* Regulation of Acid-Base Balance

0.4×10^{-7} mol/L   .0000004 mol/L   mmol/L

→ H^+ conc. in extracellular fluid is 0.00004 meq/L (40 neq/L)

↓

H^+ regulation is very essential because the activity of almost all enzymes in the body is affected by H^+ concentration.

* **Acid**:- Molecules containing hydrogen atoms that can release hydrogen ions (H^+) in the solution.

Ex:-
$$HCl \longrightarrow H^+ + Cl^-$$
$$H_2CO_3 \longrightarrow H^+ + HCO_3^-$$

* **Base**:- is an ion or molecule that can accept an H^+.

Ex:-
$$HCO_3^- + H^+ \longrightarrow H_2CO_3 \longrightarrow H_2O + CO_2$$
$$HPO_4^- + H^+ \longrightarrow H_2PO_4^-$$

Both are Base which are accepting H^+ ions.

* **Alkali**:- is a molecule formed By the combination of one or more of alkaline metals - Na^+, K^+, Li^+ etc. with highly basic ion such as a OH^- ion.

* **Alkalosis**:- excess removal of H^+ from the Body fluids.

Venous - ABG - $pH = 7.34 - 7.46$

$pH = 7.31 - 7.41$ | $pCO_2 = 35 - 45$ mmHg
$pCO_2 = 40 - 50$ | $pO_2 = 75 - 100$ mmHg
$pO_2 = 30 - 50$ | $HCO_3 = 21 - 26$ mmol/l
$HCO_3^- = 22 - 28$ | $SO_2 = 94 - 99\%$
$SO_2 = 75\%$

* **Acidosis :-** Excess addition of H^+ ions in the Body fluids.

* **Strong acid :-** is one that rapidly dissociates & release especially large amount of H^+ in solution.
  Ex :- HCl

* **Weak Acid :-** less tendency to dissociate their ions.
  Ex :- H_2CO_3

* **Strong Base :-** is one that react rapidly and strongly with H^+ & Therefore remove H^+ from the solution
  Ex : $OH^- + H^+ \longrightarrow H_2O$.

* **Weak Base :-** is one that which binds H^+ very weakly & Remove H^+ slowly from the solution.
  Ex :- $H_2CO_3^-$

* **pH & H^+ concentration :**

$\longrightarrow$ (N) H^+ concentration $= 40$ nEq/L
$\downarrow$
it can very from 3 to 5 nEq/L.
$\downarrow$
But it can goes low as much as 10 nEq/L & high as much as 160 nEq/L

pO_2 - Atmosphere = 150 mmHg
Alve. air = 104 mmHg   40 mmHg

→ pH represent the actual H^+ concentration in the fluid.

$$pH = \log \frac{1}{[H^+]}$$

$$\boxed{pH = -\log [H^+]}$$

→ pH is inversely propotional to $[H^+]$

→

	pH
- Arterial Blood →	7.4
- Venous " →	7.34
(due to extra amount of CO_2 released from the tissue to form H_2CO_3)	
- Interstitial fluid →	7.34
- Intracellular fluid →	6 to 7.4
(due to metabolism or cell produces acid in the form of H_2CO_3)	
- Urine →	4.5 to 8.0
- Gastric HCl →	0.8

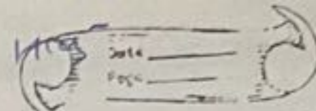
*- REGULATION OF H^+ CONCENTRATION:-

3 systems are theses.

1. Chemical acid-Base Buffer system
   ↓
   immediately combines with acid or base to prevent changes in H^+ concentration.

2. respiratory centers
   ↓
   regulates the removal of CO_2 (so H_2CO_3)

3. kidney
   ↓
   - Either excrete acidic/akaline urine
   - slow responding system



(F) <u>Bicarbonate Buffer system</u> :— H_2CO_3 6.1 10.3

- ± 1
- Not A good blood buffer
- 22 - 27 mmol/L
- $\frac{HCO_3^-}{H_2CO_3} = 20$

2 components

① WEAK ACID

↓

Ex: H_2CO_3

↓

this is formed in Body By combination of H_2O & CO_2

↓

$$H_2O + CO_2 \xrightarrow[\text{anhydrase}]{\text{carbonic}} H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$$

→ Carbonic anhydrase:
location: ① Renal tubule → to form H_2CO_3
② lung alveoli: to form H_2O & CO_2

→ H_2CO_3 weakly ionize to form H^+ & HCO_3^-

$$H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$$

② WEAK BASE

↓

$NaHCO_3$ (Bicarbonate salt)

↓

→ Mainly in ECF
→ completely ionize to form Na^+ & HCO_3^-

$$NaHCO_3 \rightleftharpoons Na^+ + HCO_3^-$$

↓

if 2 system together

$$H_2O + CO_2 \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + \underbrace{HCO_3^-}_{Na^+}$$

plant food containing. -

→ Because H_2CO_3 is weakly dissociated, H^+ concentration is small.

* If ~~strong~~ acid (HCl) is added to the Buffering system :—
(Ex:- if there is high H^+ in Body (condition like metabolic Acidosis))

$HCl \longrightarrow \uparrow H^+ + HCO_3^- \longrightarrow H_2CO_3 \xrightarrow{\text{Carbonic anhydrase}} CO_2 + H_2O$

↑ which is mainly given By $NaHCO_3$ (weak Base)

→ So more CO_2 is formed at lung alveoli
↓
stimulation of respiratory center
↓
Excess Expiration
↓
more CO_2 flush out
↓
respiratory alkalosis (compensatory to meta. acidosis)

* If strong Base (NaOH) is added to the Buffering System (Metabolic alkalosis) -

$H_2O + CO_2 \longrightarrow H_2CO_3 \xrightarrow[NaOH]{} NaHCO_3 + H_2O$

$NaOH + \cancel{H_2CO_3} \longrightarrow NaHCO_3 + H_2O$

$CO_2 + \cancel{H_2O} \longrightarrow H_2CO_3 \longrightarrow HCO_3^- + H^+$

$\quad\quad\quad\quad\quad\quad + \quad\quad\quad\quad\quad +$

$\quad\quad\quad\quad\quad NaOH \quad\quad\quad\quad Na^+$

So more CO_2 is used up.

↓

so ↓ concentration of CO_2

↓

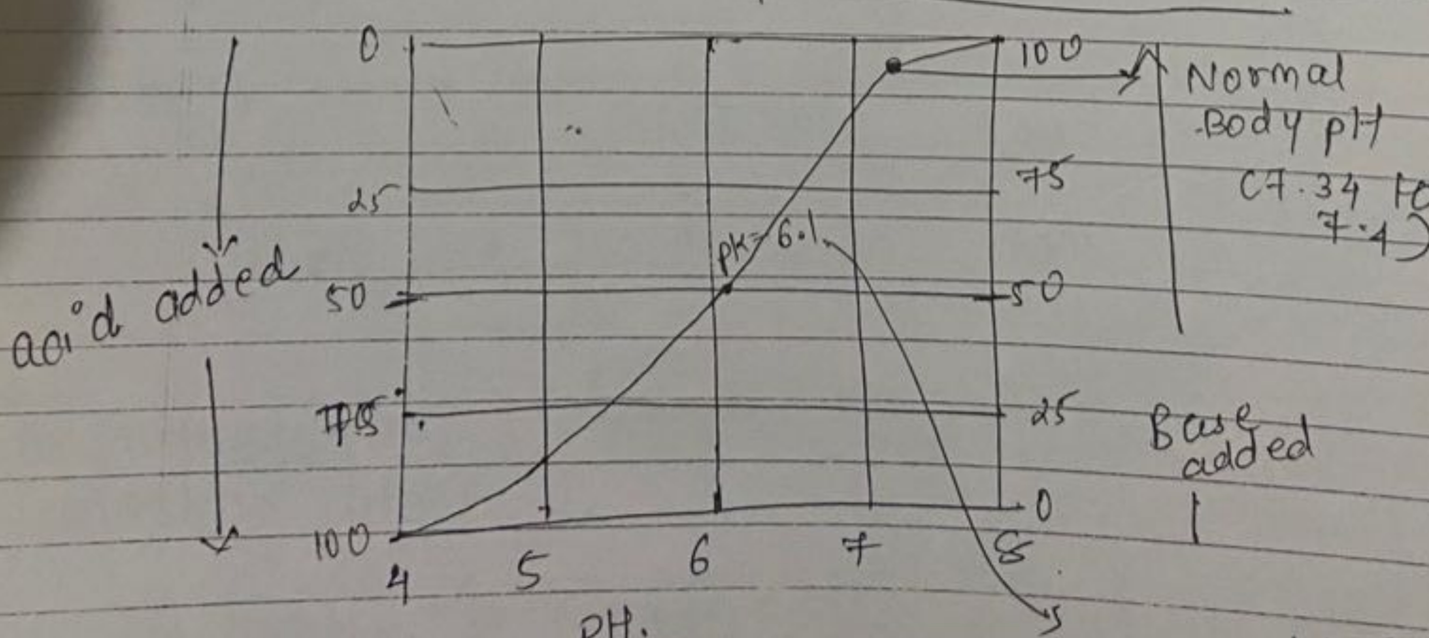
inhibition of respiration

↓

↓ rate of CO_2 expiration

→ ~~So~~ HCO_3^- concentration mainly maintained By kidney & CO_2 concentration (PCO_2) mainly maintained By Respi. system.

* Bicarbonate Buffer system Titration Curve :–



← when 50% acid & 50% Base → so pK achieved

→ Interpretation:-

? → PH = pk → when acid & Base component are 50% - 50%.

→ Buffer system is more effective at a central area (~~pH~~ pk is equal to ± 1.0 to pH)

means : 5.1 to 7.1

→ Beyond this limit bicarbonate is not act as good Buffering system.

* Bicarbonate Buffer system is most imp. ECF Buffer.

↓

Buffer system is not that much powerful

↓

(1) pH of ECF is 7.4, where as pk of H_2CO_3 buffer is 6.1

↓

So 20 times much of bicarbonate buffer system in the form of HCO_3^-, in the form of discolved CO_2 form.

(2) Conc. of CO_2 & HCO_3^- are not great.

↓

Despite that HCO_3^- buffer is good Because it is regulated By kidney & respiratory system.

1.9 • 6.8 • 3 Ph 1.5 mmol/L low capacity •

• $HPO_4^{=} \rightleftharpoons H_2PO_4^-$

• near to 7.4 good Buffer

(B) Phosphate Buffer System :

Blood

urine

Ph 4.5

→ plays a major role in buffering

Renal tubules — ICF

→ main elements of Buffer

HPO_4^- ↓ Weak Base

$H_2PO_4^-$ ↓ weak acid

→ when HCl added to system, causes formation of weak acid

$HCl + Na_2HPO_4^- \longrightarrow NaH_2PO_4 + NaCl$

weak acid

→ when NaOH is added to system, causes formation of weak base

$NaOH + NaH_2PO_4^- \longrightarrow Na_2HPO_4 + H_2O$

weak Base

⟹ phosphate Buffer is not imp ECF Buffer

↓

B'cz pk of phosphate Buffer is 6.8 which is near to 7.4

↓

So operate its maximum buffering But its conc. in ECF is only about 80% than HCO_3^- Buffer conc.

↓

So, the extracellular Fluid Buffering is less.

⟹ Phosphate is important in tubular Fluid of the kidney. ↓

(1) phosphate is greatly concentrated in tubular fluid ↓

So increase conc. increasing its buffering capacity.

(2) tubular Fluid has lower pH than ECF

↓

pH comes around 6.8 which is a pk of phosphate buffer

↓

So act powerfully.

⟹ Phosphate Buffer is imp in ICF :-

↓

BCZ concentraⁿ of phosphate higher intracellularly & pH is lower than ECF

Blood — cell — Hb
Plas

Hb (same AA)
6.8
7.4 when in Protein

(5) Proteins :-

→ In the RBC, main Buffering protein is Hemboglobin.

$$H^+ + Hb \rightleftharpoons H\text{-}Hb$$

→ approx. 60 to 70% of total chemical buffering of the body fluids is inside the cells and most of this result from ICF proteins.

→ pKs of many proteins are very close to 7.4.

* Isohydric principle :-

Any condiⁿ that changes the balance of one of the buffer systems also changes the balance of all other because the buffering system buffers one another by shifting H^+ back & forth between them.

(2) Respiratory Regulation :-

→ to control of ECF CO_2 concentration by the lung.

↑ ventilation
↓
Eliminates CO_2 from ECF
↓
↓ H^+ concentration

↓ ventilation
↓
↑ CO_2 level
↓
↑ H^+ concentration in ECF

→ CO_2 is continually formed in Intracellular metabolic processes

↓

diffuses from cells into Interstitial fluid & Blood

↓

CO_2 containing Blood transports to lungs

↓

where it diffuses into alveoli & then transferred to the atmosphere by pulmonary ventilation.

→ when pCO_2 is 40 mm Hg → CO_2 dissolved in ECF is 1.2 mol/L. → (n).

→ (1) If the rate of metabolic formaⁿ of CO_2 ↑

↓

↑ PCO_2 in ECF

↓

↑ H^+ concentration in ECF

↓

↑ Pulmonary ventilation

If the rate of metabolic formaⁿ of CO_2 ↓

↓

↓ PCO_2 in ECF

↓

↓ H^+ concentraⁿ in ECF

↓

↓ pulmonary ventilation

→ (2) if pulmonary ventilation

is high

↓

CO_2 blow off from lung

↓

↓ PCO_2 in ECF

low

↓

↑ PCO_2 in ECF

* ↑ Alveolar ventilation → ↓ ECF H^+ conc. → ↑ pH.

→ If CO_2 remains constant.

↓

~~only~~ other factor that affect PCO_2 is pulmonary ventilation.

* higher ventilation

↓

↓ PCO_2

lower ventilation

↓

↑ PCO_2

↓

↑ H_2CO_3 formaⁿ

↓

↑ H^+ concentration

↓

↓ pH

Inverse in ↓ PCO_2

* ↑ H^+ concentration

↓

Causes ↓ pH.

↓ ↑

~~alveolar~~ ↑ alveolar ventilation

↓

↑ CO_2 flushed out

↓

pH back to (n)

↓ H^+ concentration,

↓

↓ alveolar ventilation

↓

↓ O_2 added to the blood

↓

↓ PO_2

↓

stimulate ventilation rate

↓

more effective than when H^+ ↑.

* Efficiency of Respiratory system :—

↓

Respiratory control cannot return the H^+ concentration all the way back to (n) when a disturbance outside the respiratory system has altered the pH.

↓

its effectiveness is b/w 50 to 75%.

↓

it requires 3 to 12 min. to response.

↓

it acts rapidly & keeps the H^+ concen from changing too much until the kidney eliminate the imbalance.

↓

Buffering power of chemical Buffe < Respiratory system < kidney

(3) Renal control of Acid-Base Balance :

→ kidney control acid-base balance by either excreting acidic or basic urine

→ Excreting acidic urine : Excretion of H^+ ion → reduction of acid in ECF.

→ Excretion of basic urine :- removal of HCO_3^- from ECF.

→ 2 types of acids are formed

Volatile (H_2CO_3)
↓
each day 4320 meq of HCO_3^- is filtered every day.

Non volatile (other than H_2CO_3)
↓
mainly due to metabolism of protein
↓
80 meq/day produced

↓

For reabsorpn of ~~volatile~~ bicarbonate same amount of H^+ must be secreted
↓
so 4400 meq of H^+ is secreted each day.

→ Regulation of acid-base balance occur by 3 mechanism by kidney

① H^+ secretion

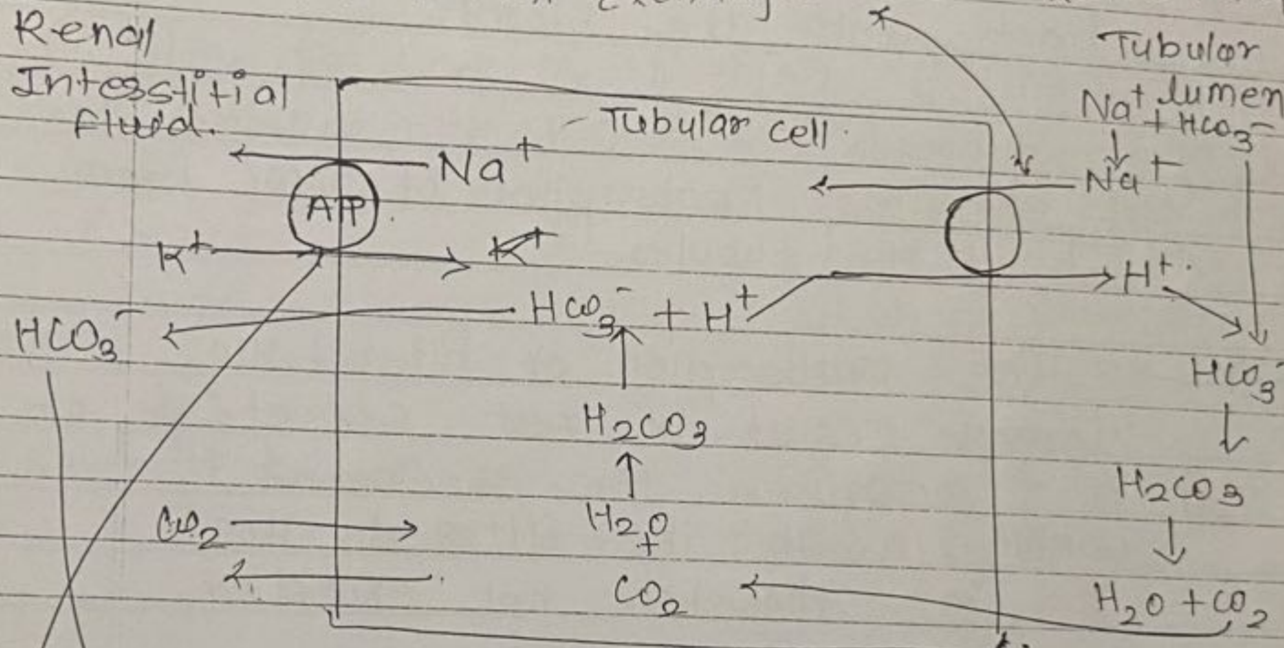
② reabsorpn of filtered HCO_3^-

③ production of New HCO_3^-

↑ H^+ → ↑ Z-crystallei → Z-cr. Phosphate repair → mRNM stable → ↑ Glutamine
→ Charge struct
R.T.C Z-cry Glutam mRN G-Dh

(a) Secretion of H^+ ion & reabsorption of HCO_3^- by Renal Tubules :—

this Na^+-H^+ Exchanges is 2ndary active transport.



HCO_3^- reabsorption occurs from (2) pathways

Na^+ - HCO_3^- cotransport — Cl^- - HCO_3^- Exchange

Primary active Transport : which causes the low Na^+ conc. into the cell

↓

So Na^+ is gradient forms

↓

Na^+ is reabsorbed from the Tubular lumen acc. to concentraⁿ gradient ↓

H^+ is exchanged from Na^+ & H^+ is secreted.

→ Thus, each time an H^+ is formed in the tubular epithelial cells

↓

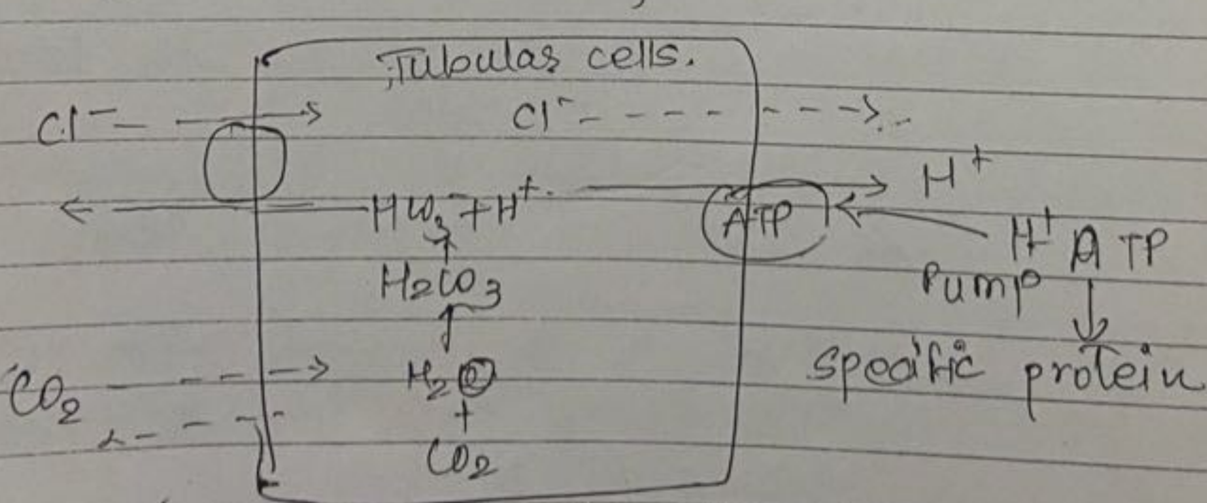
an HCO_3^- is also formed and released back into the blood.

↓

<u>Net effect</u>:- Reabsorption of HCO_3^- from the tubules.

→ The reabsorption of filtered HCO_3^- doesn't result in net secretion of H^+ because the secreted H^+ combines with the filtered HCO_3^- & is therefore not excreted.

* 1° active transport or secretion of H^+ in the <u>intercalated cells of late Distal and collecting ducts</u>:



(Intercalated cells of Late Distal & Collecting tubules)

→ H^+ secretion in these cells by two steps

(1) the dissolved CO_2 in this cell combines with H_2O to form H_2CO_3

(2) the H_2CO_3 then dissociated into HCO_3^- which is reabsorbed into blood, plus H^+ which is secreted into tubules by H^+-ATPas

→ Secreⁿ of H^+ in D.T & C.D is only about 50% than P.T.

↓

But by this secretion urine pH - acidic is formed.

* Phosphate Buffer :-

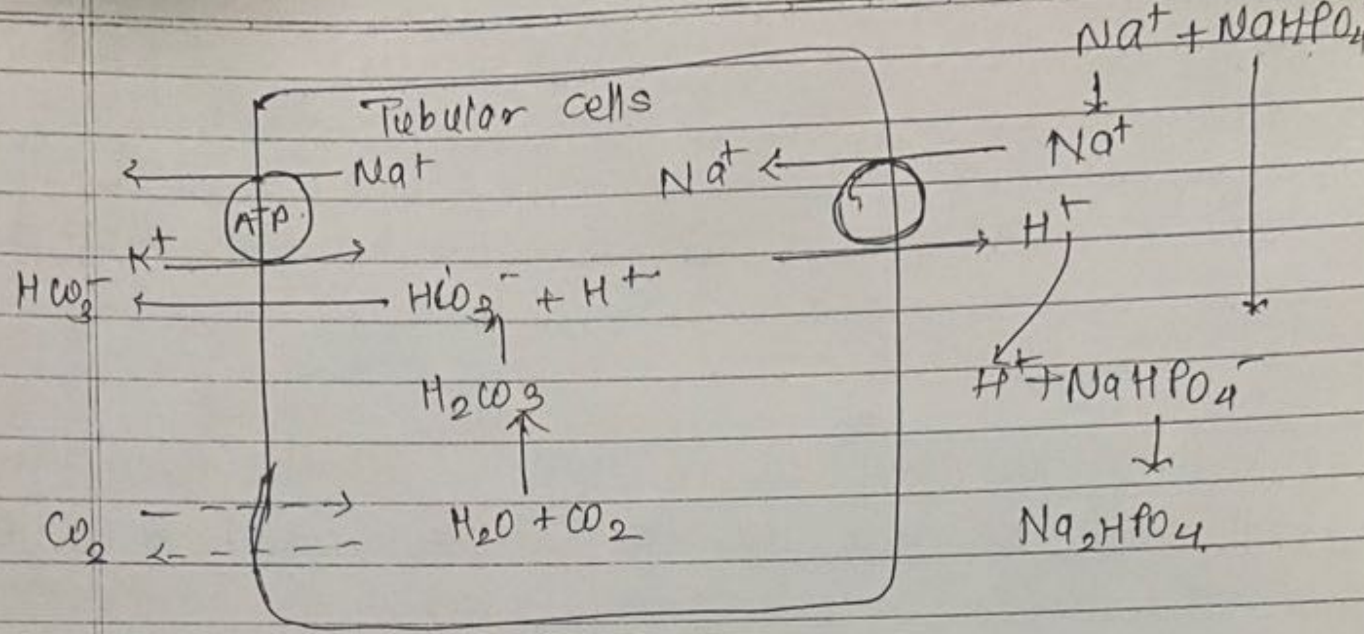
→ composed of HPO_4^- & $H_2PO_4^-$

Adv :- (1) Become concentrated in the tubular fluid because of

↓

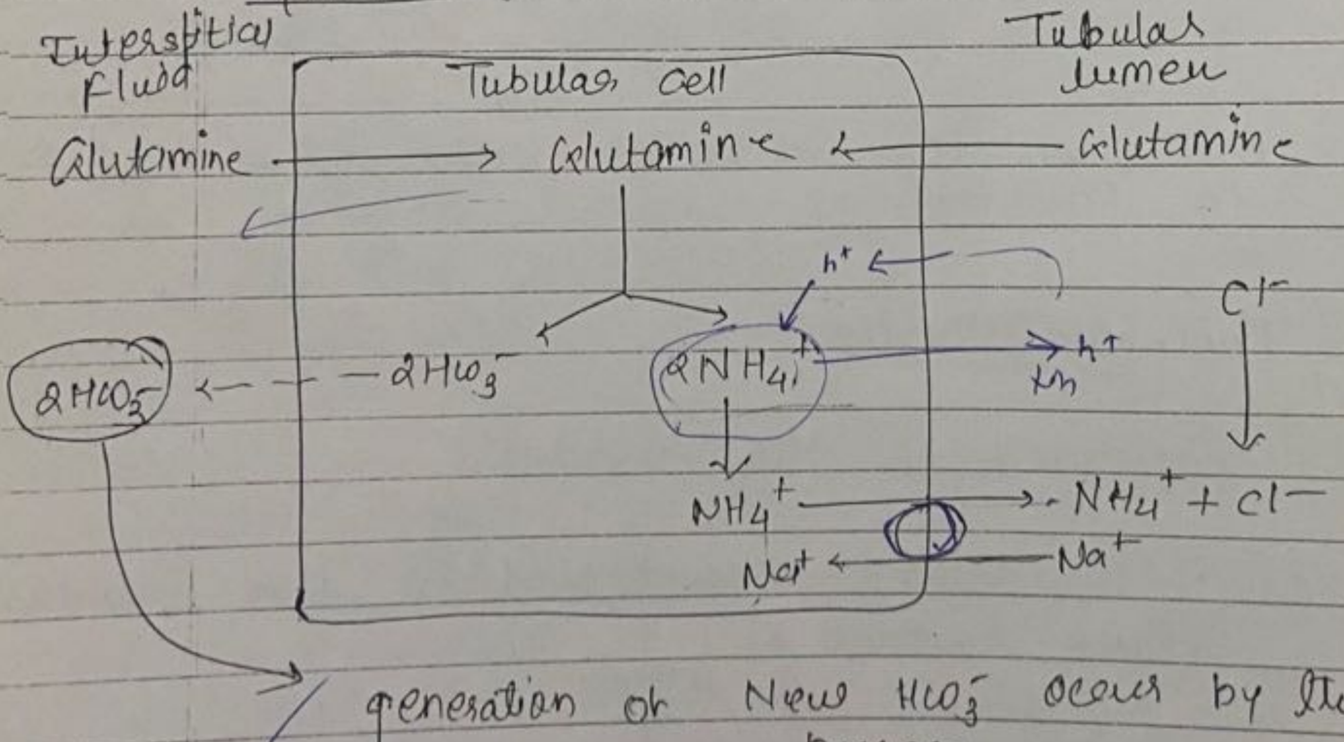
relatively poor absorption & reabsorption of water from the tubular fluid

(2) its pka is 6.8 which is nearer to pH of urine so provide good buffer.



→ this will also cause formation of new HCO_3^-

* Excretion of H^+ ion by Ammonia Buffer System :—



✓ generation of New HCO_3^- occurs by this process

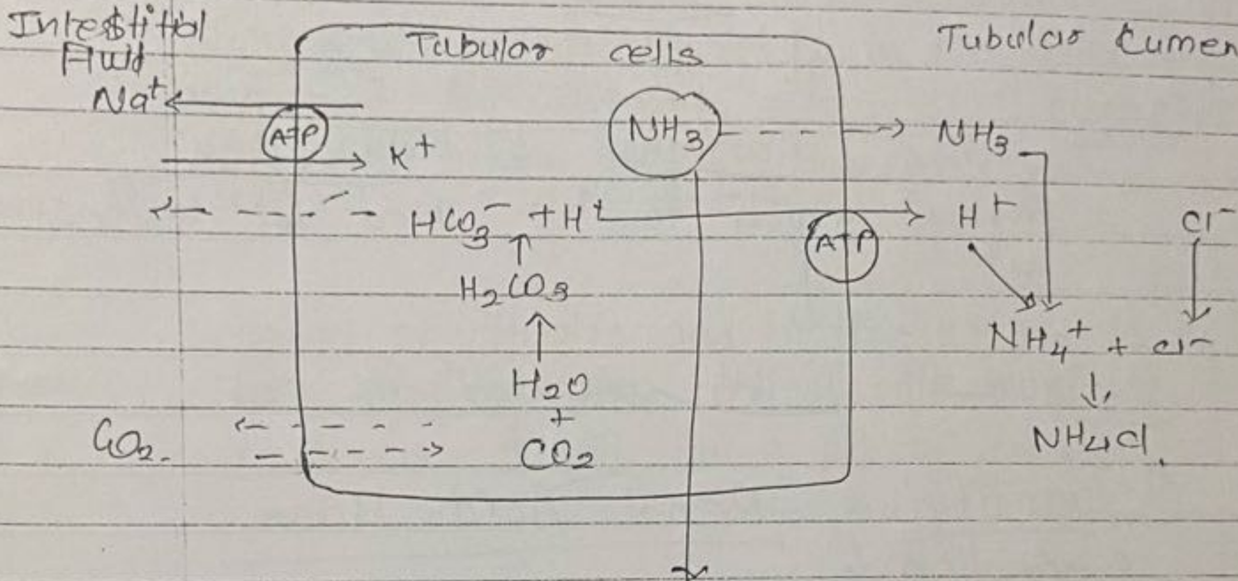
6.8 9.4

$H_2PO_4^-$, 8.6 NH_4^+ + Form

HPO_4^{--} ↓ ↓

Na H^+

But in collecting tubules →



→ Tubular membrane is very permeable to NH_3 whereas much less permeable to NH_4^+. So, once H^+ has reacted with NH_3 to for NH_4^+, NH_4^+ is trapped in the tubular lumen & is eliminated in urine.

→ In Normal condition,

↓

amount of H^+ eliminated by ammonia buffer system account for 50% of acid excretion & 50% of new HCO_3^- generation

→ But In chronic acidosis

↓

rate of NH_4^+ excretion is ↑ as much as 500 mEq/day.

↓

So, in this condiⁿ dominant mechanism by which acid is eliminated, is excreⁿ of NH_4^+

→ As ↑ H^+ concentration of ECF H^+

↓

Stimulate renal glutamine metabolism

↓

↑ NH_4^+ Formation & New HCO_3^- forman which to be used for buffering H^+

↓

Causes ↓ H^+ concentraⁿ in ECF.

* Quantifying Renal Acid- Base Excretion :

⇒ Bicarbonate Excretion = Urine Flow Rate × Urinary bicarbonate conc.

↓

This indicates that how rapidly the kidney are removing HCO_3^- from blood. (Which is same as H^+ excretion).

⇒ The amount of New HCO_3^- contributed to the Blood :– at any given time, amount of H^+ secreted that ends up in tubular lumen with noncarbohydrate urinary Buffers.

New HCO_3^- added to blood = NH_4^+ excreⁿ in urine = Urinary NH_4^+ × Urinary flow rate.

* Titrable Acid :-

→ Non- NH_4^+ buffer excreted in the urine is measured By titrable acid ex:- phosphate buffer & other organic buffers.

↓

amount of titrable acid in the urine is measured by titrating the urine with a strong base such as NaOH to a pH of 7.4

↓

This titration reverses that event that occurs in the tubular lumen when ~~the tubular~~ lumen is titrated by excreted H^+

↓

no. of meq of NaOH is required to return the urinary pH of 7.4 equal the number of meq of H^+ added to the tubular fluid that combined with phosphate & organic buffer.

↓

⟹ Titrable acid measurement does not include H^+ asso. with NH_4^+ because the pk of ammonia- ammonium reaction is 9.2 and the titration with NaOH, to a pH 7.4 doesn't remove the H^+ from NH_4^+.

Net acid excretion = NH_4^+ excreⁿ + Urinary titrable acid - Bicarbonate excreⁿ.

* ~~From Kidney~~ In Body Where H^+ comes ?

→ H^+ in the body comes from basic amino acid

→ For Acidification of urine → use NH_4Cl, lysine monohydrochloride

→ For Alkanization of urine → use sodium citrate, sodium bicarbonate, sod. lactate, sod. gluconate

citric acid can't take → it directly goes into TCA cycle → so converted into H_2O & CO_2.

→ In protein in acidic amino acid → COO^- & Na^+ → converts $CO_2 + H_2O$

$$H_2N - \underset{H}{\overset{R}{C}} - COOH \rightarrow \text{converts } H_2O \ \& \ CO_2$$

H_2N ↓ forms Ammonia

if glutamate ~~acid~~ is given

glutamic acid - Na^+

↓

AA - $COO^- Na^+$

↓

Urea + CO_2 + H_2O + OH^- + Na^+

↓

Basic

↓

Alkaline urin.

* If basic A A is given

$AA - NH_3^+ - Cl^-$

↓

$Urea + CO_2 + H_2O + H^+ + Cl^-$

↓

H^+ comes from Basic A. A

---

* Why we are substracting bicarbonate excreⁿ ??

↓

loss of HCO_3^- is the same as the addition of H^+ to the Blood

→ To maintain acid- Base balance

↓

Net acid excreⁿ must equal to the nonvolatile acid production

→ In acidosis :-

- Net acid excreⁿ ↑ greatly

↓

B'cz ↑ NH_4^+ excreⁿ & ↑ urinary titrable acid excretion

→ addition of HCO_3^- back to the blood

→ In alkalosis :-

→ titrable acid & NH_4^+ excretion drops to 0.
→ whereas HCO_3^- excretion ↑
→ So, there is nagetive net acid secretion
↓
→ So Net loss of HCO_3^- & NO New generaⁿ of HCO_3^-

* Regulation of Renal Tubular H^+ secretion :-

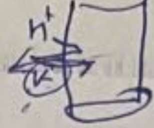
→ H^+ secretion is necessary for

① Reabsorpⁿ of HCO_3^-

② Generation of New HCO_3^-

→ Under (N) Condition :-
→ kidney must secrete at least enough H^+ secretion to reabsorb all most all filtered HCO_3^- & H^+ left over to be excreted as titrable acid / NH_4^+

* Factors affecting H^+ secreⁿ :-
(i) PCO_2 level in ECF
(ii) H^+ concentration in the ECF
(iii) Secretion of aldosteron.
(iv) any condition causes more absorpⁿ of Na^+ (like hypovolaemia) through Na^+ - H^+ exchanges in proximal tubule & thick ascending loop of Henle



H^+ ⊕ … → Al

⊖ … → Aci

ECF volume depletion

↓

Stimulates Na^+ reabsorp^n

↓ How?

↑ Angiotensin-II level

↓

directly stimulate Na^+-H^+ exchanges in renal tubules

↓

↑ Aldosterone level

↓

stimulate H^+ secretion by intercalated cells of collecting tubules.

↓

Causes HCO_3^- reabsorption due to ~~with~~ H^+ secretion

↓

alkalosis occurs.

(V) changes in K^+ concentration

↓ K^+ concentration in ECF

↓

low K^+ Exchanges with Na^+ By Na^+-K^+ ATPase

↓

So low Na^+ goes outside from the cell

→ So n more Na^+ ~~not~~ ~~…~~ ~~with~~ H^+

So ~~low H^+ secretion~~ more Na^+ is transported with H^+

↑

more H^+ secreted.

↑

alkalosis.