Lecture :.....5.....

Dr. Name :...Nayef.....

Done By :.....

■ Notes : □ Sheet

IV Regulatory Mechanism against changes in $[H^+]$ of Blood

Two types of metabolic acids produced

1. Volatile acids
   The physiologically most important is Carbonic acid
   20,000 mEq. is produced daily from metabolism

Carbonic acid

2. Fixed Acids [60-80 mEq. per day]
   - Organic acids are: Pyruvic, lactic, keto acids (e.g. acetoacetic, β-hydroxy butyric acid), uric acid
   - phosphoric and sulphuric acid produced from sulphur & phosphorus of proteins, lipoproteins and nucleoproteins

Buffering Capacity depends on:

- Conc. of buffer
- pKa of the buffer and the desired pH

Regulation of Blood pH

Bicarbonate Buffer

When CO_2 is dissolved in H_2O, there is little H_2CO_3

$$CO_2 + H_2O \rightleftharpoons H^+ + HCO_3^-$$

$$\rightarrow CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$$

$$pH = pK_a + \log \frac{[base]}{[Acid]}$$

Under physiological conditions

$$7.4 = 6.1 + \log \frac{[HCO_3^-]}{[CO_2]}$$

$$1.3 = \log \frac{[HCO_3^-]}{CO_2}$$

$$\frac{[HCO_3]}{[CO_2]} = \frac{20}{1}$$

} solubility coefficient of CO_2 0.03 mM / mm Hg

Normal values

$pH = 7.4$

$pCO_2 = 40$ mm Hg (~ 1.2 mM)

$[HCO_3^-] = 24$ mM

The Bicarbonate Buffer System

Under physiological conditions with plasma pH = 7.4 ; pKa = 6.1

$$\frac{HCO_3}{H_2CO_3} = 20/1$$

Actual pH of blood is at the upper limit of buffering range of Carbonic – bicarbonate buffer

$6.1 \pm 1 = 5.1 \text{ —— } 7.1$

Inefficiency is replenished by the reserve supply of gaseous CO_2 in lungs

$$\underset{\text{Lung}}{CO_2(g)} \rightleftharpoons \underset{\text{blood}}{CO_2(aq)}$$

$$CO_2(aq) + H_2O \overset{C.A.}{\rightleftharpoons} H_2CO_3(aq)$$

$$H_2CO_3 \rightleftharpoons HCO_3(aq) + H^+(aq)$$

These reactions also work in reverse

Excess H^+ is removed by HCO_3^-

$\longrightarrow H_2CO_3 \rightarrow CO_2(aq) \rightarrow \underbrace{CO_2(g)}$ expired by lung

Mechanism of Regulation of pH

1. Buffer mechanism - first defence
2. Respiratory mechanism — second line of defence
3. Renal Mechanism — 3rd line of defence

The first two lines of defence keep the $[H^+]$ from changing too much until the more slowly responding third line of defence, the kidneys can eliminate the excess acid or base from the body

Buffer systems of the body

Extracellular fluid	Intracellular fluid	Erythrocyte fluid
$\frac{NaHCO_3}{H_2CO_3}$ (bicarbonate)	$\frac{K_2HPO_4}{KH_2PO_4}$ (phosphate)	$\frac{KHb}{HHb}$ (Hemoglobin)
$\frac{Na_2HPO_4}{NaH_2PO_4}$ (phosphate)	$\frac{K^+ protein}{H^+ protein}$ (protein buffer)	$\frac{K_2HPO_4}{KH_2PO_4}$ (phosphate)
$\frac{Na^+ Albumin}{H^+ Albumin}$	$\frac{KHCO_3}{H_2CO_3}$	$\frac{KHCO_3}{H_2CO_3}$

Mechanism of Action of Carbonate Buffer

$$CO_2 + H_2O \rightleftharpoons H_2CO_3 \overset{pKa \sim 6.1}{\rightleftharpoons} HCO_3^- + H^+$$

- Acid added to blood

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

Excess CO_2 greatly stimulate respiration which eliminate CO_2 from extracellular fluid

- Base added to the blood

$$OH^- + H_2CO_3 \longrightarrow NaHCO_3 + H_2O$$

$CO_2 + H_2O \xrightarrow{C.A} H_2CO_3$ to replace H_2CO_3 in the above

Decrease $[CO_2]$ decreases respiration rate to derease rate of CO_2 expiration

HCO_3^- alkali reserve

$$HCO_3^-/CO_2 = \frac{25\ mmole/l}{1.25\ mmole} = \frac{20}{1}$$

Phosphate Buffer Systems :-

(4/E)

- in Tubules in kidney
- IC fluid

pKa = 7.1 – 7.2 very good

Considerable concentration in intracellular fluids and Tubular fluids of kidneys

In RBC, conc. of 2,3-BPG is 4 – 5 mmole/l is considerable conc ⟶ 16% of non-carbonate buffer contribution

Action:

$H^+ + Na_2HPO_4$

$OH^- + NaH_2PO_4$

albumin has 16 his/mole

Protein Buffers

Proteins, especially ALBUMIN, accounts for 95% of non-carbonate buffering value in the Plasma

- Presence of dissociable acidic (-COOH) and basic ($-NH_2$) groups
- In particular the side chain of histidine (imidazole gr) having $pK_a = 7.3$
- Albumin contain 16 his/mole

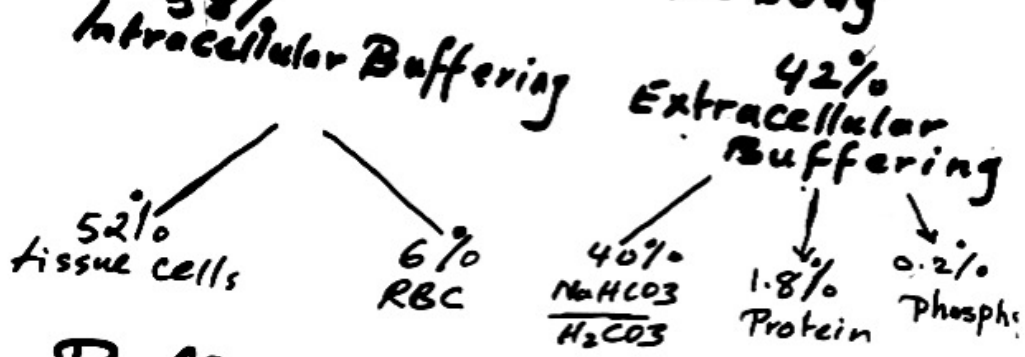
Hemoglobin Buffer

- major intracellular buffer of blood rbc
- Hb has a high conc of His (38 moles/1 mole of Hb)
- It buffers H_2CO_3 and CO_2
- It works in cooperation with the bicarbonate system

(more details in Blood & lymph system – 3rd yr)

7.38 - 7.42

Relative Capacity of the Buffer Systems in the body



- **Buffers act quickly but not permanently**
  - They don't eliminate acids from body or replinish alkali reserve
  - Respiratory and Renal mechanisr are very essential for final elimination

- **Normal pH range: 7.38 — 7.42** (7.4)

- **Acidosis**
  - when pH < 7.38
  - but when pH < 7.25 → Life is threatened
  - Acidosis → CNS depression and coma
  - when pH < 7.0 death occurs

Metabolic Acidosis: ↓[HCO3]

Untreated diabetes
Starvation diet
High protein diet
Low fat diet
→ ↑ Keton bodies (Ketosis) → ↑

Lactic acidosis, therapeutic administration of HCl, kidney disorder

Normal Metabolism

Volatile acids
H_2CO_3
~ 20,000 m Eq/day
excreted as CO_2 by lung

Fixed Acids
e.g lactic acid, keto acids, uric acid, phosphoric and sulphuric acid.
60–80 m Eq/day
Buffered and H^+ excreted by kidney

Respiratory Acidosis: ↑[CO_2]

Increased in [CO_2] caused by Pulmonary problems

e.g. chronic obstructive airway disease, asthma, emphysema, pneumonia; cardiac arrest, severe hypoxia — etc.

Alkalosis

PH > 7.42

PH > 7.55 is dangerous

> 7.60 death

induces muscular hyperexcitability and tetany

• Metabolic alkalosis

↳ Results from clinical administration in excess of alkali (e.g. $NaHCO_3$)

severe vomiting (loss of gastric juices)

Hypokalaemia (low cellular K^+)

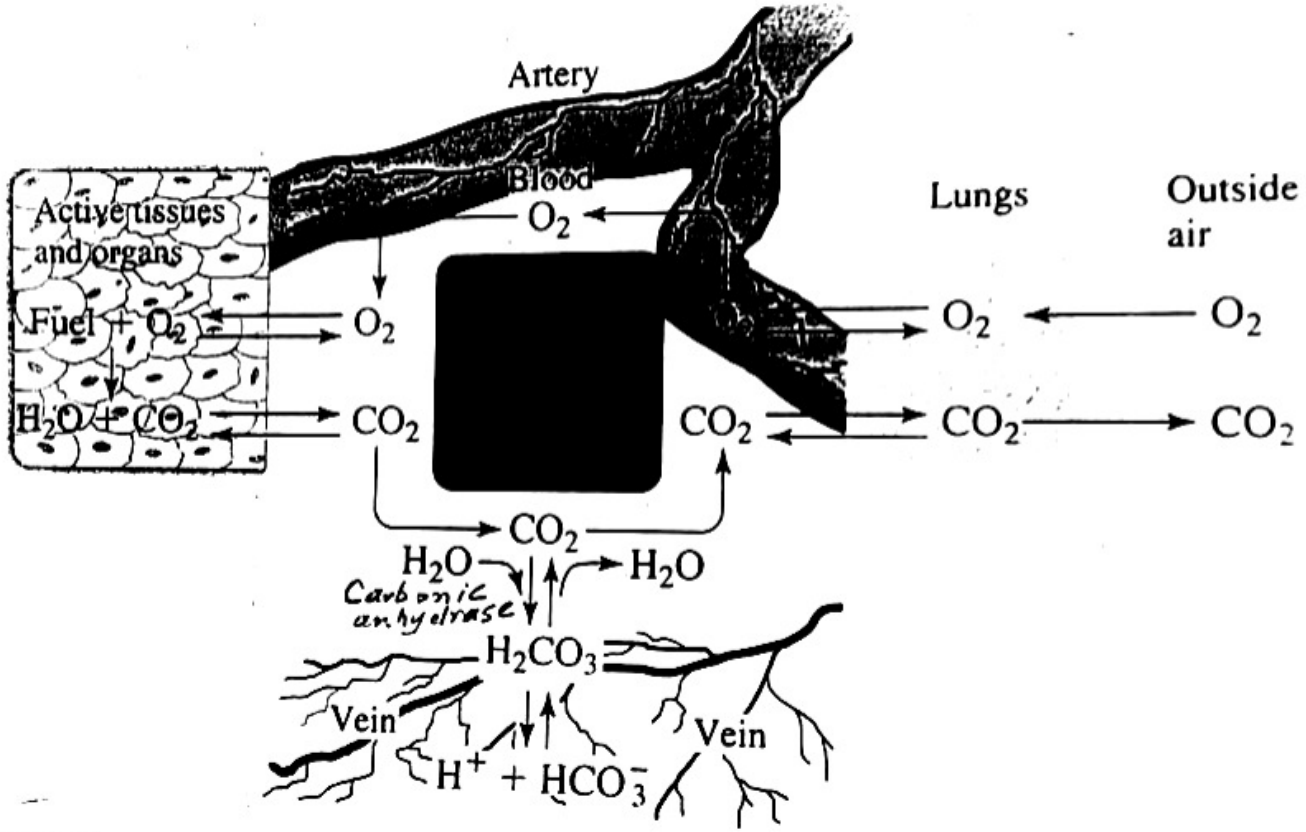
$\longrightarrow \uparrow [HCO_3^-]$

• Respiratory alkalosis

Hyperventilation $\downarrow PCO_2$ (heavy breathing)

Hysteria ↑ Anxiety ↑ altitude sickness

hot baths, working at high temp.



Unnumbered figure pg 57c Concepts in Biochemistry, 3/e

Figure 10.6 Breathing and the bicarbonate buffer system