Lecture 8
Renal regulation of acid-base balance

Learning Objectives:

By the end of the lecture the student will be able to:

1. Define the normal range for plasma pH.
2. Explain the role of the kidney in the steady state elimination of acid produced daily by metabolism.
3. Outline the defence mechanisms which act to prevent an abrupt change in pH in response to an acid load.
4. Describe the mechanism for acid transport in the different nephron segments.
5. Recognize the clinical and biochemical features of metabolic acidosis, list some causes and give an approach to the differential diagnosis.
6. Recognize metabolic alkalosis, list some causes, and explain the pathophysiology of this disturbance during prolonged vomiting.

Acid-Base Balance

- Acid-base balance means keeping the H^+ concentration in the body fluids constant. This is essential for homeostasis because the activities of almost all enzyme systems in the body are influenced by H^+ concentration. Therefore, changes in H^+ concentration alter virtually all cell and body functions.

- The normal H^+ concentration in the arterial plasma is 0.00004 mEq/litre, because it is low, H^+ concentration have been expressed on logarithm scale, using pH units. pH is related to the actual H^+ concentration.

- So the normal H^+ concentration in the arterial plasma is 7.4, whereas the pH of venous blood and interstitial fluids is about 7.35 because of the extra amounts of carbon dioxide released from the tissues to form H_2CO_3.

Coma and death ← acidosis ← 7.35 -7.4 → alkalosis→ tetany and convulsions

The body can regulate the blood pH by the following mechanisms (arranged according rapidity of action):

1) **Buffers (very rapid control):**
   Act within a fraction of a second. They are the first line of defense against changes in the blood pH, but their power is limited.
2) **The respiratory system (relatively rapid control):**
   Take 1-15 minutes to readjust the pH. It constitutes the second line of defense against changes in the blood pH.

3) **The kidney(very slow control):**
It takes several hours to several days. It constitutes the third line of defense against changes in the blood pH. They are the most powerful and most efficient buffering mechanism.

The role of the kidney

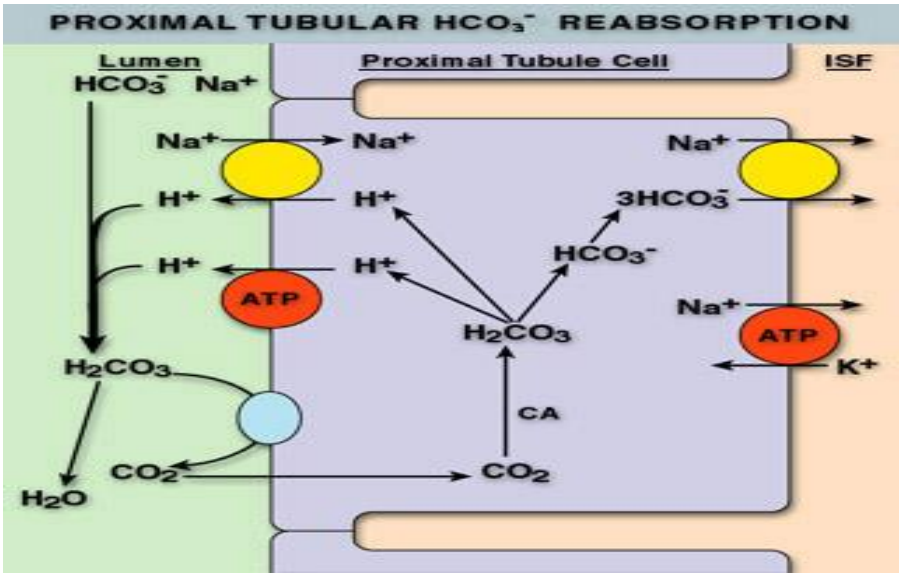
- Excreting acidic urine in cases of acidosis.
- Excreting basic urine in cases of alkalosis.
- Slow mechanism
- **Complete** as it brings the pH back to normal.
- **In cases of acidosis:**
  - increased H^+ secretion
  -increased reabsorption of filtered buffers
  -formation of titratable acids.
- **In cases of alkalosis:**
  - increased filteration of $NaHCO_3$
  - decreased reabsorption of $NaHCO_3$
  - decreased secretion of H^+.

The Renal Mechanisms in Acidosis:

1) Reabsorption of filtered HCO_3^-:

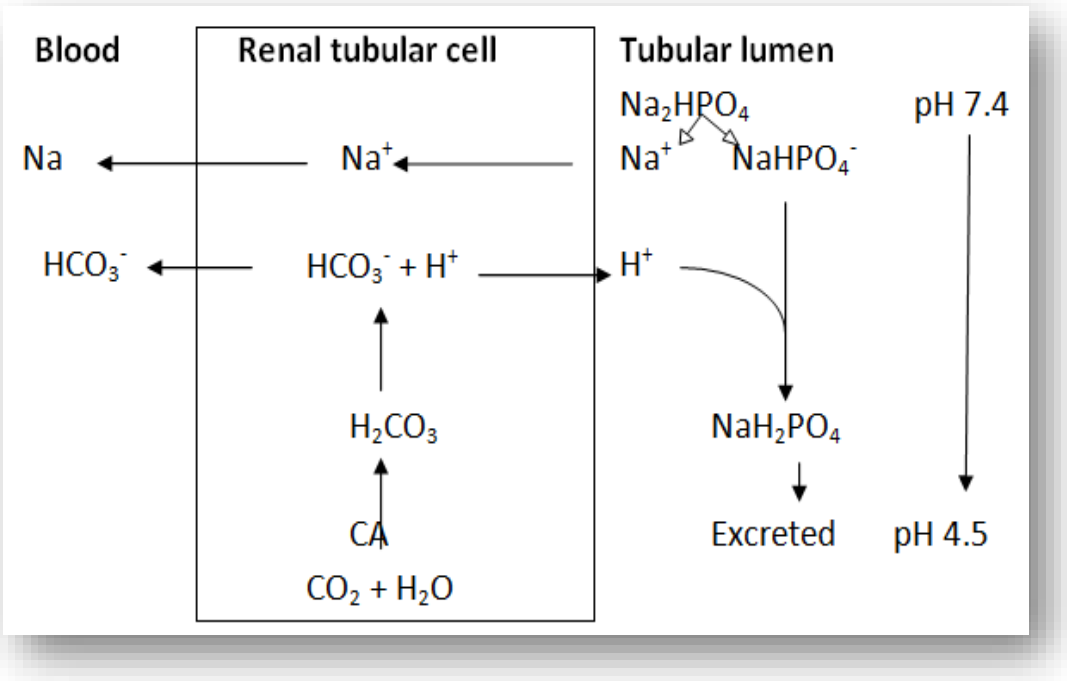
More than 99.9 of the filtered HCO_3^- is reabsorbed. Most of them in the PCT and only small quantity in LH, DCT, and CD.

In case of metabolic alkalosis, the blood HCO_3^- concentration is elevated → ↑the filtered load of HCO_3^- in the kidney which exceeds the reabsorptive capacity → HCO_3^- is excreted→ lowering blood HCO_3^- concentration to normal.



2)| Formation of titratable acids:

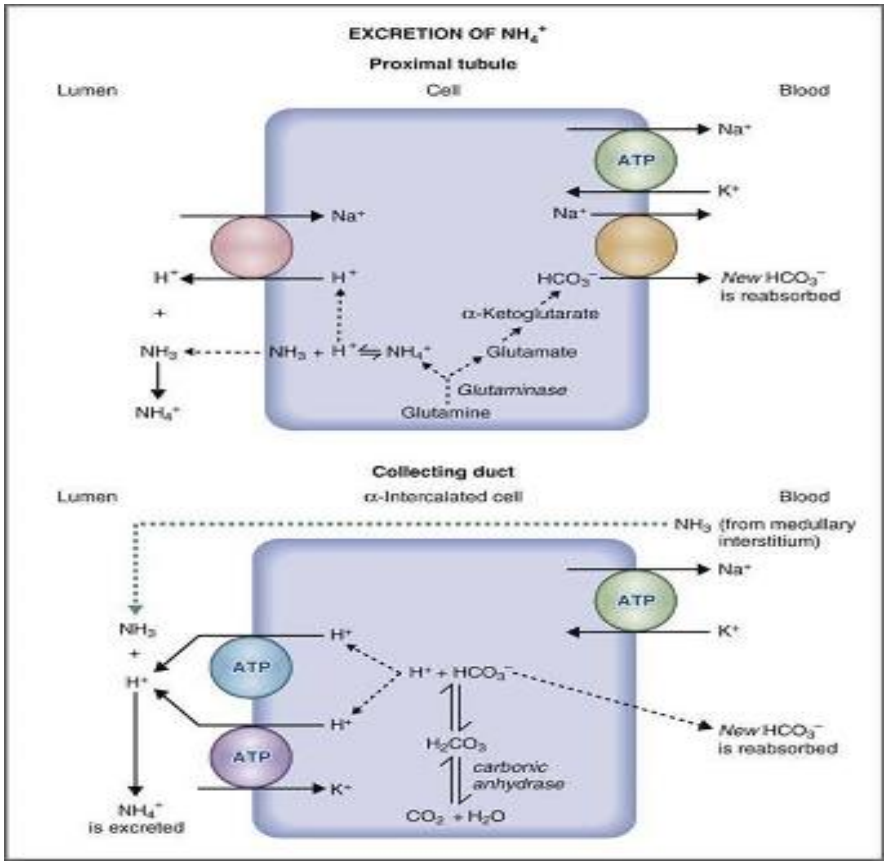
By definition, titratable acid is H^+ excreted with urinary buffers. Inorganic phosphate is the most important of these buffers because its relatively high concentration in urine and its ideal pK.
For each H^+ excreted as titratable acid, one new HCO_3^- is synthesized and reabsorbed.



2) Excretion of H^+ as NH_4^+:

If titratable acid were the only mechanism of excreting H^+, then excretion of fixed H^+ would be limited by the amount of phosphate in urine.Recall that fixed H^+ production from protein and phospholipid catabolism is approximately 50 mEq/day. On average, only 20 mEq/day is excreted as titratable H^+. The remaining 30 mEq/day is excreted by a second mechanism, as NH_4.

Mechanism of Excretion of H^+ as NH_4^+



H^+ secretion

1- H^+ is secreted in almost all parts of the the renal tubules. In PCT and early DCT it is secreted by secondary active transport, while in late DCTs and CD, it is also secreted by primary active transport (this occurs against a high H^+ gradient by the intercalated cells). However, in both instances H^+ to be secreted is formed as a result of H_2CO_3 dissociation in the cells.

2- **In PCTS**: 90% of H^+ is secreted and entirely buffered by the filtered bicarbonate. **In DCTs and CDs** 10% of H^+ is secreted and buffered by phosphate buffer and ammonia.

3- **In PCTS:** Maximal acidifying power up to 6.9. H^+ secretion occurred in exchange with Na^+ only. It is not under hormonal control. Carbonic anhydrase enzyme is essential. Reabsorption of the filtered bicarbonate (the alkali reserve) is achieved in PCT.

4- H^+ secretion in DCTs and CDs occurs only as long as the pH of the fluid in these segments is more than 4.5. If the secreted H^+ is not buffered, pH of the tubular fluid may drop below 4.5, in which further H^+ secretion would stop and acidemia may result **(significance of ammonia).**

5- **In DCTs and CDs:** Maximum acidifying power is 4.5. H^+ secretion occurred in exchange with K^+ **and** by hydrogen pump. It is under control of aldosterone hormone. Carbonic anhydrase enzyme is essential.

6- **Ammonia adaptation:** Ability of ammonia to be secreted as long as H^+ is secreted.

7- **Control of ammonia secretion:** Once ammonia is secreted it transformed into NH_4Cl (ammonium chloride) →↓level of free ammonia in tubular fluid→ maintain ammonia gradient →maintain secretion.

Clinical significance:

- **In cases of diabetic ketoacidosis**: NH_4 excretion is increased because acidosis induces the enzymes involved in glutamine metabolism, thereby increasing NH_3 synthesis.
- **In chronic renal failure**: There is metabolic acidosis. In this disease, there is progressive loss of nephrons→ ↓GFR→↓filteration load of phosphate, also ↓ synthesis of ammonia in the diseased nephrons. So persons with chronic renal failure are placed on a low-protein diet to reduce daily fixed H^+ production.

Metabolic Acidosis/Alkalosis

Metabolic acidosis (i.e. ↓ HCO_3^-):

Causes:

1. **High protein metabolism due to** the production of sulphuric and phosphoric acids.
2. **Severe muscular exercise** due to excessive formation of **lactic acid**.
3. ↑ **Fat oxidation** as in starvation and diabetes mellitus → ↑ acid ketone bodies.
4. Ingestion of **acidifying salts** as ammonium chloride.
5. **Renal failure due to** lack of ammonia formation and failure of H+ secretion.
6. Hypofunction of adrenal cortex (**Addison's disease**) due to excessive **loss** of Na+ and retention of H+
7. **Laxative abuse**. (Because intestinal secretions ordinarily contain relatively high HCO_3 concentration, diarrhea normally results in a metabolic acidosis).

Metabolic alkalosis (↑ $NaHCO_3$)

Causes:

1. High vegetable diet as it contains basic cations as K+ and Na+.
2. Ingestion of excess bicarbonate e.g. during treatment of peptic ulcer.

3. During gastric secretion (i.e. each H+ ion secreted is associated with bicarbonate ion reabsorbed → called **alkaline tide**).
4. Hyper function of adrenal cortex (**C**ushing syndrome); Na+ is reabsorbed in **exchange** with H+ which is secreted in **urine**.
5. Persistent **vomiting** due to HC1 loss.

Reference:

- First Aid for the Basic Sciences: Organ Systems, Third Edition, Pages: 630-634.
- Lippincott Illustrated Reviews:Integrated System Pages:282-283.
- Oxford Hand Book for Medical Sciences Pages: 502-503.