- Precise H^+ regulation is done as H^+ influences many activities in the body.
- Blood $[H^+]$ = 4 nEq/L pH = 7.4 [7.37 - 7.42]
- Intracellular pH is slightly lower as many acids are prod due to metabolism [pH = 7.6 - 7.4]
- ↑ $[H^+]$ ⇒ ↓ pH

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

- Regulation of $[H^+]$
  - Blood buffers system
  - Respiratory system
  - Renal system

- ① Blood buffer systems ⇒ 1st line of defense
  - A buffer combines with ~~acid~~ H^+ reversibly

$$Buffer + H^+ \rightleftharpoons H.Buffer$$

  - They react within seconds.
  - do not eliminate / add / syn H^+ but simply combine with H^+ until balance is re-established.

② Respiratory system :- 2nd line of defense
- Regulates removal of CO_2 ⇒ thus H_2CO_3
- Acts within minutes

③ Renal system (kidneys) ⇒ 3rd line of defense
- Eliminate acids & base — Most powerful acid base regulatory sys.
- Act over a period of hrs to days.

First line of defense keep $[H^+]$ from changing too much that the more slowly responding 2nd line of defense the kidneys can eliminate excess acid or base from the body.

⇒ Chemical Acid base buffer systems :-

- Regulate $[H^+]$ of body fluids with the help of Acid base buffers.
- A buffer is a substance that can reversibly combine with H^+ to form a weak acid

$$\text{Buffer} + H^+ \rightleftharpoons H\,\text{Buffer}$$

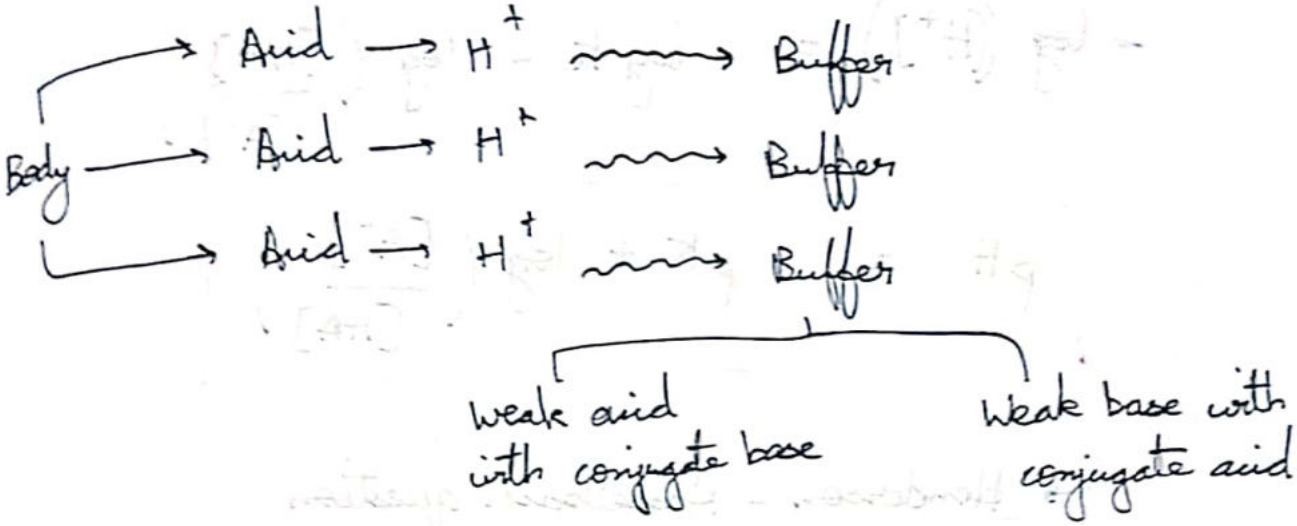
① If $[H^+]$ ↑ ⇒ Reaction shifts to right

② If $[H^+]$ ↓ ⇒ " " " left

- This system is 1st line of defense of the body against fluctuating $[H^+]$.
- Buffers simply bind to H^+ & don't eliminate from body
- Act within sec in resp to change in $[H^+]$.

* ± 0.1 ⇒ death
* Body uses mechanisms to regulate pH.

- Buffer ⇒ stops pH from rising or falling too quickly



Weak acid – H[A]
↳ does not dissociate fully in H_2O

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

↳ Equilibrium reaction ⇒

Rate of forward reaction = Rate of backward reaction

* concentrations stable

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

Equilibrium const $K = \frac{[H^+][A^-]}{[HA]} = \frac{\text{Products}}{\text{Reactants}}$

↳ High K ⇒ High H^+ ⇓ lower pH

$[H^+] = K \dfrac{[HA]}{[A^-]}$

$-\log([H^+]) = -\log\left(K \dfrac{[HA]}{[A^-]}\right)$

$-\log([H^+]) = -\log K - \log\left(\dfrac{[HA]}{[A^-]}\right)$

$$pH = pK + \log\left(\frac{[A^-]}{[HA]}\right)$$

↳ Henderson - Hasselbach question

If $[A^-] = [HA] \longrightarrow pH = pK + \log(1)$

$pH = pK$

$[A^-] < [HA] \longrightarrow pH = pK + \left[\log\left(\dfrac{[A^-]}{[HA]}\right)\right]$ ↓ negative

pH ↓

$[A^-] > [HA] \longrightarrow pH = pK + \left[\log\left(\dfrac{[A^-]}{[HA]}\right)\right]$ ↓ positive

pH ↑

→ Two components

H_2CO_3 [weak acid]

formed by CO_2 & H_2O

$NaHCO_3$ [Bicarbonate salt]

$$H_2O + CO_2 \rightleftharpoons H_2CO_3$$

↑ carbonic anhydrase [abundant in walls of alveoli, epithelial cells of renal tubules]

- weak acid ionises weakly

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

- $NaHCO_3$ ionises almost completely

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

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

$+ Na^+$ [from $NaHCO_3$]

① Addition of HCl

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

↓

↑ H_2CO_3 → ↑ CO_2 → (+) ↑ rate of respiration to remove CO_2 from ECF

Buffering Base

$$NaOH + H_2CO_3 \longrightarrow NaHCO_3 + H_2O$$

$$\hookrightarrow OH^- + H_2CO_3 \longrightarrow HCO_3^- \uparrow$$

$H_2CO_3 \downarrow \Longrightarrow \uparrow CO_2$ reacts with H_2O to form H_2CO_3

$\Downarrow$

$\downarrow$ rate of resp. $\leftarrow \downarrow CO_2$ in ECF

$\uparrow HCO_3^-$ formed, is excreted by kidneys

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

$$pH = pK + \log\left(\frac{[HCO_3^-]}{[H_2CO_3]}\right)$$

pK for Bicarbonate buffer is 6.1

$[H_2CO_3] \propto$ conc of CO_2

$$[H_2CO_3] = 0.03 \times PCO_2$$

Hence :-

$$pH = pK + \log\left(\frac{[HCO_3^-]}{0.03 \times PCO_2}\right)$$

$$pH = 6.1 + \log\left(\frac{[HCO_3^-]}{0.03 \times PCO_2}\right)$$

$\uparrow HCO_3^-$ => pH ↑ [Alkalosis]

$\uparrow pCO_2$ => pH ↓ [Acidosis]

- HCO_3^- regulated by kidneys, pCO_2 regulated by Resp system.

The coordinated efforts of both these systems maintain normal acid base homeostasis.

- Metabolic acid base disorders due to change in $[HCO_3^-]$ conc in body

Metab Acidosis ⇓ ↓ HCO_3

Metab Alkalosis ⇓ ↑ HCO_3^-

- Respiratory acid base disorder => due to change in pCO_2

Resp Acidosis pCO_2 ↑

Resp Alkalosis pCO_2 ↓

Note :- mnemonic

R O M E

Respiratory opposite

pH ↓ => pCO_2 ↑

pH ↑ => pCO_2 ↓

Metabolic equal.

pH ↑ => $[HCO_3^-]$ ↑

pH ↓ => $[HCO_3^-]$ ↓

$$pH = 6.1 + \log\left(\frac{[HCO_3^-]}{0.03 \times PCO_2}\right)$$

when HCO_3^- & CO_2 amts eq $\Rightarrow$ pH = 6.1

① $\frac{HCO_3^-}{CO_2}$ ↑ pH => > pk

eg:- addition of base ↑ HCO_3^- & ↓ CO_2

② $\frac{HCO_3^-}{CO_2}$ ↓ pH => < pk

addition of acid ↓ HCO_3^- & ↑ CO_2

- Factors determining buffering power of a buffer:-

① pH of the system:-

If pH of sys is close to pk value of buffer the buffering power ↑.

↳ change in the pH for any given amt of acid or base added is least when pH is near pk of system.

② Concentration of Buffer components:-

If low => change in pH high.

: pH of blood is more than pK of HCO_3^- buffer system (7.4 > 6.1)

Conc of CO_2 & HCO_3^- in blood is very less.

Still the HCO_3^- buffer is the most impt buffering sys of ECF as the 2 components are regulated by Resp (CO_2) & Kidneys (HCO_3^-) respectively

Bcoz of this pH precisely controlled by regulating the rate of removal/addition of HCO_3^- & rate of removal of CO_2

=> Phosphate buffer system :-

$$H_2PO_4 \rightleftharpoons HPO_4^-$$

* $pK = 6.8$
* impt in renal tubular fluids & intracellular fluids.

- HCl added

$$HCl \rightleftharpoons H^+$$
$$H^+ + HPO_4^- \longrightarrow H_2PO_4$$

- NaOH added

$$OH^- + H_2PO_4 \longrightarrow HPO_4^-$$

* Renal tubular fluid → conc of phosphate is high & ICF
pH of tubular fluid is lower than that of ECF close to pK

=> Protein buffers :-

* Most abundant in cells.

* change in pH of ICF occurs in proportion with change in pH of ECF

* Protein buffers in cells help prevent these changes...

* eg :- In RBC :- prtn buffer is Hb

$$H^+ + Hb \rightleftharpoons HHb.$$

* Approx 60 - 70% of tot chemical buffering of body fluids is inside the cells. ∴ most of this buffering results from IC prtns.

↳ Reasons :-

prtn conc in cells ↑↑ ∴ pH of ICF is close to pK of prtn buffer.

Note :-

(↑) CO_2 → (↑) H_2CO_3 formed → (↑) H^+ → pH (↓) acidic

Integrated regulation of Acid Base :-

↳ control of ECF CO_2 conc by lungs

CO_2

1·2 mol/L $\Rightarrow PCO_2 = 40$ mm Hg

- ↑ in ventilation → ↑ elimination of CO_2 $\Rightarrow$ ↓ H^+ conc

⇓

↑ pH

- ↓ in ventilation → opp occurs

- CO_2 in ECF regulation → Rate of metab formation
  → Rate of pulmonary respiration

Pulmonary exp of CO_2 balances metab formation of CO_2

↑ pulmo. ventilation → ↑ CO_2 removal

↓

↓ PCO_2

- ∴ Higher the alveolar ventilation lower is the PCO_2 provided metab formation is constant.

↑ alv. ventilation → ↑ CO_2 removal

↓

↓ $[H^+]$ in ECF

↓

↑ pH.

- ↑ $[H^+]_{ECF}$ → (+) ↑ alveolar ventilation.

↑ $[H^+]$ / ↓ pH → (+)

Resp compensation for ↑ pH is not nearly effective as resp to ↓ pH bec pH ↑ → $[H^+]$ ↓

↓ $[H^+]$ → ↓ alv vent → ↓ O_2 diffusion thru lungs

↓

↓ pO_2

↓ ⊕

↑ alv ventilation.

- Physiological type of buffer / 2nd line of defense.
  Buffering power of RS > that of all chemical buffers in body combined.
- Impairements of lungs such as emphysema can cause Resp acidosis → as there is ↓ removal of CO_2 → ↑ $[H^+]$ → ↓ pH

⇒ Renal control of Acid Base balance:-

- regulate acid base balance by excreting either an acidic urine or alkaline urine

Net loss of acid ⇓ Tubular sec of H^+ > Filtration of HCO_3^-

Net loss of base ⇓ Tub. sec of H^+ < Filtration of HCO_3^-

daily production of non volatile acids = 80 mEq
(these which cannot be excreted by lungs)

daily filtration of HCO_3^- = 4320 mEq/day

↳ preventing loss of HCO_3^- ions more impt than excreting 80 mEq of acid

∴ H^+ secretion necessary for → H^+ excretion
→ HCO_3^- reabsorption.

For each HCO_3^- reabsorbed an H^+ must be secreted.

∴ To reabsorb HCO_3^- ⇒ 4320 mEq H^+ secreted

To remove 80 mEq acids ⇒ 80 mEq H^+ secreted

4400 mEq H^+ excreted in urine each day.

Renal reg of $[H^+]_{ECF}$ →
- H^+ secretion
- Reab of filtered HCO_3^-
- Prod of new HCO_3^-

⇒ Reabsorption of HCO_3^-

↳ occurs in PCT, Thick Asc limb of HL and early DCT ~~only~~, Late DCT > collecting ducts.

Not in desc > asc thin limb of HL.

- HCO_3^- cannot diffuse thru apical mem of cell.
is reabsorbed indirectly by first being converted

CO_2

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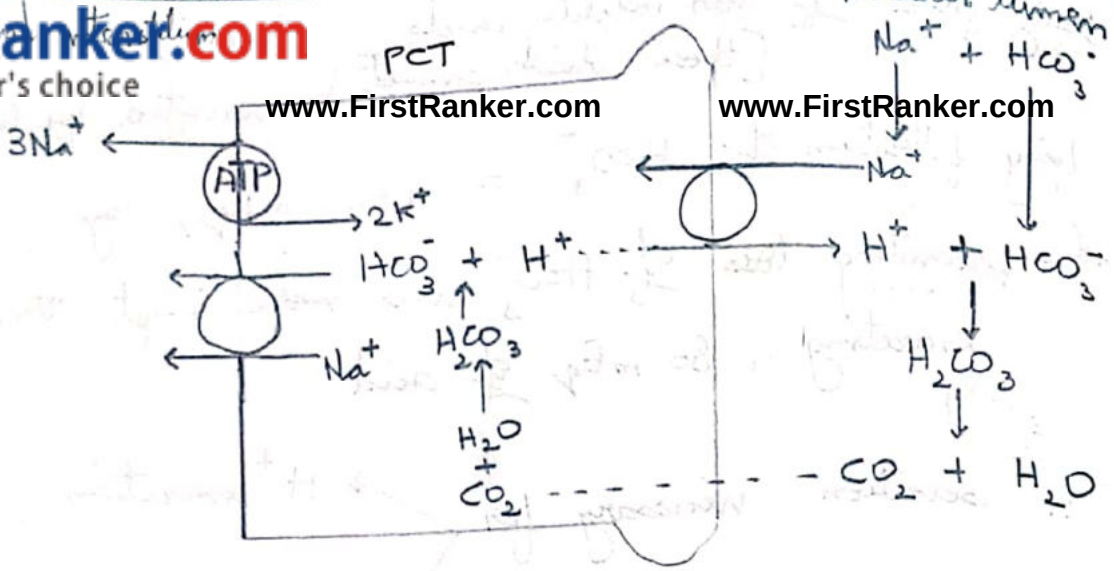


Filtered HCO_3^- combines with secreted H^+ to form H_2CO_3

↓

H_2CO_3 breaks down to give CO_2 & H_2O

↓

CO_2 diffuses into the tubular cell

↓

$$CO_2 + H_2O \xrightarrow{CA} H_2CO_3$$

↓

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

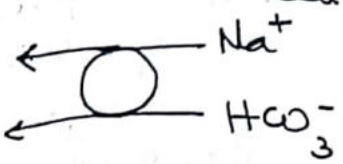
HCO_3^- → Reabsorbed ie transported across Basolateral mem into interstitum

H^+ → secreted into tubular lumen.

Transport of HCO_3^- across Basolat. mem.

Na^+/HCO_3^- cotransport cell

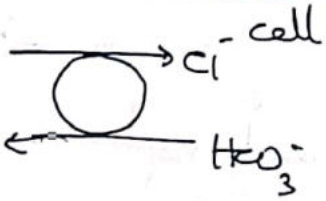
RMI



present in early PCT

Cl^-/HCO_3^- exchanger

RMI



late PCT, thick asc limb collecting tubules, ducts

HCO_3^- reabs & H^+ sec

- 80-90% PCT
- 10% in thick Asc limb
- 4-9% DCT & CD.

⇒ Secretion of H^+

Early Nephron segment
⇓
PCT, Thick Asc Limb, early DCT
⇓
Na^+/H^+ exchanger

Late Nephron segment.
⇓
Late DCT, remaining nephron.
⇓
H^+ ATPase pump
H^+/K^+ ATPase pump

Metab of Tubular cell

Diffusion ~~from lumen~~ into cell

$CO_2 + H_2O$ ← ~~from~~ in cell.

↓ carbonic anhydrase

H_2CO_3

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

HCO_3^- Reab. Thru Cl^-/HCO_3^- exch.

Secreted into lumen / ie Transported across apical mem

Early nephron
⇓
95%

Involves Sodium / hydrogen exchanger which is a secondary active transporter
Na^+/H^+ exchanger can trans H^+ against its conc gradient due to Na^+ gradient created by Na^+/K^+ ATPase.

Late nephron [type A intercalated cells]
⇓
5%
↳ involves H^+ ATPase pump or H^+/K^+ ATPase transporters
⇓
Primary active trans

In proximal tub. $[H^+]$ ↑ by 3 to 4 fold but in distal tub it is ↑ by 900 fold. even tho it contributes to 5% of H^+ secretion.

Minimum pH attained for urine = 4.5.

buffers in tubules generates "new" HCO_3^-

- When H^+ is secreted in excess of HCO_3^- filtered, only small part of excess H^+ can be excreted in ionic form [Reason of min pH of urine is 4.5 which is 0.03 mEq/L of H^+. Beyond this the pH cannot ①].

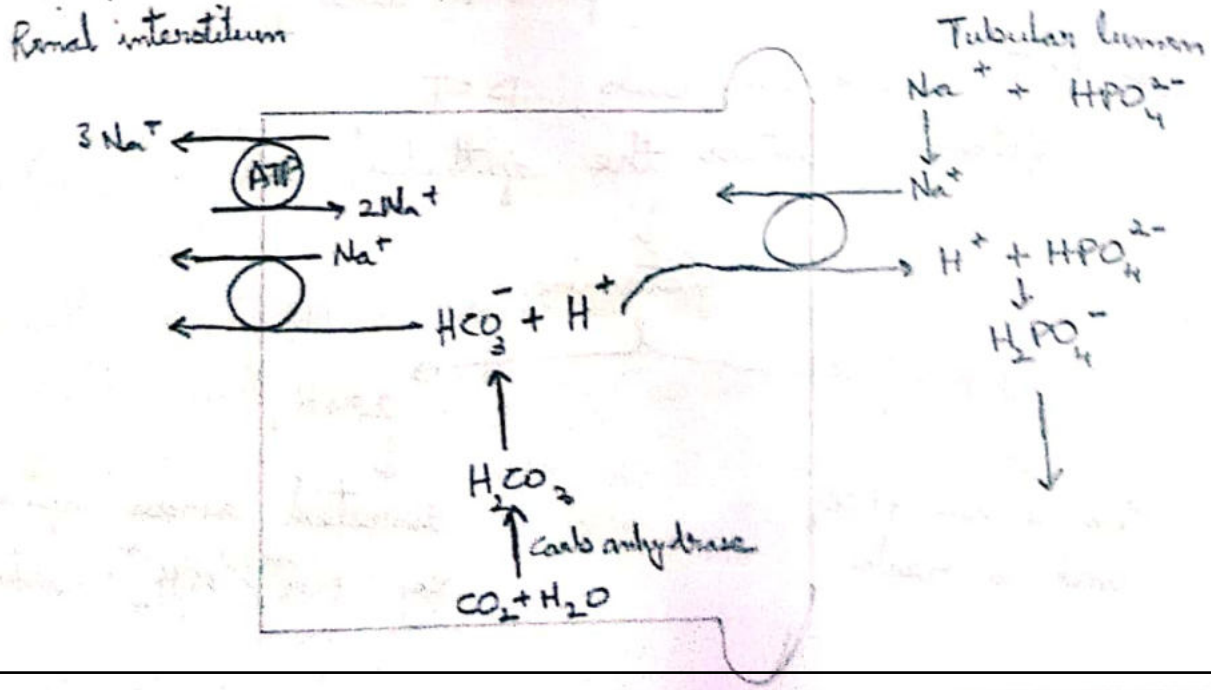
- Excretion of large amts of H^+ occurs by combining H^+ with buffers in tubular fluid.

- combination of H^+ with a non HCO_3^- buffer leads to the gen of new HCO_3^- in cell.

- ∴ when there is excess H^+ kidneys not only reabs all HCO_3^- but also form new HCO_3^-

- Buffers involved are :-

① Phosphate buffer :- $H_2PO_4^-$ / HPO_4^{2-}



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$CO_2 + H_2O \rightarrow H_2CO_3$

H_2CO_3 → HCO_3^- reabs ← New

H^+ secreted

As long as there is excess HCO_3^- within lumen H^+ combines with HCO_3^-. Once all HCO_3^- reabs. excess H^+ combines HPO_4^{2-} to form $H_2PO_4^-$ which is excreted.

Note :- HCO_3^- generated in the cell and enters the circulation, represent net gain of HCO_3^- rather than replacement of filtered HCO_3^-

- 30 – 40 mEq / day of phosphate are available for buff. normally.

(2) Ammonia buffers :-

* More impt than phosphate.

- $NH_3 \geq NH_4^+$

↳ comes from glutamine. [prod in liver]

I PCT, Thick Asc limb, DCT

glutamine enters the epithelial cell

↓

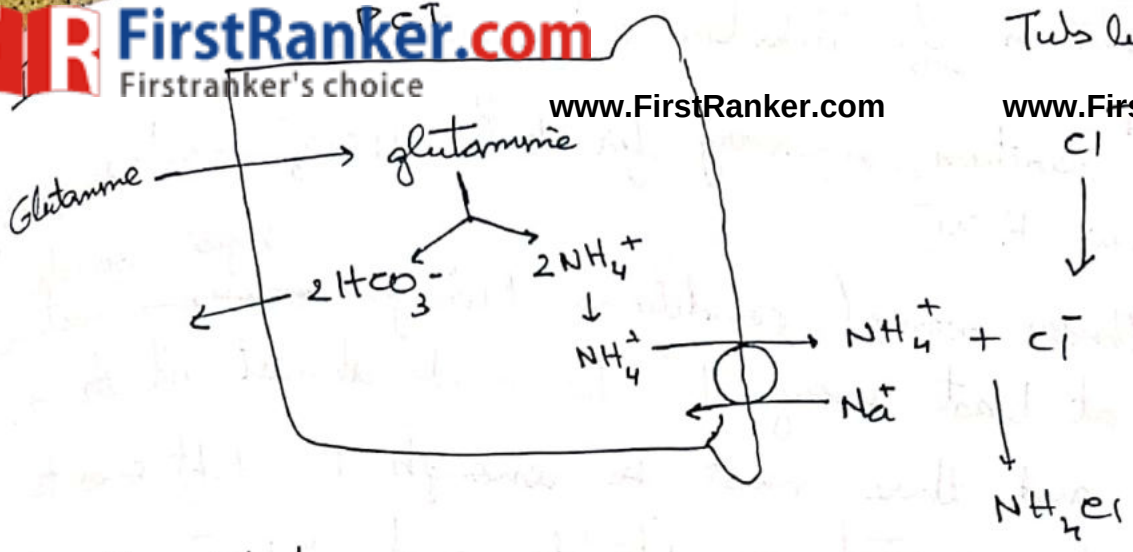
glutamine

$2HCO_3^-$ ← → $2NH_4^+$

This is new HCO_3^- and is reabs

↓

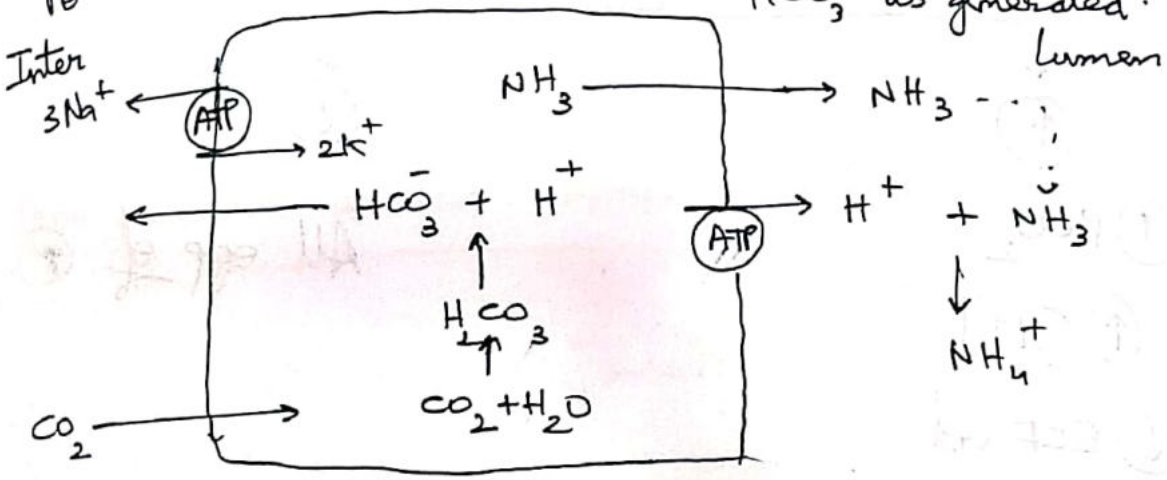
secreted across apical mem by Na^+/NH_4^+ exchanger.



collecting tubules :-

H^+ secreted into lumen where it combines with NH_3 forming NH_4^+

For each NH_4^+ excreted a new HCO_3^- is generated.



↑ ECF $[H^+]$ ⟶ ⊕ glutamine metab ⟶ ↑ formation of NH_4^+ & HCO_3^-

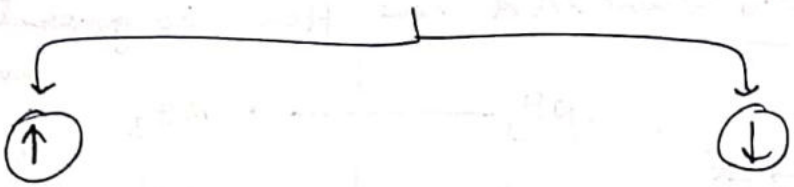
↓ $[H^+]$ ⟶ opp occurs.

- Normally amt of H^+ excreted by NH_3 buffer is 50% of total acid excreted & contributes to 50% new HCO_3^-
- chronic acidosis ⟶ ↑ NH_4^+

⇒ Tubular H^+ secretion :-

- H^+ secretion necessary for both HCO_3^- reabs & gen of new HCO_3^-
- Under normal conditions kidneys must secrete at least enough H^+ to reab almost all the HCO_3^- and there must be enough H^+ left over to be excreted as titrable acid or NH_4^+ to get rid of non volatile acids.

Factors affecting H^+ tubular sec



↑	↓
① ↑ PCO_2	All opp of ⑪.
② ↑ $[H^+]$	
③ ↓ ECF vol	
⑪ ↑ Angiotensin II	
⑤ ↑ Aldosterone	
⑥ Hypokalemia	

Normal values ⇒

PCO_2 = 40 mm Hg

$[HCO_3^-]$ = 24 mEq/L

Acidosis [pH < 7.4] → Metabolic, Respiratory

Alkalosis [pH > 7.4] → Metab, Resp.

① Metabolic acidosis :-
- Occurs primarily due to ↓ in HCO_3^- in ECF
- Features :-
  pH < 7.4
  HCO_3^- < 24 mEq/L
- Causes :-
  a) Renal tubular acidosis : chronic renal failure / Addison's disease etc.
     → Inability to reab suff HCO_3^-
     → Inability to secrete sufficient H^+
  b) Diarrhea
  c) Diabetes mellitus :- diabetic ketoacidosis.
  d) Ingestion of certain acidic poisons
     eg :- aspirin, methyl alcohol which forms HCOOH

- Compensation :-
① Respiratory :- ↑ ventilation rate → ↓ PCO_2 → ↓ H^+
② Renal :-
There is complete reab of HCO_3^- and also formation of new HCO_3^- accompanied with

H^+.

∴ Metab acidosis → pH < 7.4

$[H^+]$ ↑ | ~~$[H^+]$ ↑~~ | PCO_2 ↓ < 40 mm Hg | $[HCO_3^-]$ ↓↓ < 24 mEq/L – primary

(2) Respiratory acidosis :-

– Primary reason is ↑ in PCO_2 due to hypovent

– Clinical causes :-

(a) Damage to resp centres in CNS [medulla oblangata]

(b) Obstruction of airways :-

(c) Pneumonia

(d) Emphysema

(e) ↓ pulmo membrane surf area.

– Features :-

(1) pH < 7.4 $[H^+]$ ↑.

(2) PCO_2 ↑↑ > 40 mm Hg

(3) $[HCO_3^-]$ ↑ > 24 mEq/L

↳ Renal compensation which ↑ HCO_3^- in ECF to buffer H^+ → helps to offset the ↑ in PCO_2.

Primary reason is ↑↑ HCO_3^-

Clinical causes :-

① Diuretics :- enhance H^+ sec & HCO_3^- reab.

② ↑ Aldosterone :- ↑ Na^+ reab with ↑ H^+ sec.
[Na^+/H^+ exchanger]
↑ H^+ secretion in intercalated cells.

③ Vomiting of gastric contents

④ Ingestion of Alkaline drugs :- $NaHCO_3$

- Features :-

① pH > 7.4
$[H^+]$ ↓

② HCO_3^- ↑↑ > 24 mEq/L

③ ↑ PCO_2 > 40 mm
↳ Partial resp compensation.

④ Resp Alkalosis :-

- Primary Reason is ↓↓ PCO_2 due to hyperventilation
- clinical causes :-

① Hight altitude sickness :-

↓ PO_2 → ↑ hyperventilation → ↓↓ PCO_2 → ↓ $[H^+]$

(2) PCO_2 ↓↓ < 40 mm Hg

(3) HCO_3^- ↓ < 24 mEq/L

↳ Renal compensation.

(5) Mixed Acid Base disorder :-

Acid base disorders not accompanied by apt compensatory responses.

There are 2/more underlying causes for the acid base disturbance.

- A convinient way to diagnose acid base disorders is to use an acid base nomogram/davenport diagram

⇒ Anion Gap :-

- It is a diagnostic concept use to diagnose diff cases of metab. acid
- It is the difference between unmeasure anions and unmeasured cations.

$$\text{Anion gap} = [Na^+] - [HCO_3^-] - [Cl^-]$$

$$= 144 - 24 - 108 = 12 \text{ mEq/L}$$

↑ AG → unmeasured anions ↑ albumin, PO_4^{3-}, SO_4^{2-}

or

→ unmeasured cations ↓.

Ca^{2+}, Mg^{2+}, K^+

Anion gap range = 8 - 16 mEq/L

Metab acidosis

(↑) AG

[Normochloremia
Cl^- does not (↑) to compensate (↓) HCO_3^-]

1. diab ketoacidosis
2. Lactic acidosis
3. chronic renal failure
4. Aspirin
5. CH_3OH
6. Starvation

(N) AG

[Hyperchloremia → Cl^- (↑) to compensate (↓) HCO_3^-]

1. Diarrhea
2. Renal tubular acidosis
3. Carbonic anhydrase inhibitors
5. Addison's dzz.