(Renal Physiology 10)

Acid-Base Balance 2

Buffers System

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Learning Objectives:

- To define buffer system and discuss the role of blood buffers and to explain their relevant roles in the body
- To describe the role of kidneys in the regulation of acid-base balance
- To describe the role of lungs in the regulation of acid-base balance

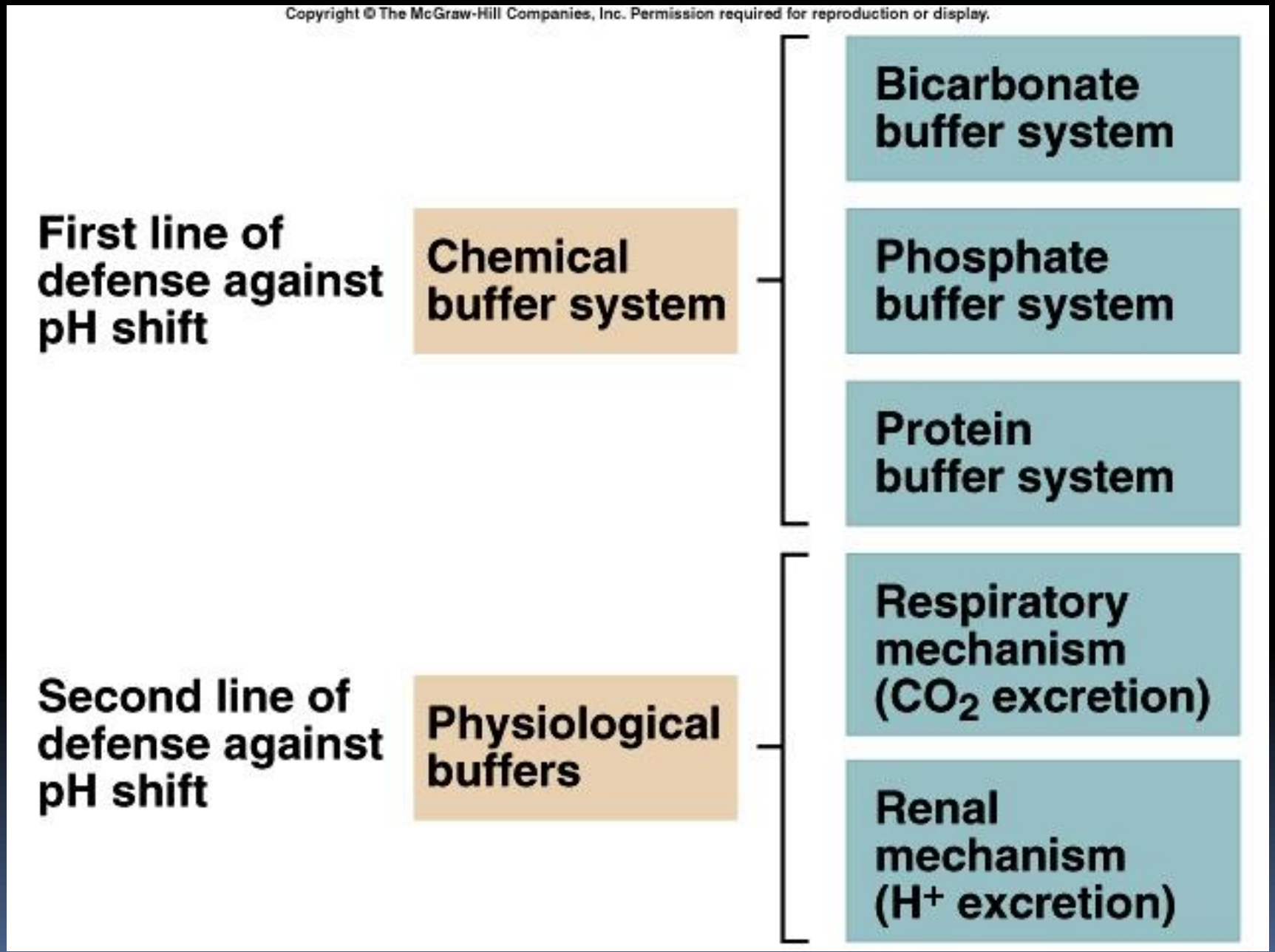
Control of $[H^+]$ - Buffers

- Buffer is substance that stabilises (limits the change of) $[H^+]$ when H^+ ions are added or removed from a solution.
- They <u>do not</u> eliminate H^+ from body – **REVERSIBLY** bind H^+ until balance is re-established.
- General form of buffering reaction usually in form of conjugate acid-base pair:

$$HA \rightleftharpoons H^+ + A^-$$

HA = undissociated acid
A^- = conjugate base (any anion)

- Reaction direction (& dissociation rate) dependent on effective concentration of each chemical species.
- If $[H^+]\uparrow$ then equation moves leftwards and *vice versa* if $[H^+]\downarrow$ - ***minimises changes in $[H^+]$.***

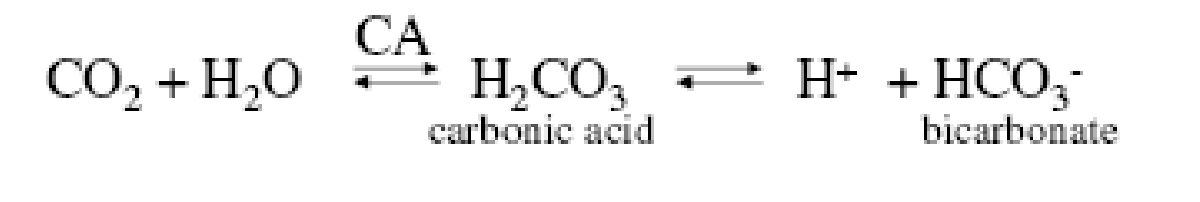


Control of [H^+] - Buffers

What buffer systems exist in the body?

1) Bicarbonate buffer system

- Most important buffering system. Works by acting as proton acceptor for carbonic acid.



$$CO_2 + H_2O \overset{CA}{\rightleftharpoons} H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$$

Control of [H^+] - Buffers

2) Phosphate Buffering System

- Phosphate buffer system not important as extracellular fluid buffer (concentration too low).
- However, major **INTRACELLULAR** buffer and important in **RENAL TUBULAR FLUID**.
- Main components are HPO_4^{2-} and $H_2PO_4^-$

$$H^+ + HPO_4^{2-} \leftrightarrow H_2PO_4^-$$

(Strong acid converted to weak acid ∴ less effect on pH)

$$OH^- + H_2PO_4^- \leftrightarrow H_2O + HPO_4^{2-}$$

(Strong base converted to weak base ∴ less effect on pH)

Note: Phosphoric acid (H_3PO_4) has three dissociable protons. The pK value of H_2PO_4 to H + HPO_4 is 6.8 making it a good ECF buffer.

Control of $[H^+]$ - Buffers

3) Protein Buffers

- Proteins among most plentiful buffers in body, particularly highly concentrated **INTRACELLULARLY.**

- ~ 60 - 70% of total chemical buffering of body fluids is located intracellularly, mostly due to intracellular proteins.

- Carboxyl and amino groups on plasma proteins are effective buffers;

$$RCOOH \leftrightarrow RCOO^- + H^+$$

$$RNH_3^+ \leftrightarrow RNH_2 + H^+$$

Control of [H^+] - Buffers

3) Protein Buffers

- Most important non-bicarbonate buffering proteins are titratable groups on **HAEMOGLOBIN** **(Hb also important for buffering CO_2)**.

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

(DeoxyHb a better buffer than OxyHb)

$$H^+ + Hb^- \Leftrightarrow HHb$$

- pH of cells changes in proportion to pH of extracellular fluid – CO_2 can rapidly traverse cell membrane.

Note: Hb represents 80% of the non-bicarbonate buffer power of the ECF. 36 of Hbs 574 amino acids are histidines which have dissociable protons on their side groups. It has an average pK value of ~6.5 making it a good buffer in the physiological range.

Control of [H^+] - Buffers

4) Bone

- Probably involved in providing a degree of buffering (by ionic exchange) in most acid-base disorders.

- However, important source of buffer in **CHRONIC** metabolic acidosis (*i.e.* renal tubular acidosis & uraemic acidosis).

- $CaCO_3$ (base) is most important buffer released from bone during metabolic acidosis.

- Results in major depletion of skeletal mineral content (*e.g.* Chronic metabolic acidosis that occurs with renal tubule acidosis (RTA) can lead to development of Rickets / osteomalacia).

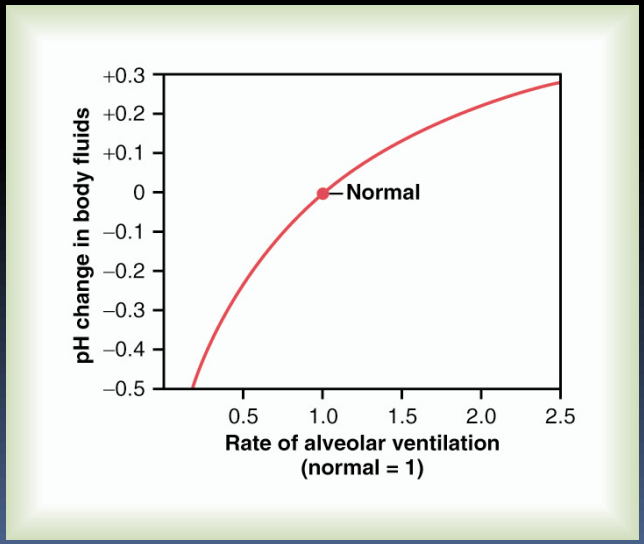
Control of [H^+] - Buffers

- Remember that all of these buffer systems work in **TANDEM**, *NOT* in isolation.
- Buffers can only ***LIMIT CHANGES*** in pH, they cannot **REVERSE** them.
- Once arterial pH has deviated from normal value, can only be returned to normal by **RESPIRATORY** or **RENAL COMPENSATION**.

Respiratory Regulation of Acid-Base Balance

Respiratory Regulation of Acid-Base Balance

- Pulmonary expiration of CO_2 normally **BALANCES** metabolic formation of CO_2.
- Changes in alveolar ventilation can alter **plasma Pco_2**
  - ↑ ventilation, ↓Pco_2, ↑pH
  - ↓ ventilation, ↑ Pco_2, ↓ pH
- Changes in [H^+] also alters **ALVEOLAR VENTILATION**.



Respiratory Regulation of Acid-Base Balance

- **POWERFUL** (1-2 x better than extracellular chemical buffers), but *cannot fully rectify* disturbances outside respiratory system, *i.e.* with fixed acids like lactic acid.

- Acts relatively **RAPIDLY** to stop $[H^+]$ changing too much until renal buffering kicks in but **DOES NOT** eliminate H^+ (or HCO_3^-) from body.

- Abnormalities of respiration can alter bodily $[H^+]$ resulting in;

  - **RESPIRATORY ACIDOSIS** or

  - **RESPIRATORY ALKALOSIS**.

Renal Regulation of Acid-Base Balance

There are three major renal mechanisms for the maintenance of normal body pH:

1. Reabsorption of filtered bicarbonate
2. Production of titratable acid.
3. Excretion of ammonia.

Each of these three mechanisms involve the secretion of hydrogen ions into the urine and the addition of bicarbonate ions to the blood.

Renal Regulation of Acid-Base

- **MOST EFFECTIVE** regulator of pH but much **SLOWER** (*i.e*. max. activity after 5-6 days) than other processes.
- Responsible for **ELIMINATING** the 80 -100 mEq of fixed **ACIDS** generated each day.
- Normally, must also **PREVENT** renal **LOSS** of freely – filterable HCO_3^- in order to preserve this primary buffer system.
- **BOTH PROCESSES** are dependent on both H^+ filtration / secretion into renal tubules and secretion / reabsorption of plasma [HCO_3^-].
- Kidneys also responsible for **COMPENSATORY CHANGES** in [HCO_3^-] during respiratory acid-base disorders.

*** IF KIDNEYS FAIL, pH BALANCE WILL FAIL ***

Renal Regulation of Acid-Base

- Overall mechanism straightforward:

  - large [HCO_3^-] continuously filtered into tubules
  - large [H^+] secreted into tubules

  $\Rightarrow$ if more H^+ secreted than HCO_3^- filtered
  = a net loss of ***acid*** $\Rightarrow$ $\uparrow$pH

  $\Rightarrow$ if more HCO_3^- filtered than H^+ secreted
  = a net loss of ***base*** $\Rightarrow$ $\downarrow$pH

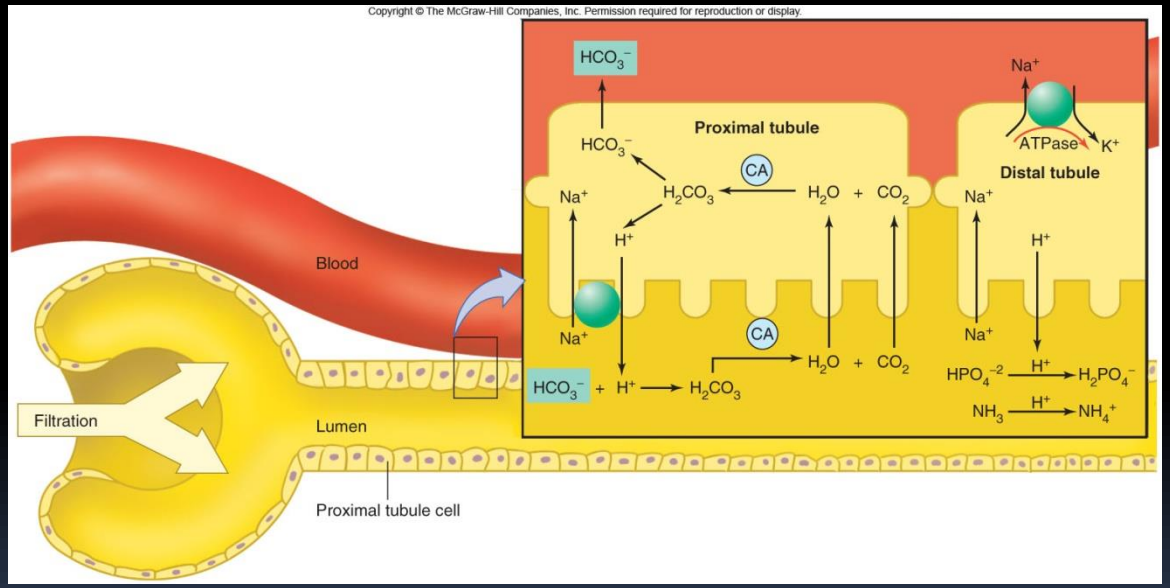
H^+ / HCO_3^- Control by the Kidney

Renal H^+ Secretion

- H^+ enters filtrate by **FILTRATION** through glomeruli and **SECRETION** into tubules.
- Most H^+ secretion (80%) occurs across wall of PCT *via* Na^+/H^+ antiporter (& H^+ - ATPase in type A cells of DCT).
- This H^+ secretion enables HCO_3^- reabsorption.
- The primary factor regulating H^+ secretion is systemic acid-base balance

a) **ACIDOSIS** stimulates H^+ secretion

b) **ALKALOSIS** reduces H^+ secretion



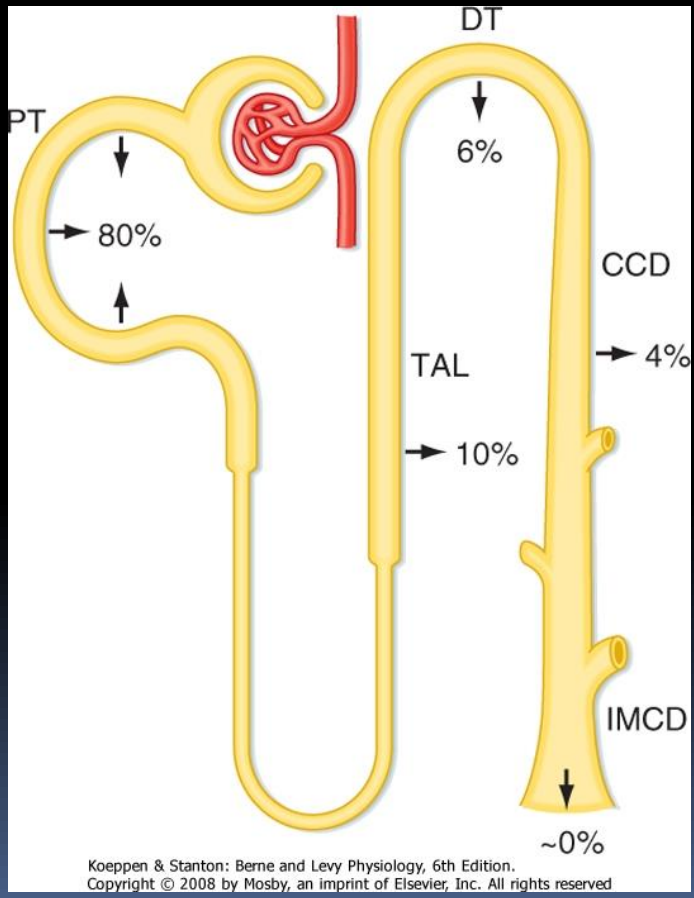
H^+ / HCO_3^- Control by the Kidney

Bicarbonate Handling

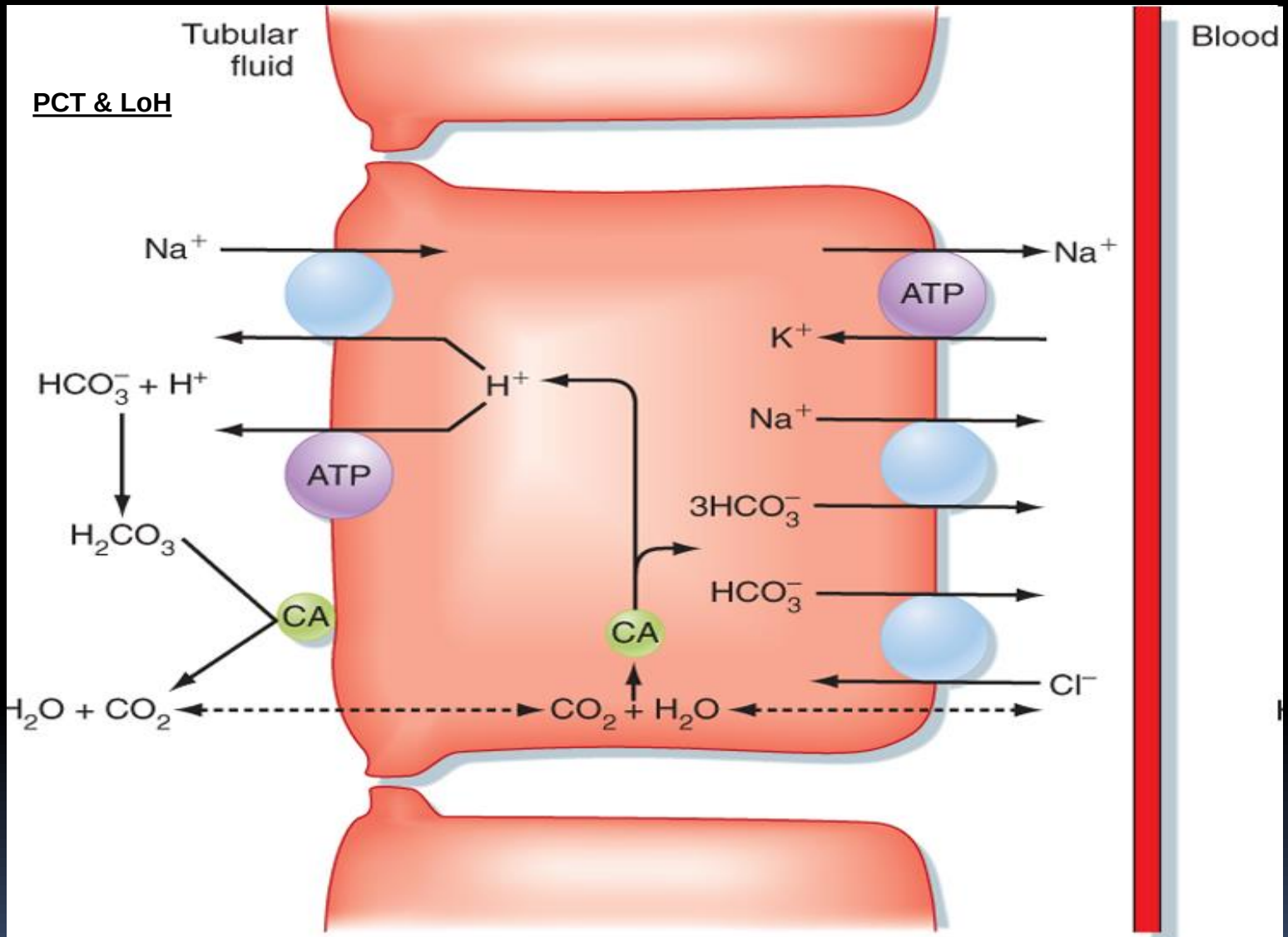
- HCO_3^- **FREELY FILTERABLE** at glomeruli (3 mM/min) and undergoes significant (> 99%) reabsorption in PCT, aLoH & cortical collecting ducts (CCDs).

- Mechanisms of HCO_3^- reabsorption at PCT (& aLoH) and CCD ***are similar but not identical*** (will look at CCD cells in acid-base practical).

- Renal HCO_3^- reabsorption is an **ACTIVE** process - **BUT** dependent on tubular secretion of H^+, **NO** ***apical*** transporter or pump for HCO_3^-.



PCT & LoH



H^+ / HCO_3^- Control by the Kidney

Bicarbonate regeneration - Metabolism of glutamine

- Renal ammonium-ammonia buffer system is subject to physiological control.
- ↑ ECF [H^+] stimulates renal glutamine metabolism ⇒ new HCO_3^- formation ⇒ ↑ buffering of H^+ (*vice versa* for ↓ ECF [H^+])
- Normally, ammonia buffer system accounts for ~ 50% of acid excreted (& HCO_3^- created)
- In **CHRONIC ACIDOSIS** ammoniagenesis can increase ~10 fold (500 mEq/day; over days) to become dominant acid excretion mechanism.

Titratable Acid Secretion and Urine pH

- Apart from generating new bicarbonate, titratable acid secretion is important for regulating urinary pH.
- Maximum urine acidity ~ **pH 4.5** $\Rightarrow$ equates to urine $[H^+]$ of **only ~ 0.03 mM/L!!**.
- If 80 mEq/L excess H^+ is ingested each day, and an equal amount of acid is excreted each day……

  $\Rightarrow$ Would need to excrete **2667 L urine / day** (normally excrete only1-2 L / day) if H^+ remained in ionised form.
- If there were no non-bicarbonate buffers present then ~ 80 mEq/ day excess of fixed H^+ would be eliminated in ionic form.


Thanks