Renal Regulation of acid-base balance :

Body Defense against changes in H+ concentration

There are three lines of defense to regulate the body's acid– base balance and maintain the blood pH (around 7.4):

1. Buffer systems of body fluid. (ex: bicarbonate buffer, Hb , plasma protein)
   - Form first line of defense and act Immediately to combine with H+ to prevent changes in H+ concentration
   - Bicarbonate buffer : **CO2 +H2O ↔H2CO3 ↔ H + HCO3**
2. Respiratory mechanism to regulate acid–base balance
   - Forms second line of defence and acts within few minutes via respiratory centre to regulate CO_2 level.
3. Renal mechanism to regulate acid–base balance
   - Is the 3rd line of defense. it is Slow, but most powerful & effective mechanism in pH regulation.

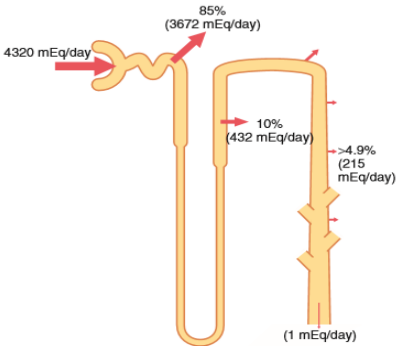
Principles

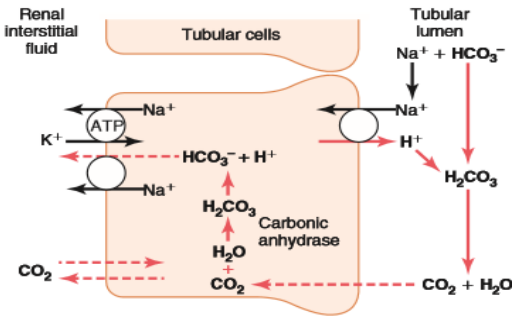
- Each day the body produces two types of acid :
  - Volatile : excreted by lung as CO2
  - Nonvolatile acids, mainly from the metabolism of proteins. These acids are called **nonvolatile** because they are not H_2CO_3 and cannot be excreted by the lungs. They are removed from the body by renal excretion .
- Each day the kidneys filter about 4320 mEq of bicarbonate (180 L/day x 24 mEq/ L); normaly almost is reabsorbed from the tubules
- Same amount of H+ must be secreted each day just to reabsorb the filtered bicarbonate→ conserving the primary buffer system of the extracellular fluid. Then an additional 80 meq of H+ must be secreted to excrete the nonvolatile acids .
- Normal Urine pH is 6 (acidic) . In certain conditions can range from 4.5-8.
- The Kidneys regulate extracellular acid base balance by :

  1. **Reabsorb filtered HCO3**
  2. **Secrete H ions**
  3. **Produce new HCO3.**

H^+ secretion and $HCO3^-$ reabsorption (by Na-H counter-transport)**:**

- Occurs in PCT and thick ascending limbs of the loop of Henle.
- In PCT about 80 to 90 %of the HCO3− reabsorption (H+ secretion) and urine pH is ↓to only 6.7 because all H ion is titrated with HCO3 .
- In the thick ascending LH, 10 % of the filtered HCO3− is reabsorbed.
- For each $HCO3^-$ reabsorbed, a H^+ must be secreted:
  - CO_2 either diffuses into the tubular cells from the blood or is formed by metabolism in the tubular epithelial cells.
  - CO_2+H_2O (by carbonic anhydrase) $\rightarrow H_2CO_3 \rightarrow HCO_3 + H^+$.The H^+ is secreted into the tubular lumen by Na-H counter transport.
  - The generated HCO_3^- moves across the basolateral membrane through: Na^+-$HCO3^-$ co-transport or Cl^-- $HCO3^-$ exchange (anion exchanger)
  - $HCO3^-$ that is filtered by the glomerulus cannot be directly reabsorbed. Instead, it combines with secreted H+ in the tubular fluid to form $H_2CO_3 \rightarrow CO_2$ and H_2O. Then CO2 can move easily into the cell.
  - The net result is that for every H^+ secreted into the tubular lumen one HCO^{3-} enters the blood





Secretion of H^+ in the late distal and collecting tubules (by aldosterone):

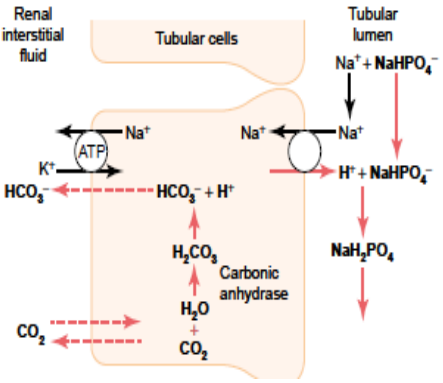
- In the late DCT and CD 5% of H+ secretes by primary active transport.(H-ATPase and H-K -ATPase transporter) in intercalated cells.
- For each H+ secreted, a HCO3− is reabsorbed, similar to the process in the proximal tubule. pH could reach as low as 4.5

Renal Buffering system:

- Normally, the rate of tubular H^+ secretion and the rate of filtration by $HCO3^-$ are equal, "titrate" each other in the tubules.
- Only small amount of excess H+ (about 80 mEq/day) is excreted as free H+ because the limiting PH is 4.5 after which the H secretion stops → excretion by combination with other urinary buffers, especially phosphate and ammonia .

Phosphate buffer system :

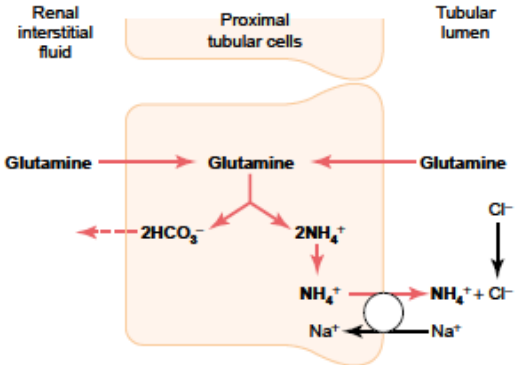
- is composed of hydrogen phosphate $HPO_4^=$ and dihydrogen phossphate $H_2PO_4^-$.
- It occurs maily in the distal tubules and collecting where it becomes concentrated
- H^+ combine with $HPO4^=$ to form $H_2PO_4^-$ .it can be excreted as a sodium salt (NaH_2PO_4)
- The generated HCO3 in the tubular cell and enters the peritubular blood represents a **net gain** of HCO3



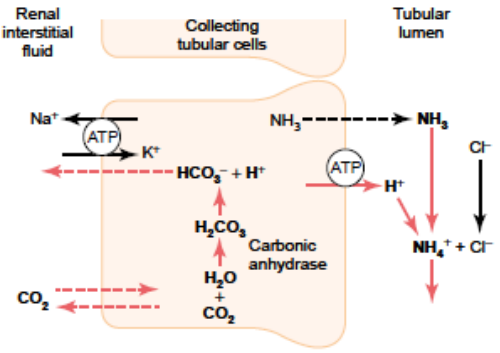
Ammonia buffer system:

- More important than phosphate buffer system
- It composed of ammonia (NH_3) and the ammonium ion ().
- NH_4^+ ion is synthesized from glutamine metabolism in the epithelial cells of the proximal tubules, thick ascending limb of the loop of Henle and distal tubules.
- Each molecule of glutamine is metabolized to form **2 $NH4^+$ and 2 HCO_3^-.**
- The NH_4+ is secreted into the tubular lumen by a counter transport mechanism in exchange with Na, The $HCO3^-$ is transported across the basolateral membrane.
- **For each Glutamine molecule metabolized ,2 new $HCO3^-$ is generated and added to the blood**
- This buffer is under physiological control : ↑H conc. in ECF stimulate renal glutamine metabolism to be used in buffering mechanism

- While In the collecting ducts , the secreted H^+ binds with **NH_3** (diffuse out of the cell) to form NH_4+ in the renal tubule and then excreted **(a $HCO3^-$ is generated for each H+ ion secreted)**



Glutamine metabolism in PCT , TAL and DCT



Buffering of H ion by ammonia in Collecting duct

Regulation of Renal Tubular Hydrogen Ion Secretion:

The most important stimuli for ↑ H+ secretion by the tubules in acidosis are

1. ↑ in H+ concentration of the extracellular fluid (↓ pH).
2. ↑ in PCO2 of the extracellular fluid: (respiratory acidosis) raises the PCO2 of the tubular cells, →↑formation of H+ in the tubular cells→stimulates the secretion of H+.
3. Aldosterone stimulates the secretion of H+ by the intercalated cells
4. Angiotensin II
5. ↓ ECF K^+ ion (hypokalemia) ↑H secretion while hyperkalemia ↓ it

Renal response to acid-Base disorder

1. Acidosis:

- Reabsorb all the filtered HCO_3 by secreting sufficient H ions
- Secretion of more H^+ , as these excreted H^+ binds to other buffers such as HPO_4^{-2} . it also generate new HCO_3^- to be added to the plasma
- ↑Tubular glutamine metabolism and ammonium excretion →Generate more HCO_3^-

result:-

- More new HCO_3^- than usual are added to blood , and plasma HCO_3^- is increased ,thereby compensating for the acidosis. The urine is acidic

2. **Alkalosis**

- ↓ reabsorption of filtered HCO_3^- (insufficient H secretion) .
- Inhibits H^+ secretion that can bind to non-bicarbonate urinary buffers.
- ↓ glutamine metabolism and ammonium excretion so that little or no new HCO_3^- is added to the plasma

result:-

- Plasma HCO_3^- concentration is decreased, thereby compensating for the alkalosis. The urine is alkaline

Micturition reflex

- it is a spinal reflex by which the urinary bladder empties when it becomes filled with urine and it is facilitated and inhibited by higher brain centre (pontine micturation center & cerebral cortex)
- **Stimulus** : The first urge to void is felt at a bladder volume of about 150 mL, and a marked sense of fullness at about 400 ml
- **The afferents** from the stretch receptors →sensory nerves along the pelvic nerves →spinal cord (S2, S3 and S4) →sacral micturition centre (sacral detrusor nucleus and sacral pudendal nucleus).
- **Efferent** are parasympathetic fibers which are excitatory to the detrusor muscle and inhibitory to the internal sphincter.
- Response:
  1. Stretch receptors initiate reflex. It is self-regenerative once it is started(initial contraction of the bladder wall →further activates the receptors to ↑ the afferents sensory impulses
  2. Reflex contraction of detrusor muscle of the bladder and relaxation of internal sphincter (involuntary) through parasympathetic nerve .
  3. Another inhibitory reflex through pudendal nerves → relaxation of external sphincter and start voiding .
- In older children and adult , If this inhibitory reflex is < potent than the voluntary constrictor signals from higher center →urination will not occur unless the bladder fills more and micturition reflex becomes more powerful or voluntary relaxation of external sphincter occur at a convenient time to urinate