Renal Acid/Base

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Acid Base Homeostasis

- **H+ conc in**
  - **body fluid** needs to maintained in narrow range for optimal cellular function
  - **Intracellular conc** is even more impt to:
    - Ensure norm functions:
      - Norm enzyme function
      - Membrane excitability
      - Energy production
    - Done by:
      - Na/H counter transporters ⇒ Extrusion of H+ ions through cell membrane
      - Intracellular buffering – by proteins
- Body makes large amount of acids (ie H+ ions):
  - **volatile acid (CO2) respiration**
  - **fixed acid from metabolism**:
    - incomplete metabolism of:
      - fats ⇒ acetoacetic acid, B hydrobuturic acid (ketones!)
      - proteins – sulphuric acid, phosphoric acid
      - carbohydrates – lactic acid
- **H+ ion conc in body fluid kept ~40nmol/L (pH 7.4) or rage 35-35 nmol/L (pH 7.35 – 7.45)**

H+ Balance

- **Production vs removal**
- **Total H+ turnover/day = 150mole s**
- **Production (mmol/day):**
  - CO2 = 15000
  - Lactate = 1500
  - Other fixed acids ~75
- **Removal:**
  - Lungs (CO2) = 15000
  - Liver (lactate) = 1500 (60% of lactate)
  - Renal:
    - Titrateable acidity (lactate) = 30 (40% of lactate)
    - NH4 = 40 - 100

Acid Base Homeostasis

- **3 impt mechanisms:**
  - buffering =
    - intracellular & extracellular mechanisms
    - minimise pH change resulting from addition of acid or alkali
    - effect almost immediate
    - No NET gain or loss of H+ from body
    - Intra vs extracellular processes:
      - Intra = phosphates & proteins (incl Hb)
      - Extra = CO2-HCO3 system
  - Compensation = physiological process which restores HCO3/PCO2 to normal
    - eg ↑or↓ ventilation, renal mechanisms etc
  - Correction = correction of underlying disorder needed eventually
Role of Kidneys in Acid-Base Homeostasis

- Plays impt compensatory role
- Can vary urinary excretion of H+ & HCO3- ions

\[
[HCO_3^-] \quad \text{← role of Kidneys}
\]

Henderson Hasselbalch: \( \text{pH} = 6.1 + \log [\text{CO}_2^*] \) ← role of Lungs

\[
[\text{CO}_2] \text{ (in mmol/L)} = \text{PCO}_2 \text{ (in mmHg)} \times 0.03 \quad \text{(Henry’s Law)}
\]

- Kidney contribute to homeostasis of ECF H+ conc by regulating serum HCO3- conc via:
  - Reabsorption of filtered HCO3
  - Addition of new HCO3 to blood
    \( \text{← see NET loss of H+ via titratable acidity of NH}_4^+ \)
  - Excretion of filtered +/- secreted HCO3

- Volatile acid ie CO2 excreted via lungs
- Kidneys role:
  - metabolise 40% of lactate (liver 60%)
    \( \text{← ie doesn’t need to be excreted in urine} \)
  - excrete rest of fixed acid load:
    - 40-100 H+ mmol/day
    - = a slow response to ↑ed excretory load
    - max excretory capacity = 700 H+ mmol/day
    - takes ~ 5days to reach max

Renal H+ Secretion

- H+ secreted into urine in:
  - prox tubule
  - distal tubule
  - collecting ducts

Proximal Mechanism

- Occurs in:
  - PCT
  - Thick ascending LOH
  - DCT
- Low gradient system – ie limiting factor is luminal pH of 7
- High capacity system = 4000-5000nmol H+ / day secretion
- 2 mechanisms:
  - Na/H Counter-transporter – 2nd active transport coupled to Na/K/ATPase
    \( \text{← shown in diagram next} \)
  - Primary Active H-ATPase – in luminal membrane

Source of Acid

- CO2 diffuses into tubular cell where: \( \text{CO}_2 + \text{H}_2\text{O} \Rightarrow \text{H}_2\text{CO}_3 \)
- H comes from dissociation of \( \text{H}_2\text{CO}_3 \):
  - \( \text{H}_2\text{CO}_3 \Rightarrow \text{H}^+ \& \text{HCO}_3^- \)
    - Carbonic anhydrase as catalyst
      \( \text{← drugs can effect action} \) : H+ secretion
  - HCO3- diffuses into interstitum/ECF
  - H+ secreted via above mentioned mechanisms
Na/H Counter-Transporter

- H movement in prox tubule = secondary active transport:
  - Extrusion of Na out of tubular cell by NaKATPase ⇒ interstitium
  - ⇒ ↓Na in cell
  - Na moves from lumen ⇒ cell along gradient
    - drives H into lumen with coupled Na-H coupled transporter
- ∴ each H+ secreted into lumen; lose 1Na & 1 HCO₃⁻ into interstitium

Factors Effecting this System
- efficiency of this system is effected by:
  - intracellular PCO₂:
    - ↑PCO₂ (resp acidosis) ⇒ ↑intracellular H₂CO₃ available ⇒ ↑acid secretion
  - K+ conc:
    - ↓K ⇒ ↑acid secretion
      - because K competes with H for secretion
  - ECF hypovolaemia ⇒ ↑ed Na/H exchange mechanism ie retaining Na drives H out
    - vice versa ie ↑ed ECF ⇒ ↓H⁺ ion excretion
    - mechanism for met alkalosis by hypovolaemia 2nd to vomit ++

Distal Mechanism of H⁺ Secretion
- Occurs in late DCT & CD
- High gradient system – minimal lumen pH 4.5 achievable
- Low capacity system = 0-700 nmol H/day
  - to reach max capacity takes ~ 5days
- Accounts for <5% total H secreted

Mechanism Intro
- H⁺ secretion is indep of Na
- Secretion performed by intercalated cells (IC)– 2 types:
  - Type A
  - Type B
- Source of acid same as proximal mechanism ie via CO₂ & H₂CO₃
Type A IC Cells

- = most numerous type
- secrete H while reabsorbing HCO3 & K
- type A cells:
  - similar to parietal cells in stomach which secrete acid
  - contain abundant carbonic anhydrase
  - contain Band 3 = anion exchange protein in basolateral cell membrane
  - functions as Cl/HCO3 exchanger ⇒ HCO3- into interstitium
- mechanism of H secretion involves:
  - luminal membrane (primary active transport):
    - H-ATPase (also seen in proximal mechanism)
    - H/K-ATPase
      - this also involved in active K reabsorption
- Fate of ions into interstitium:
  - HCO3 couple with Cl in counter transported
  - Cl diffuses by passively
  - K diffuses passively

Type B IC Cells

- Only found in cortical CDs
- Actually secrete HCO3
- Actually flip-flopped type A cells:
  - H-ATPase now on basolat membrane
  - Cl/HCO3 counter-transporter on luminal membrane
- Very few type B cells
- Excretion of HCO3 by them is not important because:
Overall handling of $\text{HCO}_3^-$ always = NET reabsorption
Excretion of $\text{HCO}_3^-$ can easily be accomplished ↓ing NET reabsorption in tubule
  ⇔ ie without needing an active secretion method

HCO$_3^-$ Effects of Prox & Distal Mechanism
- Both prox & distal mechanism cause NET addition of HCO$_3^-$ to plasma

Factors Effecting Distal Mechanism H Secretion
- ↑PaCO$_2$ ⇒ ↑H secretion
- ↑ Extracellular pH ⇒ ↑H secretion
- Hypokalaemia - ⇒ ↑H secretion (hypokalaemia leads to ↑intracellular H ⇒ ↑secretion)
- Aldosterone – see next section

Aldosterone Effects
- Renin secretion is ↑ed during metabolic acidosis ⇒ ↑aldosterone
  ⇔ mechanism unknown

  Causes:
- ↑ H secretion via distal mechanism
  - direct action on H/K-ATPase ⇒ ↑activity ⇒ ↑H secretion
- Action on Principle cells in CD:
  - ↑Na reabsorb/K or H secretion
    ⇔ either H or K secreted in exchange for Na reabsorption
    ⇔ if hypokalaemic :
      aldosterone ⇒ ↑↑H secretion ⇒ met alkalosis

NB :
  proximal & distal mechanism both have method to promote met alkalosis

Summary Mechanisms of H secretion
- primary active H-ATPase in luminal membrane
- counter-transportes in PCT & ascending LOH (H/Na-ATPase)
- H/K-ATPase in type A IC cells in CD (reabsorb K & secretes H)

Summary Factors Effecting Acid Secretion
- causes of ↑renal acid secretion:
  - intracellular PCO$_2$:
    - ↑PCO$_2$ (resp acidosis) ⇒ ↑intracellular H$_2$CO$_3$ available to buffer hydroxyl ions ⇒ ↑acid secretion
  - K+ conc:
    - ↓K ⇒ ↑acid secretion
      ⇔ because K competes with H for secretion
  - ↑renin conc:
    - ↑aldosterone ⇒ ↑Na reabsorption ⇒ ↑H+ &/or ↑K+ secretion
  - ECF hypovolaemia ⇒ ↑Na retention ⇒ ↑H secretion (prox mechanism)
- causes of ↓renal acid secretion:
  - ↓Carbonic anhydrase level: Inhibition of CA ⇒ ↓H$_2$CO$_3$ ⇒ ↓acid secretion

Fate of H+ in Urine
- max H+ gradient which pumps/transport mechanisms can work against ~ urine pH 4.5
  ⇔ ie H+ conc x1000 of plasma
- this pH norm reached in collecting ducts
- buffers then required to ‘tie up’ H+ so that further H+ secretion can continue
- 3 reactions with free H+:
  - (H+ secreted & HCO$_3^-$ & Na reabsorbed – does not involve NET excretion of H+ or use of buffers)
  - formation of titratable acid
  - ammonium excretion
1. HCO3 Reabsorption

H+ & HCO3- ⇒ H2CO3 ⇒ CO2 & H2O ⇒ H2CO3 ⇒ CO2 & H2O ⇒ H+ & HCO3-

• 85% filtered HCO3 reabsorbed in PCT (rest in DCT)
• tubular fluid = free of HCO3 @ pH 6.2
• PCT reabsorption depends on H+ secretion
• CO2 & H2O & carbonic anhydrase essential for supply of H ions
  (reaction explained in PCT section prev)
• CA found
  o inside tubular cell
  o brush border of lumen –
    ▪ facilitates breakdown of H2CO3 which prev been formed by H+ secreted and filtered
      HCO3 in lumen fluid
    ▪ CO2 then free to diffuse into cell where it rejoins with H2O
    ▪ Then broken down in cell again by CA
      (reaction explained in PCT section prev)
• NET effect = 1H out, 1 Na in, 1 HCO3 in ∴ no NET H excretion over HCO3
• HCO3 reabsorption in ↓ed by unknown mechanism when ECF volume is expanded
• 4000-5000 mmol HCO3 filtered/day (24hrs x 180)
• normal state⇒ metabolism produces ↑H+ compared to HCO3 ∴
  o all filtered HCO3 is reabsorbed
  o Excess H is excreted as titratable acidity or ammonium ions
• @ serum HCO3 28mmol/L = H being secreted at max rate & all being used to reabsorb HCO3
• @ serum HCO3 >28 = excess HCO3 ⇒ urine becomes alkali & HCO3 excreted in urine

2. Formation of Titratable Acid

• titratable acid (TA) = H+ buffered in form of non HCO3 buffers:
  o dihydrogen phosphate (H2PO4)
  o acidic form of creatinine
  o ketoacids
• normally 20-30mmol H=/day excreted as TA
• most TA formed by reaction with HPO42-:
  o H+ & HPO42- ⇒ H2PO4-
• H+ reacts with dibasic phosphate (HPO42-) ⇒ monobasic phosphate (H2PO4-)
• Reaction greatest in distal & collecting ducts
  (cos phosphate which escaped prox tubule reabsorption is most concentrated here cos of water
  reabsorption)
• At max urinary acidity (pH 4.5): almost all filtered phosphate in H2PO4- state
• Filtered creatinine (pKa 4.9):
  o Accounts for small fraction of titratable acidity
  o @max urine acidity ⇒
    ▪ 2/3 filtered creatinine will be in acidic form
    ▪ account for 25% of urinary TA
• Ketoacids:
  o Also contribute to TA
  o In severe DKA:
    ▪ B-hydroxybuturate (despite pKa 4.8) becomes major component of TA
      (because being excreted in such large amounts)
3. Ammonia Secretion

- Ammonia (NH₃) = formed mainly in PCT but also rest of nephron (except thin LOH)
- Ammonia can exist in 2 forms:
  - NH₃ = ammonia (non acidic form)
  - NH₄⁺ = ammonium (acidic form)

  \[ \text{H}^+ \text{ & NH}_3 \Rightarrow \text{NH}_4^+ \]

- Ammonia excretion:
  - 30% - secreted by tubular epithelium from free arterial NH₃
  - 60% from deamination of glutamine

  ! glutamine come from:
  - 80% peritubular capillary blood
  - 20% glomerular filtrate
  - trace amount direct from glutamate

- NH₃ produced in cells by:

  \[
  \begin{align*}
  \text{Glutamine} & \xrightarrow{\text{glutaminase}} \text{glutamate + NH}_3 \\
  \text{Glutamate} & \xrightarrow{\text{Glutamic dehydrogenase}} \alpha\text{-ketoglutarate + NH}_3
  \end{align*}
  \]

- Further metabolism of \( \alpha \)-ketoglutarate uses 2H⁺ & frees 2HCO₃⁻
  ! either to glucose/CO₂/H₂O

- Reactions in tubular cells: \( \text{NH}_3 + \text{H} \Rightarrow \text{NH}_4^+ & \text{HCO}_3^- \)

- NH₄⁺ is equilibrium with NH₃ & H⁺ in cells (pKa = 9 ie very high)

  ! ratio NH₃ : NH₄⁺ = 1:100 at pH 7 . virtually all NH₄ at physiological pH

- NH₄ form is unable to passively cross membrane . actively secreted into lumen
  - NH₄⁺ being moved actively into tubular fluid,
  - dissociates into NH₃⁺, giving off H⁺
  - gradient for moving NH₄⁺ is maintained
  - NH₃ then diffuses back into tubular cell

  ! = example of non-ionic diffusion

  ! salicylates secreted under same method

- Overall product of complete deamination of glutamine are:
  - 2 molesulces NH₄⁺ (effectively 2 H⁺ ions included in NH₄⁺)
  - 2 molecules HCO₃⁻

- In chronic acidosis:
  - ↑NH₄⁺ excreted at any given urine pH because more NH₃ drawn into urine from cells
  - cause of ↑NH₃ movement is unknown
  - PCT does majority of ↑ed workload
  - Acidosis in these cells ⇒ ↑↑production of glutaminase
  - result is more H⁺ used up making NH₄⁺ from NH₃.: ↑enhancement of H⁺ secretion

  ! normally 30-50mmol/d of H⁺ is excreted as NH₄

  ! severe acidosis ⇒ ↑700mmol/day but takes up to 5 days to achieve

**pH Changes Along Nephron**

- mod drop in pH along prox tubule

  ! because most H⁺ secreted has little effect on pH because of: \( \text{H}^+ \text{ & HCO}_3^- \Rightarrow \text{CO}_2 \text{ & H}_2\text{O} \)
• distal tubule greater change in pH
   ⇨ even though less capacity to secrete H+

**Summary of Renal Bicarbonate Excretion**

- \(\text{HCO}_3^-\) filtered freely at glomerulus = 24mmol/L x 180L/day = 4320mmol/day
  ⇨ most will be reabsorbed
- ↓\(\text{HCO}_3^-\) reabsorption as result of:
  - ↑ECF volume
  - ↑plasma \(\text{HCO}_3^-\) (ie need to correct alkalosis):
    - >26-28mEq/L (renal threshold) ⇒ \(\text{HCO}_3^-\) appears in urine ⇒ alkaline urine
- ↑\(\text{HCO}_3^-\) reabsorption as result of:
  - ↓plasma \(\text{HCO}_3^-\) (ie need to correct acidosis):
    - 28 and above – all H+ used to reabsorb \(\text{HCO}_3^-\)
    - <26 now free H+ to combine with other buffer anions
      ⇨ ↓plasma \(\text{HCO}_3^-\) ⇒ ↑acid urine & ↑NH4+ urine content
  - ∴: excretion of H ion in urine = equivalent to adding 1 \(\text{HCO}_3^-\) to blood
    ⇨ & vice versa
- of filtered \(\text{HCO}_3^-\):
  - 85% reabsorb in PCT
  - 10-15% in thick ascending LOH
  - rest in DCT & cortical CD
- glomerulotubular balance exists for prox \(\text{HCO}_3^-\) reabsorption ie remains constant ~ 85% filtered load
  ⇨ similar to system for \(\text{Na}\)

**Effects of Urinary pH Changes**

- pH of urine 4.5 – 8
- depends on:
  - H+ secretion
  - NH4+ production
  - \(\text{HCO}_3^-\) excretion
- For every H+
  - excreted in urine, 1 Na+ is conserved
  - excreted with phosphate or NH4+, 
  - 1 \(\text{HCO}_3^-\) is conserved
- when base added to body:
  - OH- ions are buffered ⇒ ↑plasma \(\text{HCO}_3^-\)
  - Plasma \(\text{HCO}_3^-\) >28 ⇒ extra \(\text{HCO}_3^-\) into urine ⇒ ↑alkaline urine

**Defence of H+ Concentration**

- Intracellular H+ conc and ECF H+ concentrations different
  ⇨ although H+ [in] is sensitive to [out]
- pH of blood = pH of true plasma
  ⇨ because rbc Hb is one of most imp blood buffers

**H+ Balance**

**Liver**
- liver metabolises amino acids for gluconeogenesis
- products:
  - NH4+ & \(\text{HCO}_3^-\)
    - NH4+ ⇒ urea
    - \(\text{HCO}_3^-\) buffered intracellularly
      ⇨ ↓: little acid load into plasma
  - Other amino acids create strong acids which enter circ
Sulphur containing amino acids $\Rightarrow$ H$_2$SO$_4$

Phosphorylated amino acids $\Rightarrow$ H$_3$PO$_4$

Tissues
- CO$_2$ from metabolism $\Rightarrow$ H$_2$CO$_3$
- H$^+$ load = 12500 mEq/d
- Most excreted by lungs $\therefore$ only small amount H$^+$ left for kidneys to excrete

Other Acid Loads
- Lactic acid
- Diabetic ketosis
- Ingestion of acid
- Failure of kidney to excrete H$^+$

Alkaline Loads
- Fruits main dietary source of alkali:
  - Contain Na & K salts metabolised to CO$_2$ leaving:
    - Na & CO$_2$ $\Rightarrow$ NaHCO$_3$
    - K & CO$_2$ $\Rightarrow$ KHCO$_3$
- More common alkalosis from los of body acid by vomiting gastric juice with HCl

Buffering
- In met acidosis:
  - 15-20% acid load buffered by H$_2$CO$_3$-HCO$_3^-$ system in ECF
  - remainder buffered in cells
- in met alkalosis:
  - 30-35% of OH$^-$ load buffered in cells
- resp acid & alkalosis all buffering is intracellular

Summary
- strong acid into blood:
  - buffer reactions are driven to L
  - $\therefore$ blood levels of buffer anions drop:
    - $\downarrow$Hb-
    - $\downarrow$Prot-
    - $\downarrow$HCO$_3^-$
  - anions of added acid filtered into renal tubules accompanied by Na$^+$
  - tubules replace Na with H$^+$ which causes:
    - reabsorb equal amount of HCO$_3^-$ as Na$^+$
  - $\therefore$ overall effect:
    - conserve cation (HCO$_3^-$)
    - eliminate acid
    - restore supply of buffer anions to normal
- if CO$_2$ added to blood:
  - similar reactions but H$_2$CO$_3$ formed $\Rightarrow$ HCO$_3^-$ (rather than $\downarrow$)
Renal Compensation to Resp Acidosis / Alkalosis

- HCO3- reabsorption depends on:
  - Filtered load of HCO3-
    \[ \text{product of plasma HCO}_3^- \text{ & GFR} \]
  - Rate of secretion of H+ which directly influences rate of HCO3- reabsorption
    \[ \text{1:1 exchange} \]
  - \( \propto \) to PaCO2 – because:
    - ↑CO2 available to form H2CO3 in cells
      \[ \text{↑H2CO}_3 \text{ in cells ⇒ ↑H+ available for secretion} \]
    - ↑CO2 ⇒ ↑intracellular acidosis ⇒ ↑diffusion gradient for H+ ⇒ ↑H secretion
  - \( \therefore \) resp acidosis:
    - ↑renal secretion of H+
    - ↑renal ammonium secretion
    - ↑HCO3- reabsorption even though plasma HCO3- already high
    - ↑Cl- excretion ⇒ ↓plasma Cl- with ↑plasma HCO3-

- \( \therefore \) resp alkalosis:
  - low PCO2 ⇒ ↓renal H+ secretion ⇒ ↓HCO3 reabsorption ⇒ ↑excretion HCO3 ⇒ ↓plasma HCO3 ⇒ ↓pH back to normal level

Metabolic Acidosis

- eg add acid H2SO4 ⇒ met acidosis

Buffering (secs)
- serum buffering of H+:
  - ↓serum buffers ie ↓Hb-, ↓Prot-, ↓HCO3-
  - HCO3 & H+ ⇒ H2CO3 ⇒ H2O & CO2

Resp compensation (min/hrs)
- occurs first:
  - ↑H+ stimulates resp ⇒ CO2 rapidly excreted via lungs
  - ↑pH to norm levels
- renal compensation aim to excrete extra H+ to allow buffer systems to return to norm
Renal Compensation (days)

- Initially ↓ed simple tubular H because of low serum HCO3
  - but: tubular H secretion is enough to:
    - reabsorb all filtered HCO3
    - urinary excretion of H ions as phosphate (even when PCO2 low in hypervent)
- BUT in time (days) actually see large amounts of H+ secreted into urine via NH4 & H2PO4 systems:
  - All filtered HCO3- reabsorbed (couple with H secretion)
  - ↑glutamine synthesis in liver:
    - uses some of NH4+ which usually converted to urea
    - ↑glutamine provides kidneys with more NH4+
  - ↑NH3 secretion over days ⇒ ↑buffering of H+ in urine
  - glutamine from liver ⇒ glutamate ⇒ α-ketoglutarate ⇒ ↑HCO3-
    ▶ enters plasma and buffers acid
  - ↑H2PO4 excretion

Blood Reaction to Strong Acid

Eg H2SO4 added:

\[
2\text{NaHCO}_3 + \text{H}_2\text{SO}_4 \rightarrow \text{Na}_2\text{SO}_4 + 2\text{H}_2\text{CO}_3
\]

- each H+ added, 1 NaHCO3 is lost
- kidney then reverses the reaction:

\[
\text{Na}_2\text{SO}_4 + 2\text{H}_2\text{CO}_3 \rightarrow 2\text{NaHCO}_3 + 2\text{H}^+ + \text{SO}_4^{2-}
\]

- H+ & SO4^{2-} are excreted

Respiratory Effects on Met Acidosis

- Resp compensation actually inhibits renal response:
  - ↓PCO2 ⇒ ↓acid secretion
  - but it also ↓filtered load of HCO3- ⇒ cancelling each other out

Metabolic Alkalosis

- ↑plasma HCO3 & pH ⇒ ↑ed filtered HCO3-
  - if HCO3- > 26-28 ⇒ ↑ed HCO3- in urine
- resp compensation =
  - ↓H+ conc ⇒ ↓ventilation ⇒ ↑PCO2
  - amount of compensation limited by periph chemoreceptors
- renal changes:
  - ↓H secretion is not enough:
    - to reabsorb ↑ed filtered load of HCO3- ⇒ NET HCO3 excretion
    - for excretion of H ions as phosphate (H2PO4)
  - ↓ed tubular ammonium ions 2nd to low extracellular H conc
- this all occurs even with ↑ed PCO2 which should inhibits renal compensation by facilitating acid secretion
  - but effect is small