RENAL TUBULAR ACIDOSIS – An Overview

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What is Renal Tubular Acidosis (RTA)?

Two simple definition of RTA:

- **RTA**: group of disorders of Renal Tubules that result in Normal Anion Gap Hyperchloremic Metabolic Acidosis in the presence of Normal Glomerular Function;

- **RTA:** group of disorders in which there is Metabolic Acidosis due to defect in Renal Tubular Acidification Mechanism used to maintain normal Plasma Bicarbonate (HCO_3^- ions) concentration and blood pH

IMPORTANT TO NOTE

- Control of pH is needed for normal metabolism,
- Large quantities of **Anions** (Sulphate, Phosphate, Lactate) are produced during metabolism,
- They are collectively called “Unmeasured Anions”
  - Accumulation of Anions causes increase in Plasma Anion gap,
- Renal Tubules play major role in:
  - Elimination of the unmeasured anions,
  - Regulation of H^+ ions,
  - Control of pH in body fluids;
- Failure of Renal tubules to regulate H^+ ions may cause metabolic acidosis,

How is Acid-Base balance regulated by the kidneys?

- Kidney regulates Acid-Base Balance by controlling:
  - Re-absorption of Bicarbonate ions (HCO_3^-),
  - Secretion of Hydrogen ions (H^+),
- Both processes depend on formation of HCO_3^- & H^+ ions from CO_2 and H_2O **within Renal Tubular cells**:

Carbonic Anhydrase

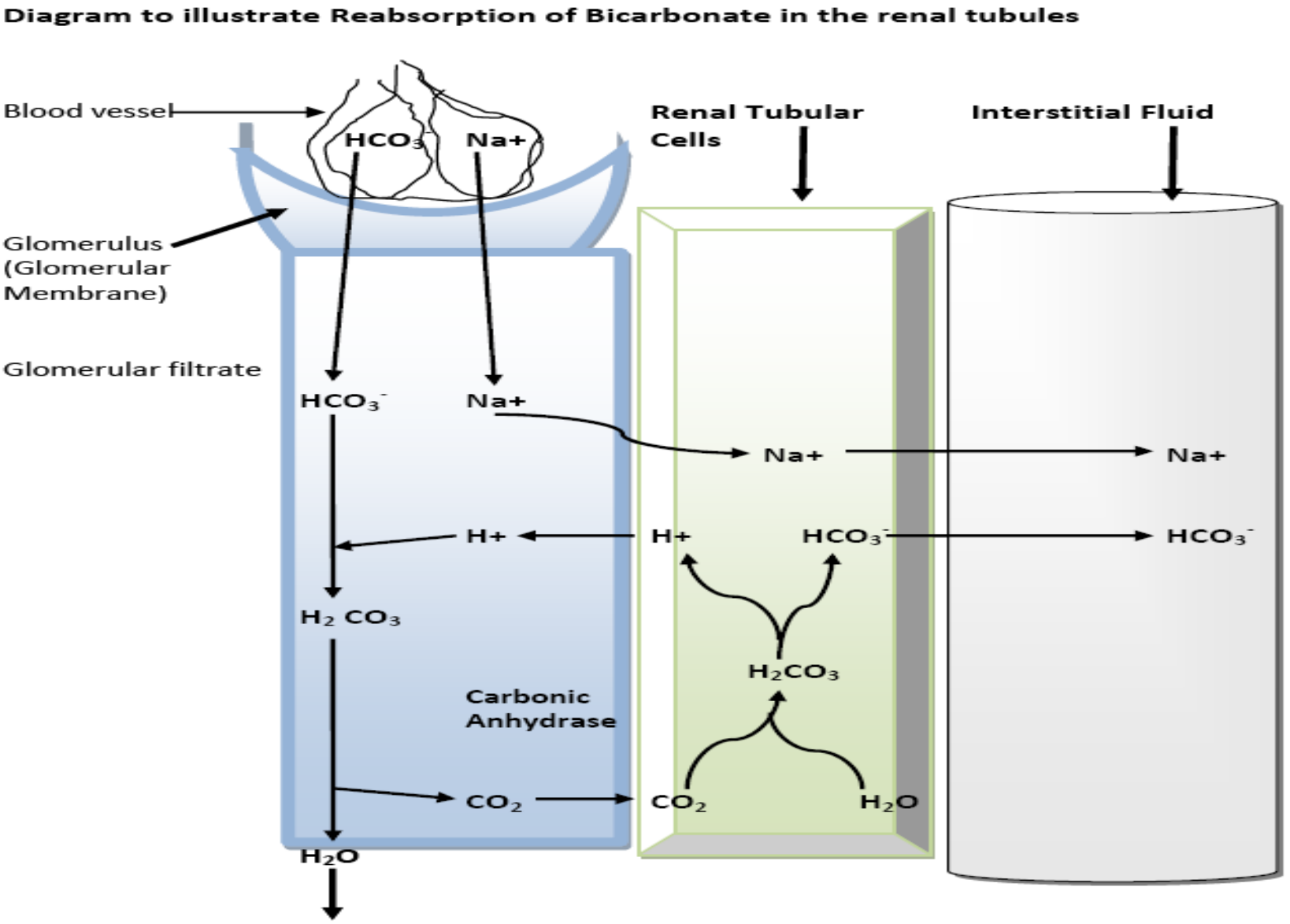
$$\mathbf{CO_2 + H_2O \leftrightarrows H_2CO_3 \leftrightarrows H^+ + HCO_3^-}$$

- H^+ ions formed are actively secreted into Tubule fluid in exchange for Na^+

What mechanisms are used by renal tubules for regulation of Acids Base Balance?

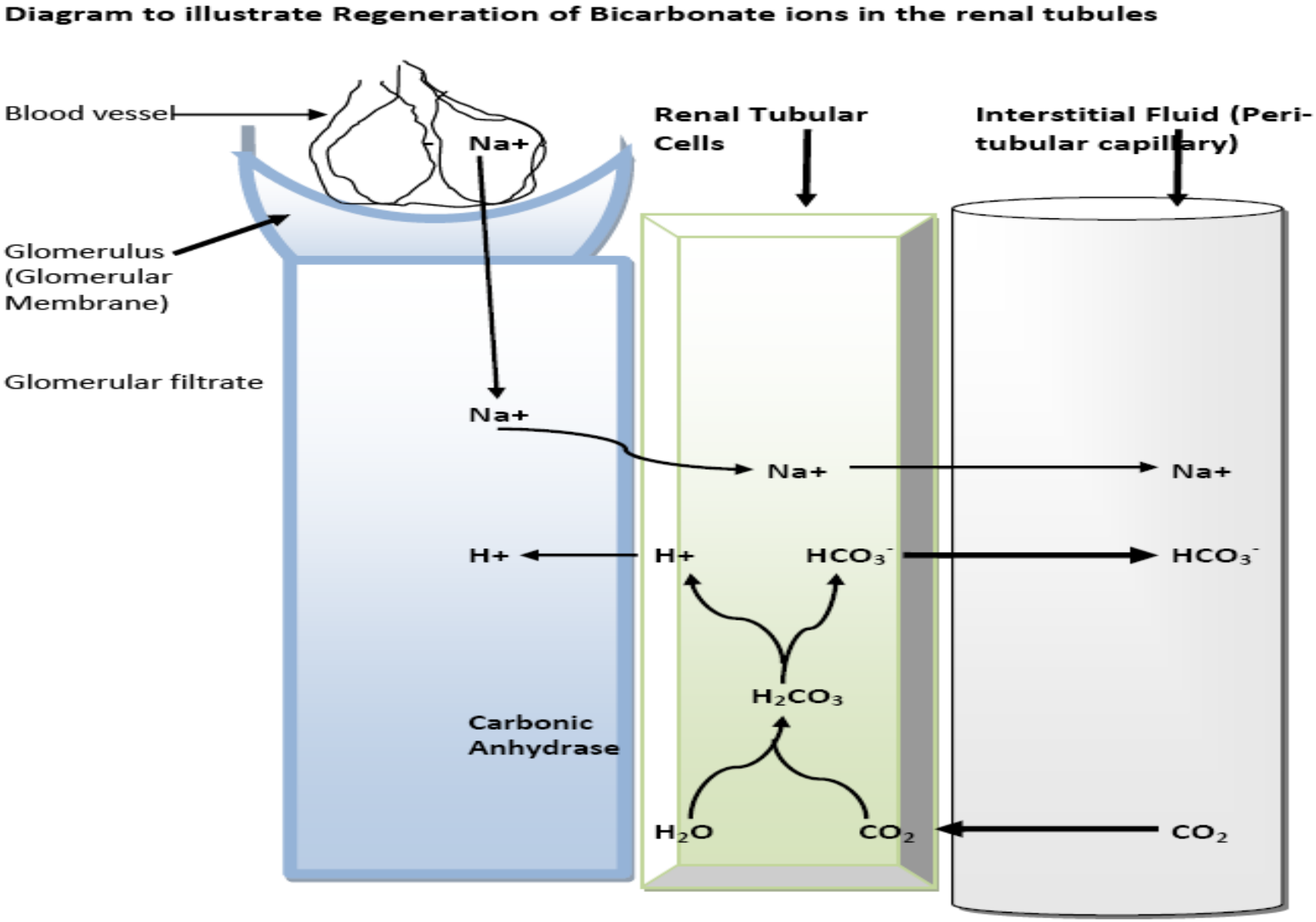
- Renal acidification mechanisms keep the blood pH within a narrow range of 7.35 – 7.45 that is vital for normal function of cellular and tissue metabolism,
- Renal Tubules regulate Acid Base Balance by the following mechanisms:
- **Re-absorption** of Sodium Bicarbonate (**$NaHCO_3$**) by Proximal Renal Tubules, (**Fig. 1**),
  - Proximal Tubule reabsorbs about 85 to 90% of filtered Bicarbonate ions (HCO_3^-),
    - **Failure of this process leads to reduction of HCO_3^- ions in the systemic blood,**
    - **Resulting in Metabolic Acidosis;**

Fig. 1: Reabsorption of Bicarbonate by Renal Tubules



- **Regeneration** of HCO^-_3 ions by Distal Tubules:
  - Distal tubule reabsorbs the remaining filtered HCO_3^- ion,
- However, after all the HCO_3^- ions have been reabsorbed, any **deficit that occurs** is **regenerated** by **Distal Tubules** (**Fig. 2**);

Fig. 2: Regeneration of Bicarbonate ions by Renal Tubules



- **Secretion of H^+ ions** and **Buffering of the H^+ ions by Ammonium and Phosphate buffers by Distal Tubule;**
- These processes include the following:
  - Formation of **Phosphate buffer** in Distal Tubules; (**Fig. 3**)
  - Production of **Ammonia (NH_3)** by Distal Renal Tubules for formation of Ammonium buffer; (**Fig. 4**),

Fig. 3: Formation of Phosphate Buffer in Renal Tubules

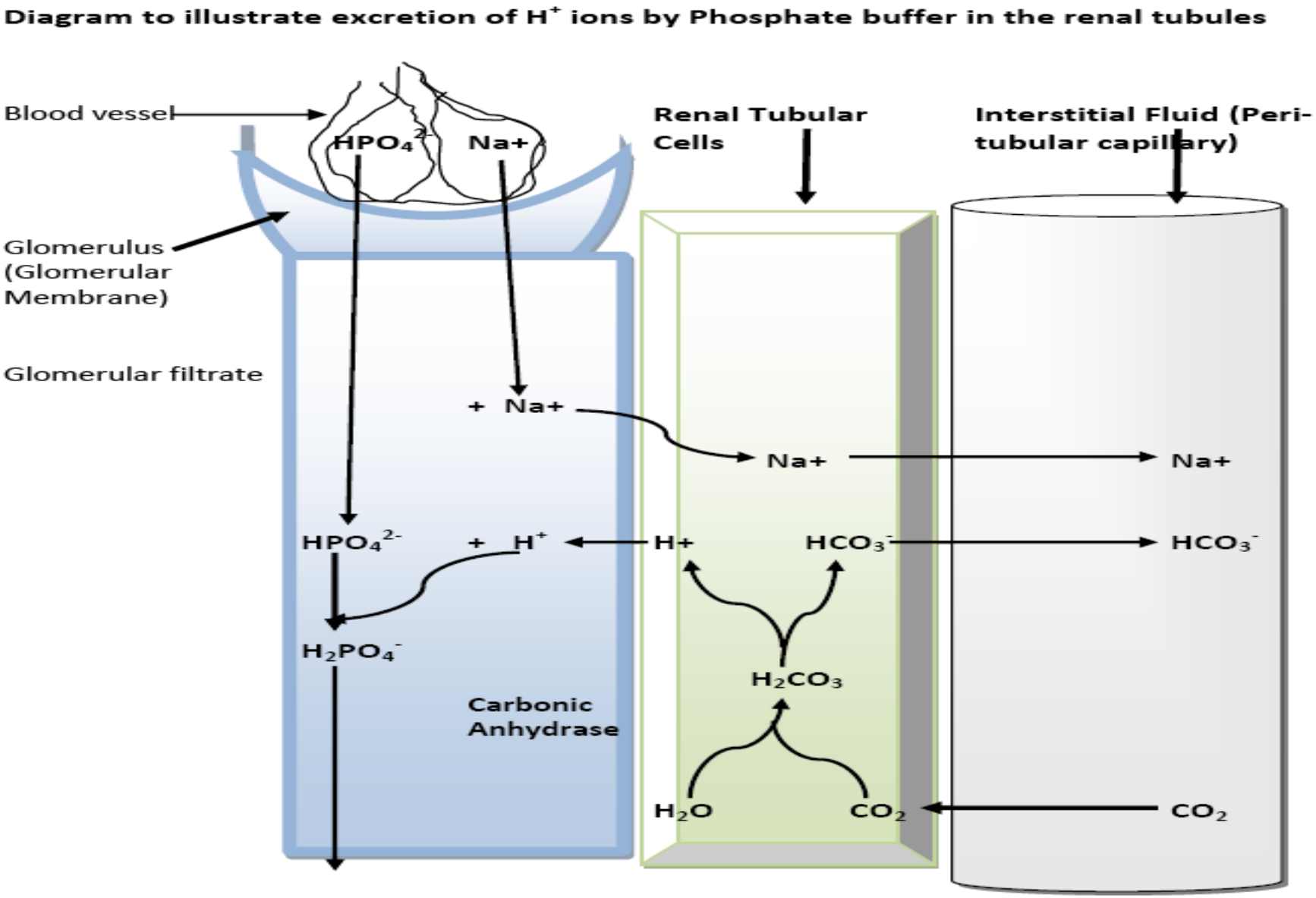
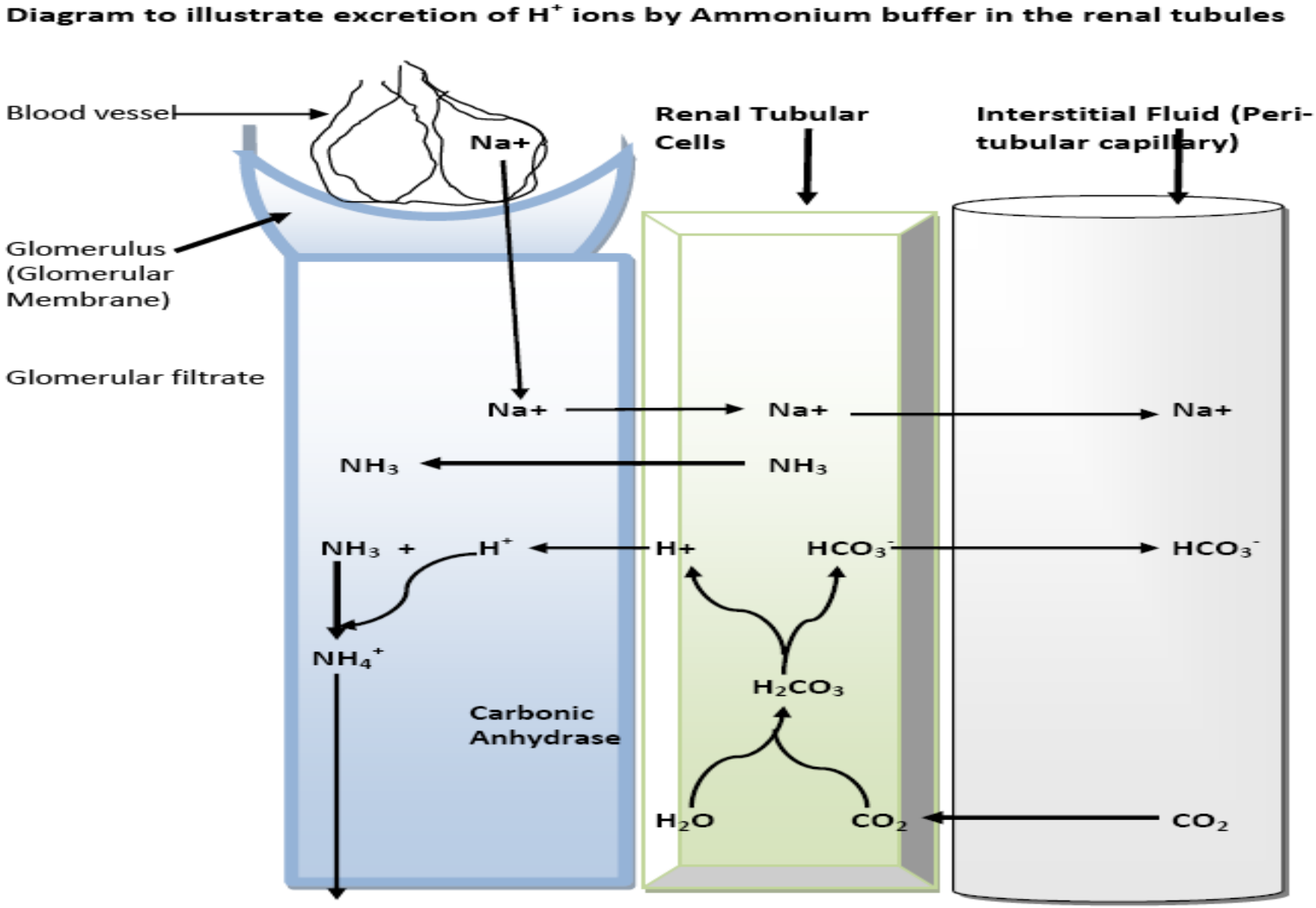


Fig. 4: Formation of Ammonium Buffer in Renal Tubules



What are the major conditions that impair handling of HCO_3^- by Kidneys?

- The major conditions include:
  - **Renal Failure,**
  - **Renal Tubular Acidosis,**
- Both involve defect in Renal Tubules,
- HCO_3^- ions reabsorption and regeneration are tubular functions;
- It is Tubular defect that causes Metabolic Acidosis,
- **Important to note**: Renal Failure also involves marked defect in Glomerular Filtration,

What are some of the possible causes of RTA in children?

- RTA in children in majority of cases is Congenital;
  - Can be Inherited as Recessive or Dominant trait,
  - Can be associated with Genetic disorders like Salt Loosing Congenital Adrenal Hyperplasia,
- Sickle cell disease,
- Carbonic Anhydrase II deficiency,
- Some cases are acquired, may be due to use of drugs like outdated Tetracycline, or by Heavy metals, etc,
- Withdrawal of the causative agent can result in cure,

What are some of the signs and symptoms of RTA in infants?

- When other disease conditions are excluded (e.g. Diarrhoea) a number of signs and symptoms can be considered, when due to no apparent cause a child:
  - Fails to put on weight or loses weight,
  - Becomes Dehydrated,
  - Excessive urine output (Polyuria),
  - Excessive Thirst,
  - Weakness,
  - Poor appetite,
  - Vomiting,
  - Constipation,

- Muscle weakness, which may be severe enough to cause Paralysis of respiratory muscles due to Low Serum Potassium levels (Hypokalemia),
- Breathlessness with air hunger type of breathing due to Acidosis may be seen in severe cases,
- Rickets & Bony Deformities occur late in the disease,
- Skeletal deformities due to RTA occur because Calcium from the bones is mobilized to buffer excess H^+ ions and bones become Demineralised, Deformed, Bowed and can sustain fractures;

- In clinically suspected cases, Arterial Blood Gas estimation will reveal Low Serum HCO^-_3 /pCO_2 level with Low blood pH and Normal Anion Gap,
- Urinary pH may be inappropriately high (>5.5) for the level of Acidosis in distal RTA,

What is Anion Gap?

- **Anion Gap (AG)** calculation is the sum of routinely measured Cations minus routinely measured Anions:

$$\textbf{Anion Gap} = (Na^+ + K^+) - (Cl^- + HCO_3^-)$$

- However, because K^+ is a small value it is usually omitted from the AG equation; the most commonly use equation is:

$$\textbf{Anion Gap} = Na^+ - (Cl^- + HCO_3^-)$$

- Venous value of HCO_3^- should be used in calculation;
- Venous value of CO_2 can be used in place of Bicarbonate

The equation will then be: **$AG = Na^+ - (Cl^- + CO_2)$**

- Normal AG calculated without K^+ is about **12.4mEq/L;**

What causes Anion Gap?

- Anion Gap exists because not all Electrolytes are routinely measured;
- Normally there is electrochemical balance in cells; thus

  Total Anions = Total Cations;
- However, several Anions are not measured routinely, leading to the Anion Gap;
- Anion Gap is thus an artifact of measurement, and not a Physiologic reality;

How can Distal RTA (Type I RTA) be characterised?

Distal RTA (Type I RTA):

- Reduced capacity of Distal Tubule to lower pH in Luminal fluid,
- Defect may be due to:
  - Failure to eliminate H^+ ions,
  - Failure in H^+ ions secretion, or
  - Retention of H^+ ions in the renal tubular lumen,

Consequences of Distal RTA

- High Urinary pH (above 5.5),
- Reduced Excretion of Titrable Acid and Ammonium ions,
- Mild Bicarbonaturia (HCO_3^- ions in urine), because a small amount of HCO_3^- is reabsorbed distally,
- Plasma [HCO_3^-] is often below 10mmol/L,
  - Severe Hypobicarbonatemia,
- Plasma [K^+] usually low, but may be normal,
- GFR relatively normal,
- **Subdivisions of Type I RTA**:
  - Related to difficulties in maintaining a secretory H^+ ion gradient in Distal Tubule,

How can Proximal RTA (Type II RTA) be characterised?

Proximal (Type II) RTA:

- Relative decrease in ability of Proximal Tubule to reabsorb filtered HCO_3^- ions causing metabolic acidosis,
  - Associated with loss or failure to reabsorb HCO_3^-
- Decreased Ammonium excretion into Tubule lumen,
- Type II RTA is often part of Fanconi syndrome:
  - Proximal Tubule loss of Glucose, Calcium, Phosphate, other Electrolytes, and Organic Acids,
- Inhibitors of Carbonic Anhydrase cause Type II RTA,

Consequences of Type II RTA

- Clinically associated with failure to thrive,
- Urine pH above 5.5 as Acidosis develops,
- Urine pH below 5.5 when Acidosis is fully established,
- Plasma [HCO_3^-] typically 15 – 20mmol/L,
  - Moderate Hypobicarbonatemia;
- Plasma [K^+] usually low, but may be normal,
- Substantial Bicarbonaturia (high HCO_3^- in urine),
- GFR relatively normal,

How can Type IV RTA be characterized?

Type IV: Hyperaldosteronism, Aldosterone resistance, Hyperkalemic RTA):

- Typically diagnosed when RTA is associated with Hyperkalemia,
- Causative defect is decreased Aldosterone Secretion, often secondary to Low Renal Renin secretion ("Hyporeninemic Hypoaldosteronism"),
  - Acidosis Inhibiting production of NH_4^+ ion,

- Defect in Distal Tubule Aldosterone Receptor ("Aldosterone Resistance") may be present,
- In some case, a receptor defect is the sole cause,
- Type IV RTA can result from numerous causes:
  - Decreased Aldosterone,
  - Increased Renal Resistance to Aldosterone,
  - Presence of Aldosterone Antagonist, example: Spironolactone,

Consequences of Type IV RTA

- Associated with Increased Renin Activity,
- Hyponatraemia,
- Hyperkalemia and Volume Depletion,
- Urine pH usually below 5.5,
- Plasma [HCO_3^-] typically 15 – 20mmol/L,
  - Moderate Hypobicarbonatemia,
- Plasma [K^+] High,

Some Laboratory Tests Useful in Diagnosis of RTA

Urine pH:

- Urine pH greater than 5.5 in the presence of Acidosis is diagnostic of Type I RTA (Distal RTA) if the following conditions are excluded:
  - Urea-splitting UTI (which raises urine pH),
  - Hypokalemia (which stimulates NH_3 production, buffering free protons),
  - Avid salt retentive state,
- Other lab tests include:
  - Net Acid Excretion; Urine Acidification Tests;
  - Na_2 SO4 administration;
  - Fractional Excretion of HCO_3^- (Fe_{HCO3}^-);

REFERENCES

- Textbook of Biochemistry, with clinical correlations, Ed. By T. M. Devlin, 4th Ed.
- Harper's Illustrated Biochemistry 26th Edition; 2003; Ed. By R. K. Murray et. al.
- Biochemistry, By V. L. Davidson & D. B. Sittman. 3rd Edition.
- Hames BD, Hooper NM, JD Houghton; Instant Notes in Biochemistry, Bios Scientific Pub, Springer; UK.
- VJ Temple Biochemistry 1001: Review and Viva Voce Questions and Answers Approach; Sterling Publishers Private Limited, 2012, New Delhi-110 – 020.