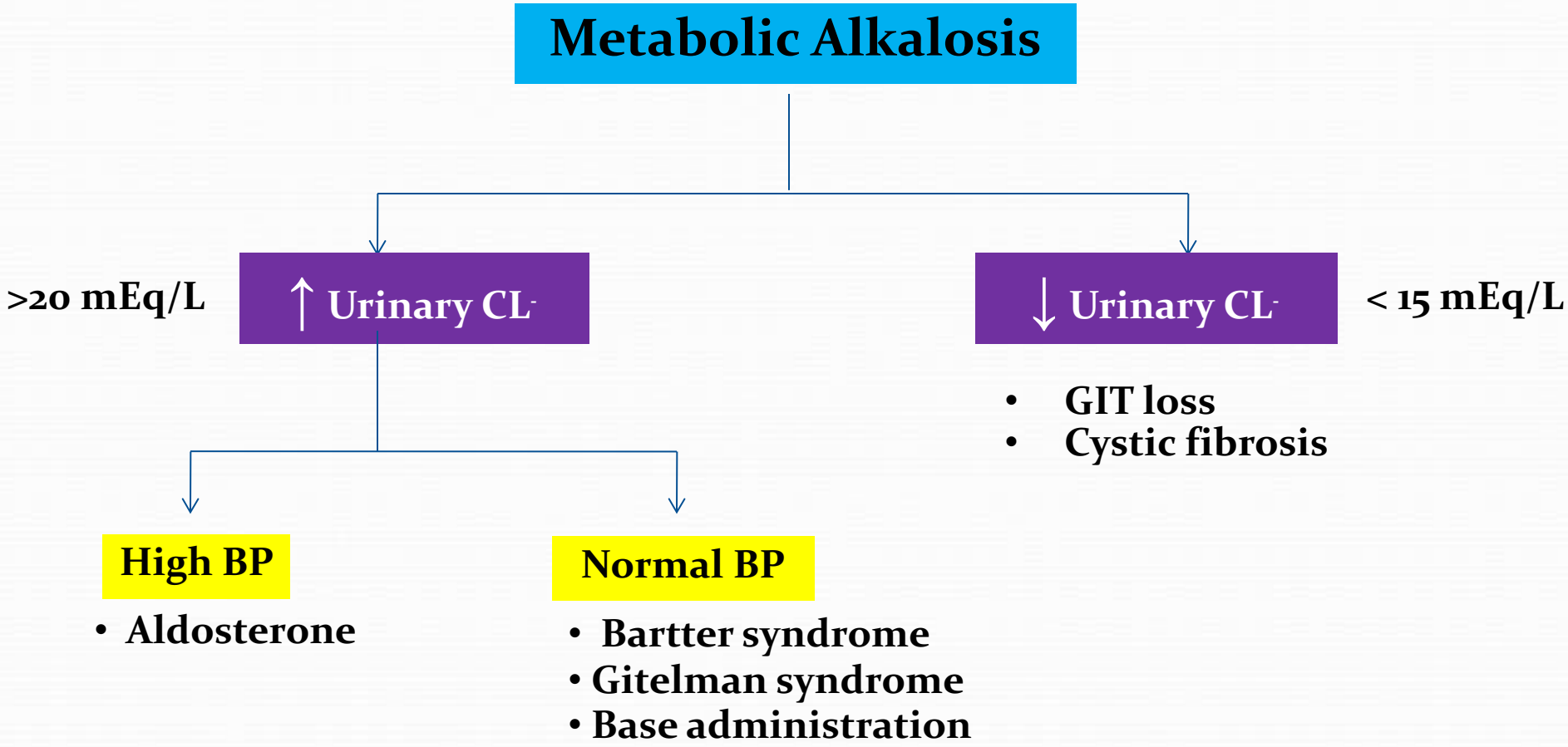

Distal convoluted tubule
Cortex
Proximal convoluted tubule
50%
Proximal straight tubule
15%
35%
Connecting tubule
Collecting duct
5%
3%
20%
Thick ascending limb
Outer medulla
7%
Inner medulla
Thin ascending limb
Thin ascending limb
<1%
B

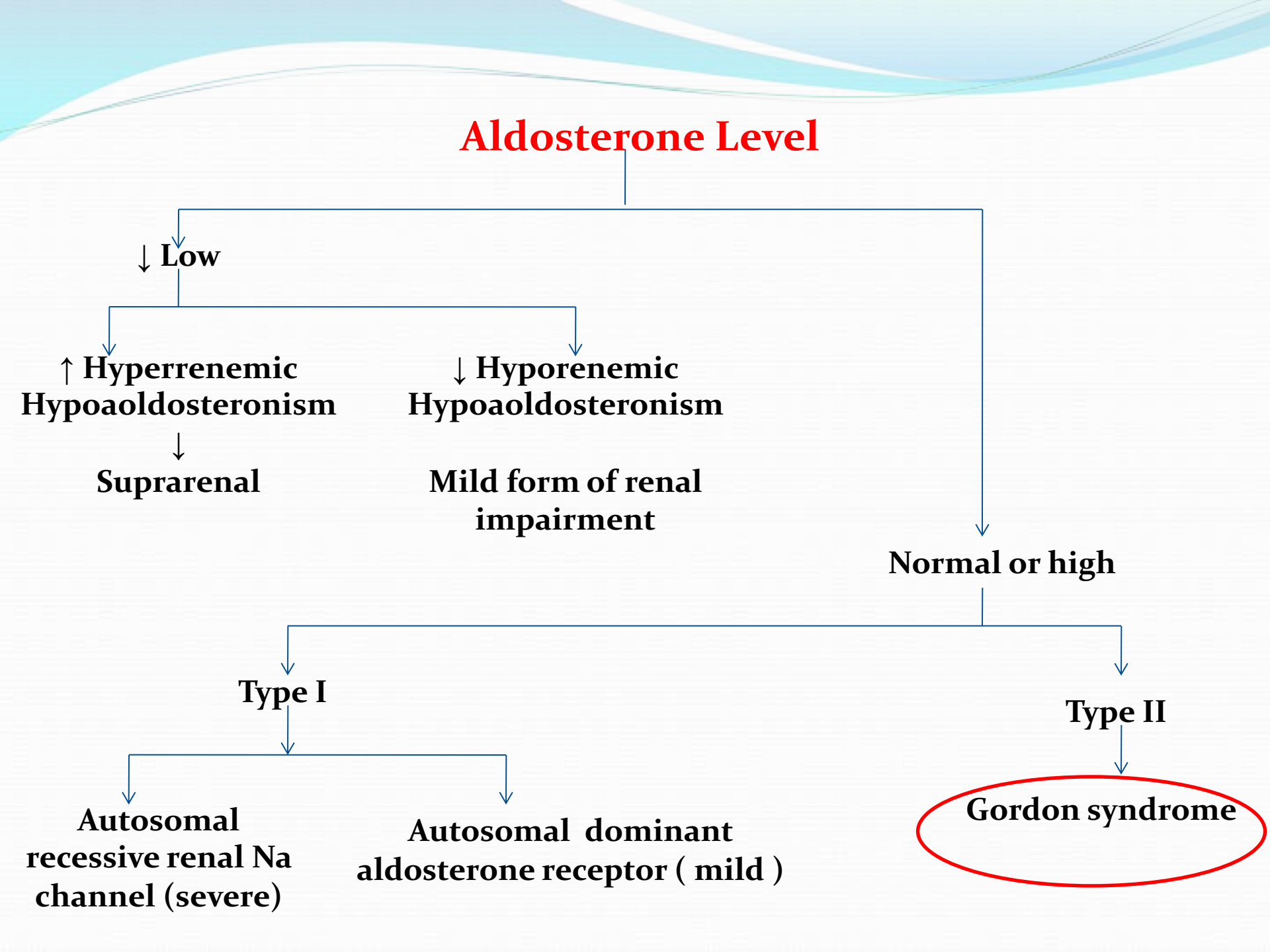

Apical Surface
H⁺ATPase
H⁺K⁺ATP -ase
K⁺
H⁺ + HCO₃⁻ ⟷ H₂O + CO₂
Carbonic Anhydrase 2
Cl⁻
kAE1
K⁺ Cl⁻
Basolateral Surface

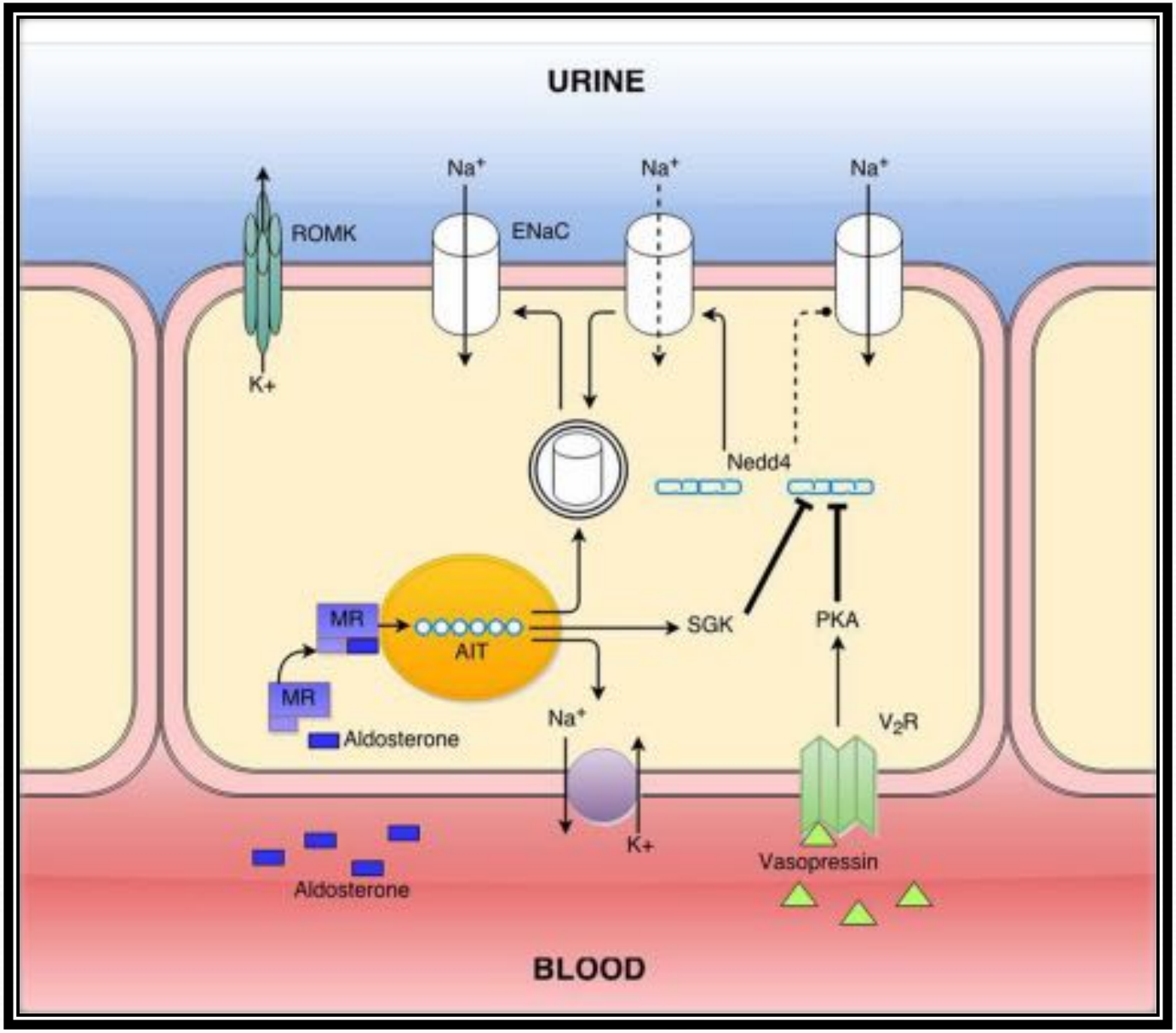

Lumen-
urine
Collecting
tubule
Interstitium-
blood
Cl -
Principal cell
ENaC
R
Aldosterone
Na+
K+
Na +
ATP
K+
Intercalated cell
ATP
HCO 3−
H+
Cl -


Urine
Principal cells
Blood
Aldostérone
ENaC
Na+
Na+
Na/K ATPase
Luminal induced
electronegativity
K+
K+
ROMK
Tight junctions
Cl-
H+
ATPase
HCO3-
H+
K+
ATPase
CA
H20 +C02
Type A intercalated cells
HCO3-
H+
ATPase
Cl-
Pendrin
CA
H20 +C02
Type B intercalated cells


Diabetes insipidus
Water deprivation test
Central Diabetes Insipidus
Nephrogenic Diabetes Insipidus
Psychogenic


Metabolic Alkalosis
>20 mEq/L
↑ Urinary CL-
↓ Urinary CL-
< 15 mEq/L
• GIT loss
• Cystic fibrosis
High BP
• Aldosterone
Normal BP
• Bartter syndrome
• Gitelman syndrome
• Base administration


Aldosterone Level
↓ Low
↑ Hyperrenemic Hypoaldosteronism
↓
Suprarenal
↓ Hyporenemic Hypoaldosteronism
Mild form of renal impairment
Normal or high
Type I
Autosomal recessive renal Na channel (severe)
Autosomal dominant aldosterone receptor (mild)
Type II
Gordon syndrome


URINE
Na+
Na+
Na+
ROMK
ENaC
K+
Nedd4
MR
AIT
SGK
PKA
MR
Aldosterone
Na+
V2R
K+
Vasopressin
Aldosterone
BLOOD