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Renal Tubular Acidosis

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Renal tubular acidosis (RTA)

- Group of disorders characterized by normal anion gap metabolic acidosis with either hypokalemia or hyperkalemia and relatively well preserved GFR

- **Normal anion gap metabolic acidosis with hypokalemia**:

  - Proximal RTA (type 2) caused by reduced ability to reabsorb bicarbonate (HCO_3) in the proximal tubules

  - Distal RTA (type 1) caused by defects in distal H ion excretion

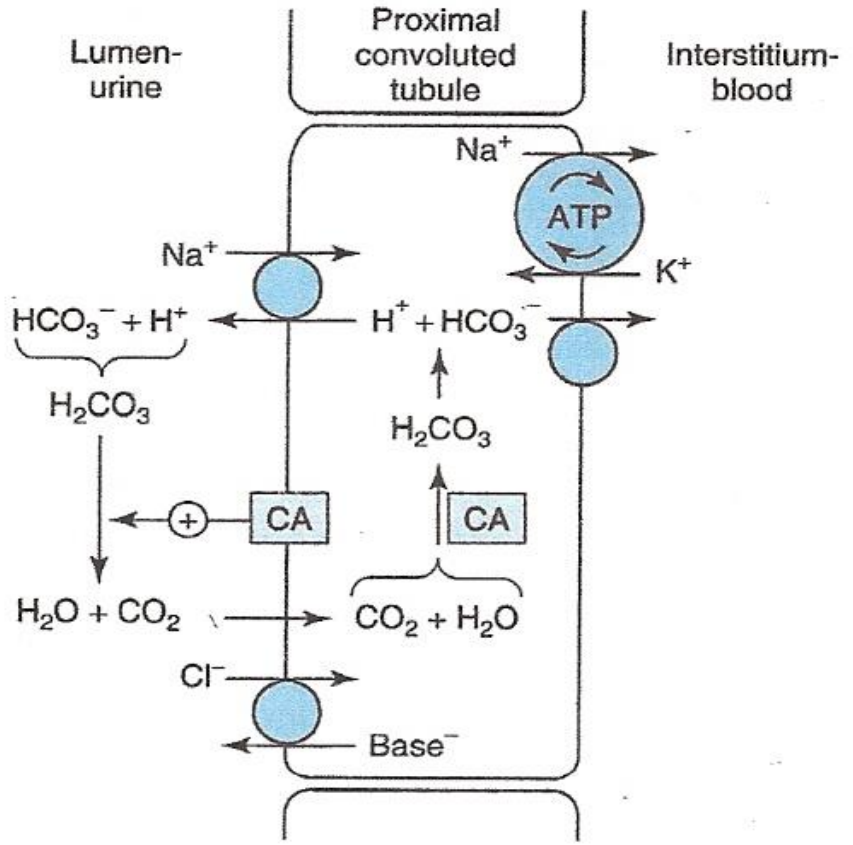
- **Normal anion gap metabolic acidosis with hyperkalemia:**

-Type 4 RTA is due to either aldosterone deficiency or tubular resistance to the action of aldosterone and is the commonest among RTAs

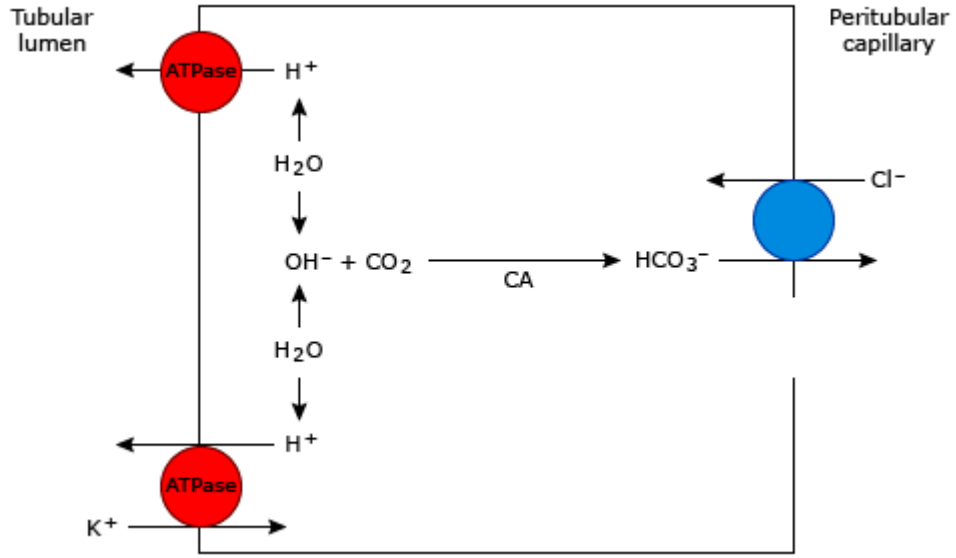
Proximal RTA (Type 2 RTA)

- Isolated defect in proximal HCO3 reabsorption or with impaired reabsorption of phosphate, glucose, uric acid, and amino acids (Fanconi syndrome)
- **Urinary pH usually <5.5 due to compensatory increased in H secretion by distal tubules**
- Acidosis usually not very severe because as serum HCO3 falls, less HCO3 is filtered, and less is excreted into the urine
- **Fanconi syndrome often suspected in normal anion gap metabolic acidosis with hypokalaemia , glycosuria AND low plasma phosphate and uric acid levels**

85 to 90% HCO3 reabsorbed in PCT with help from CARBONIC ANHYDRASE(CA)



10 to 15% HCO3 reabsorbed (with K) along with H secretion in the type A intercalated cells in CD



Causes of type 2 RTA

- Monoclonal gammopathies: Multiple myeloma, amyloidosis, light chain proximal tubulopathy
- Drugs: Carbonic anhydrase inhibitors – Acetazolamide and topiramate; Tenofovir and other antiretroviral drugs; Aminoglycosides; Oxaliplatin/cisplatin; Ifosfamide
- Heavy metals: Lead, cadmium, mercury and copper
- Wilson disease, Cystinosis, Lowe syndrome, outdated tetracycline, PNH

Distal RTA (Type 1 RTA)

- Type 1 RTA is caused by inability of the distal tubules to secrete H
- **Characterised by urinary pH >5.5 due to lack of H in urine THUS differentiating from type 2 RTA**
- **Incomplete distal RTA**
  - Inability to reduce the urine pH to <5.3, normal serum bicarbonate concentration and low K
  - Patients have reduced urine citrate levels and may present with or develop calcium stones
  - Reduced urinary citrate supports diagnosis

Causes of distal RTA

- **Sjogren's syndrome**, SLE, hypergammaglobulinemic states, primary biliary cirrhosis, autoimmune hepatitis, chronic obstructive uropathy, renal transplantation and glue sniffing
- Drugs : lithium, ibuprofen, ifosfamide and amphotericin
- Hypercalciuric conditions: Hyperparathyroidism, Vit D intoxication, sarcoidosis
- Genetic associations: Marfan syndrome and Ehler Danlos syndrome
- Toluene inhalation due to glue sniffing

My patient has diarrhea……

- Metabolic acidosis and hypokalaemia in diarrhea due to

  -Faecal loss of bicarbonate rich pancreatic secretions

  - Intravascular depletion and RAAS activation
- *How do I differentiate from RTA?*

Urine anion gap (UAG)

- UAG = Urine(Na + K − Cl)
- UAG is positive in healthy individuals
- With metabolic acidosis from any cause, the kidney will appropriately respond by excreting a heavy load of H *(except in type1 RTA where H excretion is characteristically defective)*
- NH3 in urine accepts H to form NH4 which combines with the negatively charge Cl to form NH4Cl
- **UAG is positive in type 1 RTA (lack of H and hence low NH4Cl) and negative in metabolic acidosis due to any cause including diarrhea (excess H and hence high NH4Cl in urine)**

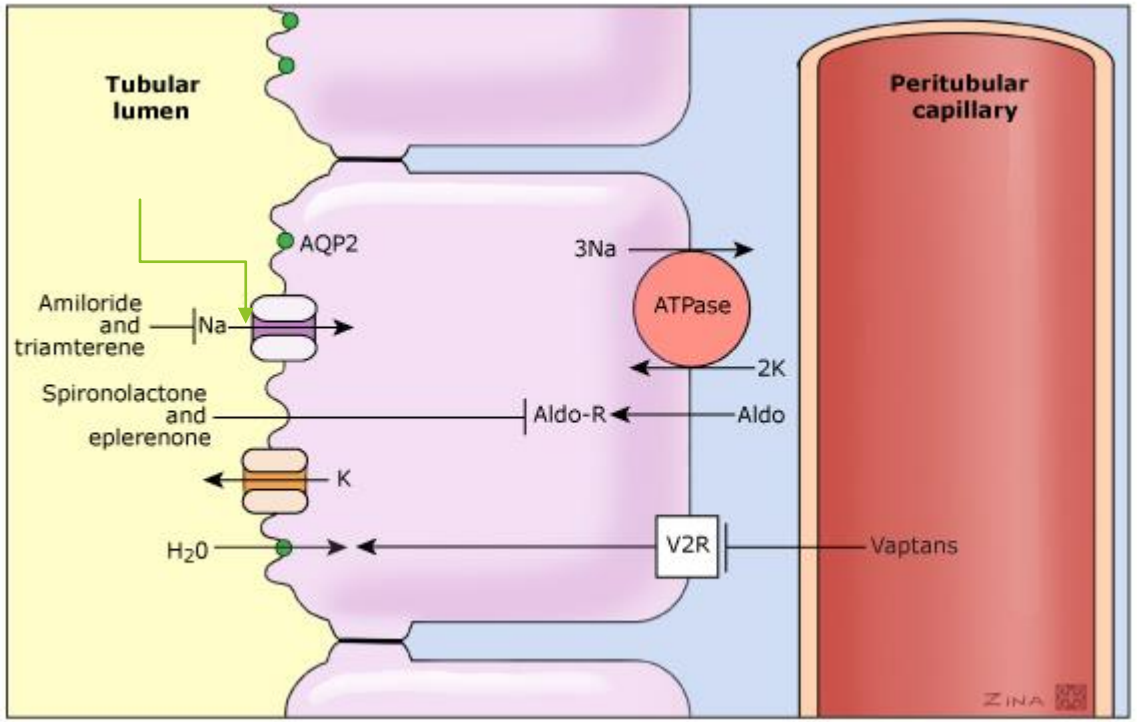
Bones and stones in RTA

- Metabolic acidosis causes bones to release calcium phosphate as buffer (causing progressive osteomalacia and osteopenia over time)
- Kidneys try to eliminate the excess Ca
- Normally urinary citrate binds Ca and keeps it soluble
- In type 1 RTA, the proximal reabsorption of citrate is enhanced
- Low urinary citrate and high urinary pH in type 1 RTA predisposes to Ca stones

Type 1 RTA (distal RTA)	Type 2 RTA (Proximal RTA)
Inability to secrete H+	Inability to reabsorb HCO3
Urine pH >5.5 (low H+ in urine)	Urine pH <5.5 (compensatory increase in distal tubular H^+ secretion)
Nephrolithiasis and nephrocalcinosis	No renal stones
No Fanconi syndrome	May have Fanconi syndrome: glycosuria, phosphaturia, uric aciduria and aminoaciduria
Treat with alkali and K+ replacement	Same treatment but often need bigger doses of alkali

Treatment of types 1 and 2 RTA

- Alkali and potassium replacement
- Higher doses of alkali needed in type 2 RTA
- Potassium citrate useful in patients with hypokalemia or stones
- Patients with severe or symptomatic hypokalemia should be given potassium prior to or concomitantly with sodium bicarbonate therapy



Aldosterone revision needed to understand Type 4 RTA

- Absorption of Na^+ and excretion of K^+ while water passively reabsorbed
- Indirect excretion of H^+
- *Arrow- epithelial sodium channel(EnaC)*

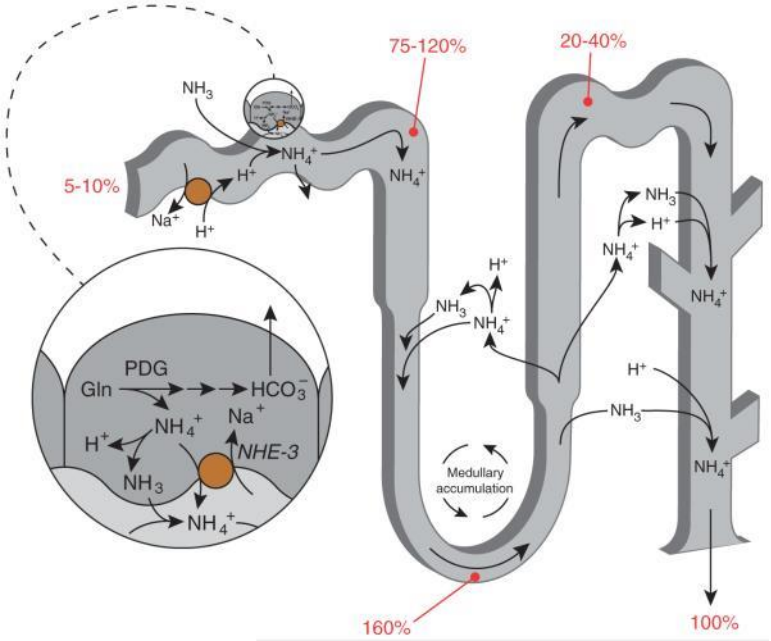
Type 4 RTA

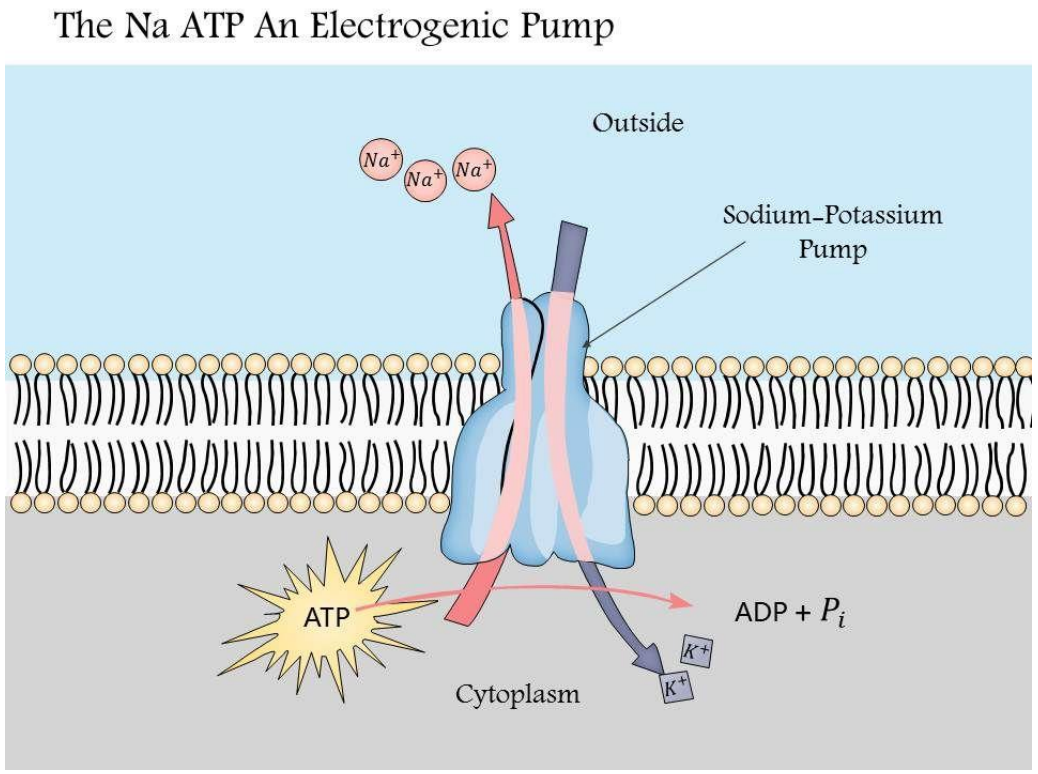
- Characterised by normal anion gap metabolic acidosis which is usually mild and hyperkalaemia
- Associated with
  - Hypoaldosteronism often due to hyporeninism
  - Diminished tubular response to aldosterone
  - Inherited or acquired defect in the sodium transport mechanisms in the principal cells
- All three above would interfere with K excretion in the urine leading to hyperkalemia

Pathophysiology of acidosis in Type 4 RTA

- Hyperkalaemia decreases renal ammonia generation:
  - H+ in the urine needs buffers otherwise urine would quickly become saturated
  - Chief buffer is ammonia which becomes ammonium after accepting the H^+ { $NH3 + H^+ \leftrightarrow NH4^+$ }
  - Ammonia is derived from breakdown of glutamine by phosphate dependent glutaminase (PDG) in the PCT cells
  - **Hyperkalemia decreases glutaminase activity and therefore decreases ammonia production**
- In the CD, the basolateral Na-K-ATPase can also function as an Na-NH_4 exchanger, permitting uptake of NH_4 from the interstitium and subsequent secretion into the urine
- K competes with NH_4 for this exchanger, and therefore hyperkalaemia impairs the capacity of the pump to carry ammonium into the cell

Renal ammonia metabolism
Gln-Glutamine; PDG-Phosphate Dependent Glutaminase





Na-K-ATPase pump can also function as Na-NH_4 exchanger

Type 4 RTA

- Common in diabetics especially those with diabetic nephropathy
- Caused by ACEI, ARBs, K-sparing diuretics, Calcineurin inhibitors (cyclosporine and tacrolimus), NSAIDs, heparin, trimethoprim
- May be seen in chronic interstitial nephritis of any cause or sickle cell disease
- Treatment:

Treatment of Type 4 RTA

- Synthetic mineralocorticoid such as fludrocortisone
- In patients with hypertension or fluid overload, thiazide or loop diuretic may help

Q/1

- Normal anion gap metabolic acidosis with hypokalaemia is an indicator of either type1 (distal) or 2 (proximal) RTA and the best way to differentiate these two is by checking:

a. Urinary Chloride

b. Urinary protein

c. Urinary anion gap

d. Urinary pH

e. Serum K concentration

Answer time

- Answer is d.
- Both RTAs 1 and 2 are characterised by normal anion gap metabolic acidosis with hypokalaemia.

  - Proximal RTA (type 2) caused by reduced ability to reabsorb bicarbonate (HCO_3) in the proximal tubules

  - Distal RTA (type 1) caused by defects in distal H ion excretion
- Remember any cause of acidosis will cause the kidney to compensate by excreting extra H^+ ions (acidic urine i.e. pH<5.5). The problem in RTA 1 is INABILITY to excrete H^+
- Type 1 RTA is characterised by urinary pH >5.5 due to lack of H in urine THUS differentiating from type 2 RTA or any other cause of metabolic acidosis.

Q/2

- Fanconi syndrome should be suspected in-
  a. Hyperuricemia
  b. Hyperphosphatemia
  c. Hypophosphatemia
  d. Hyperkalaemia
  e. Alkalosis

Answer time

- Answer is C
- Type 2 RTA is due to a proximal tubular defect in the reabsorption of $HCO3^-$ leading to urinary loss of $HCO3^-$ and metabolic acidosis with hypokalaemia.
- The absorption of HCO3- in this segment is linked to the coupled exchange of H^+ and Na^+. As this reabsorption of Na^+ is linked to the reabsorption of glucose, amino acids, phosphate and uric acid, the patient may present with glycosuria, hypophosphatemia and hypouricemia (due to urinary losses of phosphate and uric acid respectively) and this condition is termed as Fanconi syndrome.

Q/3

- A 52-year-old woman presents to ED feeling generally unwell. Blood tests reveal metabolic acidosis with a normal anion gap and hypokalaemia. Her urinary pH is 5.7. The rest of the blood tests including phosphate and uric acid are normal. What could have led to this condition-?

  a. Myeloma

  b. Sjogren's syndrome

  c. Wilson's disease

  d. Diabetes mellitus

Q/4

- What is the diagnosis in the above case?

a. RTA type 4

b. RTA type 1

c. RTA type 2

d. RTA type 3

Answer to both q/3 and 4 is b.

- The normal anion gap acidosis with hypokalaemia points towards either RTA 1 or 2 but the urinary pH > 5.5 is suggestive of RTA 1 which may be associated with Sjogren's syndrome.
- Myeloma has a strong association with type 2 RTA.
- A reminder of differentials of **normal anion gap metabolic acidosis with hypokalaemia**:

  - Proximal RTA (type 2) caused by reduced ability to reabsorb bicarbonate (HCO_3) in the proximal tubules

  - Distal RTA (type 1) caused by defects in distal H ion excretion- characterised by urinary pH >5.5 due to lack of H in urine THUS differentiating from type 2 RTA

Thank you

“Information is not knowledge”

-Albert Einstein