UGS

Physiology

Doctor 2021

Sheet (3)

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Acid-Base Balance

The **renal system** works with the **respiratory system** in a harmony to maintain acid-base balance in our bodies. Additionally, the **buffer system** plays a crucial contributory role in this process.

The PH in our bodies must be maintained in a narrow range (**7.2-7.4**) to preserve the normal function of the enzymes which perform their function within that narrow pH.

PH value represents the acidity, which mainly mirrors the H^+ level in the body. H^+ is precisely regulated at 3-5 x 10^{-8} moles/L (pH range 7.2 -7.4).

Metabolic activity in our bodies produces acids, which are classified according to the way the body gets rid of them into **volatile** and **non-volatile acids**.
Volatile acids are eliminated by CO_2 expiration. **Nonvolatile** acids are organic acids produced in larger quantities than volatile acids and cannot be eliminated simply by CO_2 expiration. However, they get titrated before excretion.

What is the reason behind maintaining a PH within a narrow range despite the continuous production of acids from the body?

❁ The body uses three main systems to regulate the concentration of hydrogen ions (H+) in the body fluids. (which helps prevent conditions like acidosis or alkalosis):

1. **Body fluid chemical buffers** → first-line, rapid but temporary.
   (Ex. Bicarbonate, ammonia and ammonium, proteins, and phosphate).

2. **Lungs** → second line, **rapid**, eliminate volatile acids by CO_2 expiration.
   ❖ They cannot work alone and perfectly regulate the pH due to the presence of non-volatile acids that cannot be eliminated through the lungs.

3. **Kidneys** → the most powerful but **slower**, so it is in the third line, eliminate non-volatile acids. By secreting H^+, reabsorbing HCO_3^- or they may generate new HCO_3^-.
   ❖ This is important when the production of H^+ is more than what the body can titrate. In such cases, the kidneys play a crucial role in eliminating the excess H^+ and generating new $HCO3^-$ to restore the acid-base balance.

Buffer Systems in the Body

Buffer: a chemical compound resists the significant drop or increase in the pH; by accepting H^+/ releasing H^+, or accepting OH^-. Therefore, resist changes in the PH.

Main body fluid compartment: ICF, ECF (plasma and interstitial), and urine.
For each one of these compartments, we have an **important buffer** (Bicarbonate, ammonia and ammonium, proteins, and phosphate).

The **effectiveness** of the buffer system depends on:

- The concentration of reactants (buffer substances) in the compartment.
- pK of system and pH of body fluids, and their proximity to each other; buffers work most effectively in a pH **close** to their pk. pk is the constant dissociation of the buffer.

1. Bicarbonate: most important **ECF** buffer.

$$H_2O + CO_2 \leftrightarrows H_2CO_3 \leftrightarrows H^+ + HCO_3^-$$

- H_2CO_3 is a weak acid, so it does not disassociate easily. It disassociates into H^+ and HCO_3^-.
- The direction of the reaction goes in both ways depending on the body's needs.
- The reaction is catalyzed by carbonic anhydrase enzyme.
- To calculate the PH by **Henderson-Hasselbalch Equation**, we need:
  ✓ **pk** of the Bicarbonate. ✓ the **concentration of Bicarbonate**. ✓ the **concentration of CO_2**. But because the concentration of CO_2 is hard to obtain, so we calculate the **partial pressure of CO_2** and multiply it by a **constant (a).** ✓ The Henderson-Hasselbalch Equation:

$$pH = pK + \log \frac{HCO_3^-}{\alpha \; pCO_2}$$

$\alpha = 0.03$
$pK = 6.1$

✓ If HCO_3^- concentration equals CO_2 concentration, pH will equal pk.

Titration curve for bicarbonate buffer system:

- **The normal operating point in the body** differs for each buffer. for bicarbonate, it's when pH equals 7.4. The effectiveness here is **NOT** at its best, (The effectiveness at best when pk = pH), but their concentration is very high, and the components of the system (CO_2, HCO_3^-) are closely regulated by the lungs and the kidneys, so it's considered the **best buffer**.

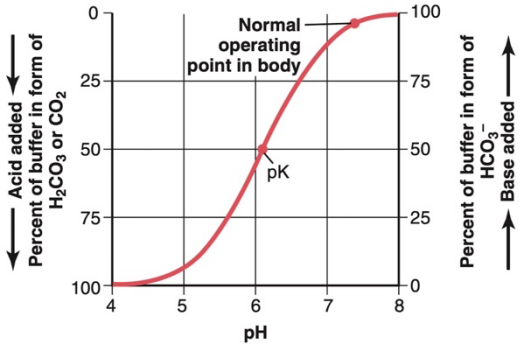


Figure 31-1. Titration curve for bicarbonate buffer system showing the pH of extracellular fluid when the percentages of buffer in the form of HCO_3^- and CO_2 (or H_2CO_3) are altered.

- When there is 50% from both reactants (acid and base) in the compartment, pH will equal pK and equal 6.

2. **Phosphate**: it is an important **renal tubular** buffer; why?

- The phosphate buffer system is an important **renal tubular buffer** due to the high concentration of phosphate ions ($PO4^{3-}$) present in the tubular fluid. This is because phosphate is a major intracellular electrolyte that is also found in high amounts in the tubular fluid, but not the extracellular compartment. The tubular fluid also contains a high concentration of hydrogen ions (H^+) due to filtration and reabsorption processes in the nephrons. The phosphate buffer system helps maintain the pH of the tubular fluid and urine by neutralizing these excess H^+ ions, ensuring that the urine pH does not drop below 4.5. pK for phosphate is 6.8 which is close to the pH of urine. $HPO_4^- + H^+ \leftrightarrows H_2PO_4^-$

3. **Ammonia**: important **renal tubular** buffer. $NH_3 + H^+ \leftrightarrows NH_4^+$

4. **Proteins**: important **intracellular** buffer. By looking at the amount of the protein in our bodies, it must be the most effective candidate for the buffering capacity. However, because the proteins are mostly intracellular, it's hard for acids to enter the cell to get titrated by proteins so they're very slow and need hours or maybe days to be titered.
   -As a result, they make a relatively minimal direct contribution to the extracellular buffer system responsible for maintaining the overall PH balance in the body.
   Ex. Hemoglobin in the RBCs
   $H^+ + Hb \leftrightarrows HHb$

❖ 60-70% of buffering capacity is in the cells. mostly due to the presence of proteins.

Importance of Buffer Systems

- Normal H^+ concentration = 0.00004 mmol/L ($4 * 10^{-5}$ mmol/L)
- Amount of **non-volatile** acid produced ~ 60-80 mmol/day. 80 mmol /42 L = 1.9 mmol/L = 47,500 times > normal H^+ concentration.
- We need a high buffering capacity to titrate the non-volatile acid that is produced, to maintain the pH within the normal narrow range.
- The minimum and maximum pH of the body with which a person **can live for only a few hours** is 6.8-8.

Respiratory Regulation of Acid-Base Balance

$$H_2O + CO_2 \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^-$$

The respiratory system eliminates **volatile** acids by CO_2 expiration, thus increasing H^+ loss.

Acidosis → activation of respiratory centers → adjusting the rate of ventilation → rapid compensation by elimination of volatile acids in the form of CO2.

Alkalosis → reducing the rate of ventilation → keeps H^+ in the body to titrate the Alkalinity.

Feedback Gain = 1.0 to 3.0 (corrects 50 to 75 %) but we still need the kidney.

Renal Regulation of Acid-Base Balance

The kidney eliminates **non-volatile** acids by:
- Secretes H^+ mainly by intercalated cells.
- Adjust the reabsorption of HCO_3^-.
- Generates new HCO_3^-.

The kidney conserves HCO_3^- and excretes acidic or basic urine depending on the body's needs.

Reabsorption of bicarbonate (and H^+ secretion) in different segments of the renal tubule.

- Key point: For each HCO_3^- reabsorbed, there must be an H^+ secreted (1:1).
- Filtration of HCO_3^- (~ 4320 mmol/day).
- In PCT, 70-80% of the filtered bicarbonate will be reabsorbed.
- In Thin Henle, no change in bicarbonate concentration.

- In Thick Henle, 10% of the filtered bicarbonate will be reabsorbed.
- Late Distal and Collecting tubules; a variable range of reabsorbing; fine-tuning to the bicarbonate level in the blood according to the body's needs. More acidosis leads to more reabsorption of bicarbonate, more alkalosis leads to more excretion of bicarbonate.
- Finally, (1mEq/day) of bicarbonate will execrate, and 4319 mmol of H^+ is secreted.
- This could differ according to the acid-base balance in the body.

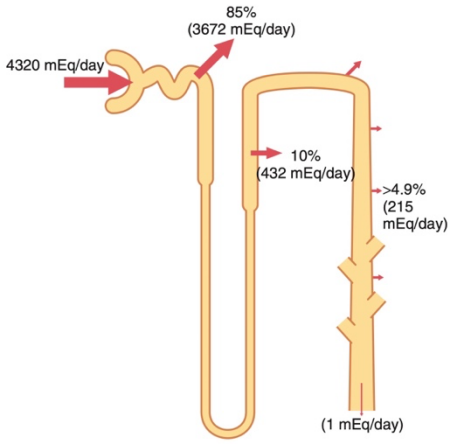


Figure 31-4. Reabsorption of bicarbonate in different segments of the renal tubule. The percentages of the filtered load of HCO_3^- absorbed by the various tubular segments are shown, as well as the number of milliequivalents reabsorbed per day under normal conditions.

Mechanisms for HCO_3^- reabsorption, and Na+ - H^+ exchange in the proximal tubule and thick loop of Henle.

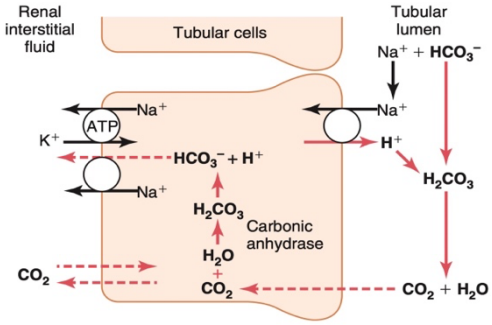


Figure 31-5. Cellular mechanisms for (1) active secretion of H^+ into the renal tubule; (2) tubular reabsorption of HCO_3^- by combination with H^+ to form carbonic acid, which dissociates to form carbon dioxide and water; and (3) sodium ion reabsorption in exchange for H^+ secreted. This pattern of H^+ secretion occurs in the proximal tubule, the thick ascending segment of the loop of Henle, and the early distal tubule.

- In the basal surface of tubular cells, we have Na^+/K^+ ATPase and HCO_3^- / Na^+ co-transporter, which is a secondary active transporter that depends on the Na^+/K^+ ATPase's gradient.
- On the proximal surface of tubular cells, we have Na^+/H^+ exchangers.
- HCO_3^- and H^+ will generate in the tubular cells by dissociation of carbonic acid.
- HCO_3^- reabsorption via HCO_3^- / Na^+ co-transporters. H^+ secretion via Na^+/H^+ exchangers.
- In the tubular lumen, secreted H^+ will bind with filtered HCO_3^- to produce carbonic acid which will disassociate into water and CO_2.
- CO_2 diffuses into the cell and binds with the water to produce carbonic acid which will generate HCO_3^- and H^+.
- H^+ secreted, HCO_3^- reabsorbed. This will be repeated over and over, (continuous process).
- For each HCO_3^- reabsorbed, there must be an H^+ secreted (1:1).
- Minimal pH results from these mechanisms ~ 6.7.

HCO_3^- reabsorption and H^+ secretion in intercalated cells of late distal and collecting tubules.

- Two types of intercalated cells; A and B.

- Type A intercalated cells; in the proximal surface of tubular cells, we have H^+ ATPase pumps and H^+/K^+ antiporters which are both primary active transporters that work against gradient by consuming ATP.
- In the basal surface of tubular cells, we have HCO_3^-/Cl^- exchangers (facilitated diffusion).
- HCO_3^- and H^+ will generate in the tubular cells by dissociation of carbonic acid.
- H^+ secretion via H^+ ATPase pumps and H^+/K^+ antiporters.
- HCO_3^- reabsorption via HCO_3^-/Cl^- exchangers.
- For each HCO_3^- reabsorbed, there must be an H^+ secreted (1:1).
- Minimal pH results from these mechanisms ~4.5, so it's more efficient in increasing urine acidity. (More acidifying the urine).

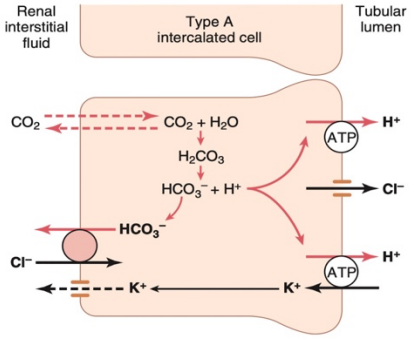


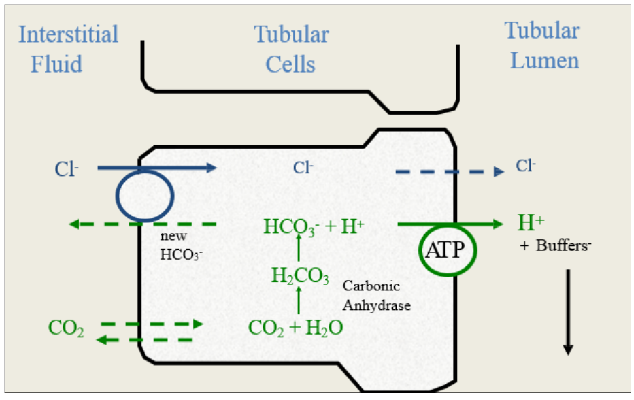
Figure 31-6. Active secretion of H^+ through the luminal membrane of the type A intercalated epithelial cells of the late distal and collecting tubules. Type A cells contain hydrogen–adenosine triphosphatase (ATPase) and hydrogen-potassium-ATPase in the luminal membrane and secrete hydrogen ions while reabsorbing bicarbonate and potassium ions in acidosis. Note that one HCO_3^- is absorbed for each H^+ secreted, and one chloride ion is passively secreted along with H^+.

Regulation of H^+ secretion by the kidney

- Increased **plasma CO_2** increases H^+ secretion. → **respiratory acidosis**, Increased plasma CO_2 means that the lung doesn't eliminate CO_2 efficiently.
- Increased **extracellular H^+** increases H^+ secretion. → **metabolic, or respiratory acidosis.**
- Increased **tubular fluid buffers** increase H^+ secretion. → **metabolic, or respiratory acidosis.**

Generates New Bicarbonate

- In acidosis (more H^+), the body will compensate by secrete H^+ and reabsorb HCO_3^- (1:1).
- But we have a huge amount of H^+ thus, we will reach a point where all the filtered bicarbonate is reabsorbed and **not** all the excess hydrogen is excreted. (Still there H^+ not titrated by HCO_3^-).
- Excess H^+ in the tubular lumen will be buffered by a **different buffer other than bicarbonate.**
- For each H^+ secreted **without bicarbonate** reabsorption, this considers **a new bicarbonate generation** to the system.
- This mechanism increases the efficiency of the kidney by buffering all the excess H^+ even without bicarbonate with the generation of new ones.



Importance of Renal Tubular Buffers

Minimum urine pH = 4.5 → corresponding to an H+ concentration of 10−4.5 mEq/L, or 0.03 mEq/L (remember mmol = mEq / valence)

The maximal [H^+] of urine is 0.03 mmol/L Yet, the kidneys must excrete, under normal conditions, at least **60 mmol of non-volatile acids** each day. To excrete this as free H^+ would require:

$$\frac{60 \text{ mmol}}{.03 \text{mmol/L}} = 2000 \text{ L per day !!!}$$

So, tubular fluid volume must be **2000 L** to excrete **60 mmol of non-volatile acids,** which is impossible. However, there must be other buffers than bicarbonate.

(Titrating secreted H^+ with HCO_3^- and any excess H^+ with a **different buffer** other than HCO_3^-):

Important **renal tubular** buffers mentioned earlier : **phosphate and ammonia.**

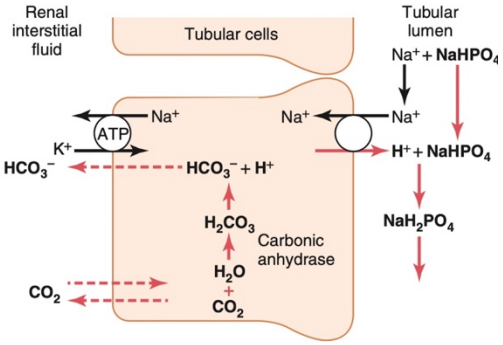


Figure 31-7. Buffering of secreted H^+ by filtered phosphate ($NaHPO_4$). Note that a new HCO_3^- is returned to the blood for each $NaHPO_4$ that reacts with a secreted H^+.

1. phosphate

- Once the phosphate is filtered into the tubular lumen, it is united with H^+ that has been secreted (excess hydrogen that has not been buffered by bicarbonate).
- H^+ binds $NaHPO_4^-$ in the tubular lumen forming NaH_2PO_4.

$$NaHPO_4^- + H^+ \leftrightarrows NaH_2PO_4$$

- For each H^+ titrated by phosphate, we consider **the generation of new bicarbonate** (buffering the hydrogen with other buffers than bicarbonate).
- Phosphate normally buffers about 30 mmol/day of H^+ (about 100 mmol/day phosphate is filtered but 70 % is reabsorbed).

- In **chronic acidosis**, phosphate is **not** the major tubular buffer; Phosphate buffering capacity does not change much with acid-base disturbances (the body doesn't physiologically regulate the phosphate production in chronic acidosis).

2. Ammonia and Ammonium

- In the tubular cell of the proximal tubules, thick Henle, and distal tubules, **Glutamine** is broken down into **bicarbonate and ammonium**.
- **Ammonium NH_4^+** is secreted in exchange for Na^+ and bicarbonate will be reabsorbed, so we have a generation of new bicarbonate.
- In the tubular cell of the collecting ducts, ammonium could be broken down into H^+ and ammonia NH_3^-.
- **Ammonia** secretes into the tubular lumen and binds with the secreted H^+ that is not buffered by bicarbonate or any other buffer to form **ammonium**.
- titration without consuming bicarbonate considers the generation of new bicarbonate.
- The source of ammonia in the tubular lumen is either absorbed from the blood into the tubular cell and then secreted into the lumen or is present in the tubular lumen in high concentration.

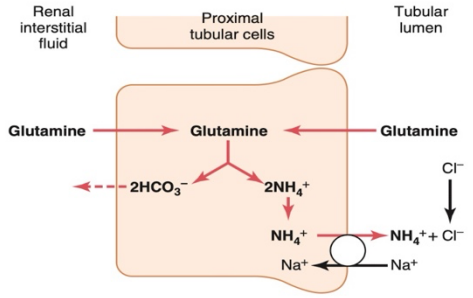


Figure 31-8. Production and secretion of ammonium ion (NH_4^+) by proximal tubular cells. Glutamine is metabolized in the cell, yielding NH_4^+ and bicarbonate. The NH_4^+ is secreted into the lumen by a sodium-NH_4^+ exchanger. For each glutamine molecule metabolized, two NH_4^+ are produced and secreted and two HCO_3^- are returned to the blood.

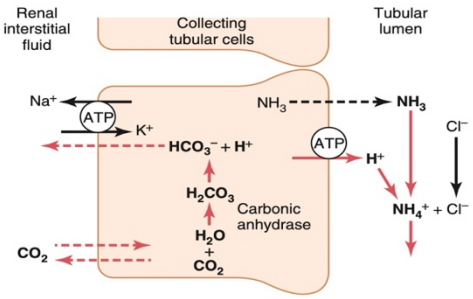
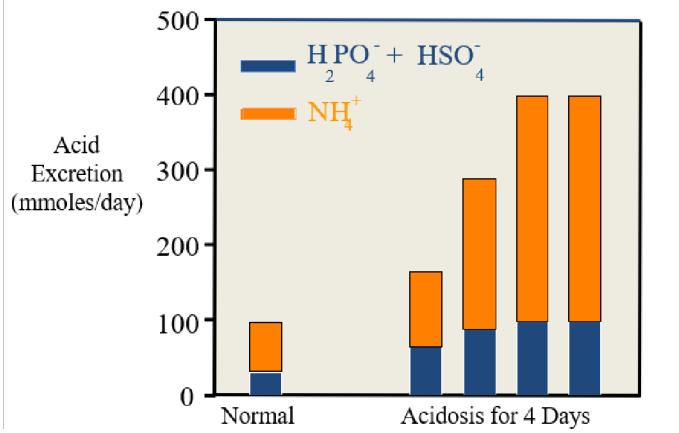


Figure 31-9. Buffering of hydrogen ion secretion by ammonia (NH_3) in the collecting tubules. Ammonia diffuses into the tubular lumen, where it reacts with secreted H^+) to form NH_4^+, which is then excreted. For each NH_4^+ excreted, a new HCO_3^- is formed in the tubular cells and returned to the blood.

Ammonia is more important than phosphate in **chronic acidosis**; the level of phosphate production in the tubular fluid doesn't change in response to chronic acidosis whereas the level of ammonium **increases**. this is because of the physiological regulation on the production of ammonium.

This graph illustrates a comparison between phosphate and ammonium buffers in chronic acidosis.



Quantification of Normal Renal Acid-Base Regulation

Total H+ secretion =
4320 mEq of H^+ secreted (reabsorbed HCO_3^-) + **60 mEq** of H+ non-volatile= 4380 mEq

- Total H+ secretion = 4380 mmol/day.
- Non-votile ⇒ $NaHPO_4^-$ and NH_4^+

⇒ HCO_3^- reabsorption **(4320 mmol/d)** + titratable acid ($NaHPO_4^-$) **(30 mmol/d)** + NH_4^+ excretion **(30 mmol/d)** = **4380 mmol/day**

❖ Titratable acid refers to the amount of acid that can be neutralized by titrating with a base until a specific endpoint, such as a target pH, is reached.

Net H^+ excretion=
H^+ excreted by buffers not bicarbonate (new bicarb) - new H^+ added to blood (HCO3- excreted).

- Net H^+ excretion = 59 mmol/day

= titratable acid **(30 mmol/d)** + NH_4^+ excretion **(30 mmol/d)** - HCO excretion **(1 mmol/d)** (or new H to blood).

- If the net H^+ excretion is negative, this means the body is in an alkalosis state. In this case, the body starts reabsorbing H^+ instead of secreting it.