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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 = 150moles
- 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

- Henderson Hasselbalch: $pH = 6.1 + \log \frac{[\mathbf{HCO_3}]}{[CO_2]^*}$ ← role of Kidneys ← role of Lungs

$[CO_2]$ (in mmol/L) = PCO_2 (in mmHg) x 0.03 (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
    ↳ see NET loss of H+ via titratable acidity of NH4+
  - Excretion of filtered +/- secreted HCO3
- Volatile acid ie CO2 excreted via lungs
- Kidneys role:
  - metabolise 40% of lactate (liver 60%)
    ↳ 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

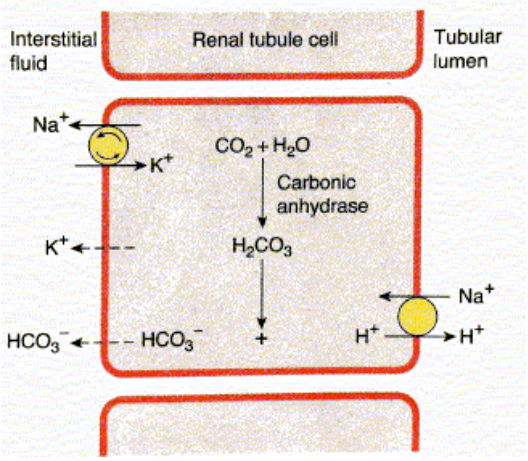
Proximal Mechanism

- 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
    (↳ shown in diagram next)
  - Primary Active H-ATPase – in luminal membrane

Source of Acid

- CO2 diffuses into tubular cell where: CO2 + H20 ⇒ H2CO3
- H comes from dissociation of H2CO3:
  - H2CO3 ⇒ H+ & HCO3-
    - Carbonic anhydrase as catalyst
      ↳drugs can effect action ∴ H+ secretion
- HCO3- diffuses into interstitum/ECF
- H+ secreted via above mentioned mechanisms

Na/H Counter-Transporter



- Dashed line = diffusion

- 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

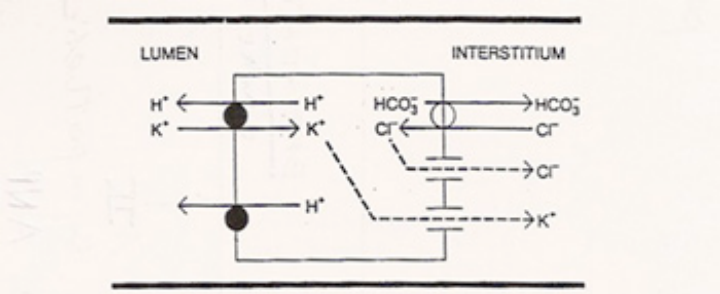


Fig. 9-2 Model of hydrogen-ion secretion by type-A intercalated cells of the collecting-duct system. This cell type possesses both H-ATPases and H,K-ATPases in its luminal membranes. Bicarbonate exits the cell "downhill" via Cl/HCO_3 countertransporters (which are identical to the band-3 erythrocyte countertransporter). Note that in addition to secreting hydrogen ions this cell actively reabsorbs potassium, as stated in Chapter 8.

- = 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:
  - lumimal 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 interstitum:
  - HCO3 couple with Cl in counter transported
  - Cl diffuses by passively
  - K diffuses passively

Type B IC Cells

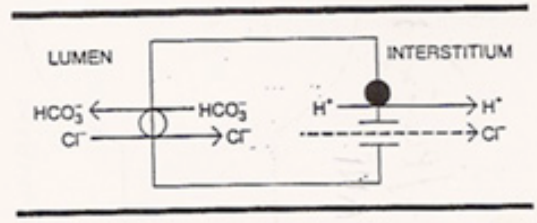


Fig. 9-4 Model of bicarbonate secretion by type-B intercalated cells. Compare this figure to Fig. 9-2, and you will see that the type-B cell is basically a "flipped-around" type-A cell. (It probably also has the expected H,K-ATPases on the basolateral membrane.) Also note that the luminal-membrane Cl/HCO_3 countertransporter provides the secondary active step (driven by the downhill movement of bicarbonate) for the active reabsorption of chloride by these cells, as described in Chapter 6.

- 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 HCO3 always = NET reabsorption
- Excretion of HCO3 can easily be accomplished ↓ing NET reabsorption in tubule
  ↳ ie without needing an active secretion method

HCO3 Effects of Prox & Distal Mechanism

- Both prox & distal mechanism cause NET addition of HCO3 to plasma

Factors Effecting Distal Mechanism H Secretion

- ↑PaCO2 ⇒ ↑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 PCO2:
    - ↑PCO2 (resp acidosis) ⇒ ↑intracellular H2CO3 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 ⇒ ↓H2CO3 ⇒ ↓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 & HCO3 & 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 & H20 ⇒ H2CO3 ⇒ CO2 & H20 ⇒ 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 & H20 & carbonic anhydrase essential for supply of H ions
  ↳ (reaction explained in PCT section prev)
- CA found
  - inside tubular cell
  - 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 H20
    - Then broken down in cell again by CA
      ↳ ie circular motion
- 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 ∴
  - all filtered HCO3 is reabsorbed
  - Excess H is excreted as titrateable 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:
  - dihydrogen hosphate (H2PO4)
  - acidic form of creatinine
  - ketoacids
- normally 20-30mmol H=/day excreted as TA
- most TA formed by reaction with HPO_4^{2-}:
  - H+ & HPO_4^{2-} ⇒ $H_2PO_4^-$
- H+ reacts with dibasic phosphate (HPO_4^{2-}) ⇒ monobasic phosphate ($H_2PO_4^-$)
- 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 $H_2PO_4^-$ state
- Filtered creatinine (pKa 4.9):
  - Accounts for small fraction of titrateable acidity
  - @max urine acidity ⇒
    - 2/3 filtered creatinine will be in acidic form
    - account for 25% of urinary TA
- Ketoacids:
  - Also contribute to TA
  - 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 (NH_3) = formed mainly in PCT but also rest of nephron (except thin LOH)
- Ammonia can exist in 2 forms:
  - NH_3 = ammonia (non acidic form)
  - NH_4 = ammonium (acidic form)

$H^+ \ \& \ NH_3 \Rightarrow NH_4^+$

- Ammonia excretion:
  - 30% - secreted by tubular epithelium from free arterial NH_3
  - 60% from deamination of glutamine
    ↳glutamine come from:
    - 80% peritubular capillary blood
    - 20% glomerular filtrate
    - trace amount direct from glutamate

- NH_3 produced in cells by:

$$\text{Glutamine} \xrightarrow{\text{glutaminase}} \text{glutamate} + NH_3$$

$$\text{Glutamate} \xrightarrow{\text{Glutamic dehydrogenase}} \alpha\text{-ketoglutarate} + NH_3$$

- Further metabolism of α-ketoglutarate uses $2H^+$ & frees $2HCO_3^-$
  ↳ either to glucose/CO_2/H_2O
- Reactions in tubular cells: $NH_3 + H \Rightarrow NH_4^+ \ \& \ HCO_3^-$
-
- NH_4^+ is equilibrium with NH_3 & H^+ in cells (pKa = 9 ie very high)
  ↳ratio $NH_3 : NH_4^+ = 1:100$ at pH 7 ∴ virtually all NH_4 at physiological pH
- NH_4 form is unable to passively cross membrane ∴ actively secreted into lumen
  - NH_4^+ being moved actively into tubular fluid,
  - dissociates into NH_3^+, giving off H^+
  - ∴ gradient for moving NH_4^+ is maintained
  - NH_3 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 NH_4^+ (effectively 2 H^+ ions included in NH_4^+)
  - 2 molecules HCO_3

- In chronic acidosis:
  - ↑NH_4^+ excreted at any given urine pH because more NH_3 drawn into urine from cells
  - cause of ↑NH_3 movement is unknown
  - PCT does majority of ↑ed workload
  - Acidosis in these cells ⇒ ↑↑production of glutaminase
  - result is more H^+ used up making NH_4^+ from NH_3 ∴ ↑enhancement of H^+ secretion
- normally 30-50mmol/d of H^+ is excreted as NH_4
- 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: $H^+ \ \& \ HCO_3^- \Rightarrow CO_2 \ \& \ H_2O$

- distal tubule greater change in pH
  ↳even though less capacity to secrete H+

Summary of Renal Bicarbonate Excretion

- HCO3- filtered freely at glomerulus = 24mmol/L x 180L/day = 4320mmol/day
  ↳ most will be reabsorbed
- ↓HCO3 reabsorption as result of:
  - ↑ECF volume
  - ↑plasma HCO3 (ie need to correct alkalosis):
    - >26-28mEq/L (renal threshold) ⇒ HCO3- appears in urine ⇒ alkaline urine
- ↑HCO3- reabsorption as result of:
  - ↓plamsa HCO3 (ie need to correct acidosis) :
    - 28 and above – all H+ used to reabsorb HCO3-
    - <26 now free H+ to combine with other buffer anions

    ↳↓plasma HCO3- ⇒ ↑acid urine & ↑NH4+ urine content
- ∴ excretion of H ion in urine = equivalent to adding 1 HCO3 to blood
  ↳ & vice versa
- of filtered HCO3:
  - 85% reabsorb in PCT
  - 10-15% in thick ascending LOH
  - rest in DCT & cortical CD
- glomerulotubular balance exists for prox HCO3 reabsorption ie remains constant ~ 85% filtered load
  ↳ similar to system for Na

Effects of Urinary pH Changes

- pH of urine 4.5 – 8
- depends on:
  - H+ secretion
  - NH4+ production
  - HCO3- excretion
- For every H+
  - excreted in urine, 1 Na+ is conserved
  - excreted with phosphate or NH4+,
  - 1 HCO3- is conserved
- when base added to body:
  - OH- ions are buffered ⇒ ↑plasma HCO3-
  - Plasma HCO3 >28 ⇒ extra HCO3- 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 impt blood buffers

H+ Balance

Liver

- liver metabolises amino acids for gluconeogenesis
- products:
  - NH4+ & HCO3-
    - NH4 + ⇒ urea
    - HCO3- buffered intracellulary

    ↳∴ little acid load into plasma
  - Other amino acids create strong acids which enter circ

↳present major H+ load to buffers (50mEq/d)
- Sulphur containing amino acids ⇒ H_2SO_4
- Phosphorylated amino acids ⇒ H_3PO_4

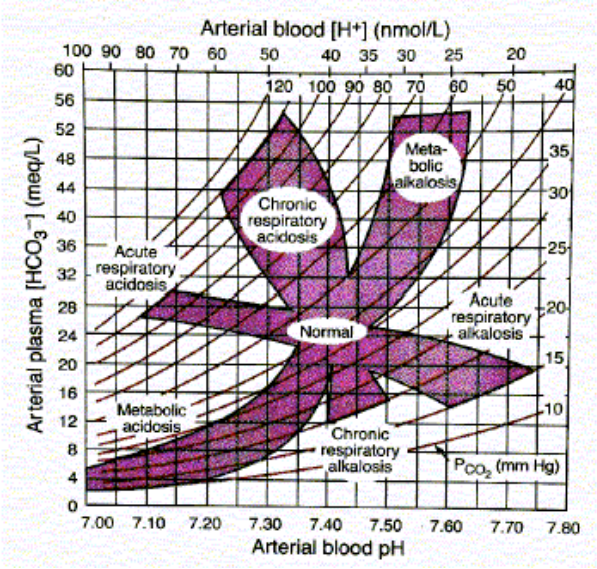
Tissues
- CO2 from metabolism ⇒H2CO3
- H+ load = 12500 mEq/d
- Most excreted by lungs ∴ only small amount H+ left for kidneys to excrete

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 CO2 leaving:
    - Na & CO2 ⇒ NaHCO3
    - K & CO2 ⇒ KHCO3
- More common alkalosis from los of body acid by vomiting gastric juice with HCl

Buffering
- In met acidosis:
  - 15-20% acid load buffered by H2CO3-HCO3- 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
  - ∴ blood levels of buffer anions drop:
    - ↓Hb-
    - ↓Prot-
    - ↓HCO3-
  - anions of added acid filtered into renal tubules accompanied by Na+
  - tubules replace Na with H+ which causes:
    - reabsorb equal amount of HCO3- as Na+
  - ∴ overall effect:
    - conserve cation (HCO3-)
    - eliminate acid
    - restore supply of buffer anions to normal
- if CO2 added to blood:
  - similar reactions but H2CO3 formed ⇒ ↑HCO3- (rather than ↓)



Renal Compensation to Resp Acidosis / Alkalosis

- HCO3- reabsorption depends on:
  - Filtered load of HCO3-
    ↳product of plasma HCO3- & GFR
  - Rate of secretion of H+ which directly influences rate of HCO3- reabsorption
    ↳1:1 exchange
    ↳depends on:
    - ∝ to PaCO2 – because:
      - ↑CO2 available to form H2CO3 in cells
        ↳↑H2CO3 in cells ⇒ ↑H+ available for secretion
      - ↑CO2 ⇒ ↑intracellular acidosis ⇒ ↑diffusion gradient for H+ ⇒ ↑H secretion
- ∴ resp acidosis:
  - ↑renal secretion of H+
  - ↑renal ammonium secretion
  - ↑HCO3- reabsorption even though plasma HCO3- already high
  - ↑Cl- excretion ⇒ ↓plasma Cl- with ↑plasma HCO3-
    ↳chloride shift
- ∴ resp alkalosis:
  - low PCo2 ⇒ ↓renal H+ secretion ⇒ ↓HCO3 reabsorption ⇒ ↑excretion HCO3 ⇒ ↓plasma HCO3 ⇒ ↓pH back to normal level

Metabolic Acidosis

- eg add acid H_2SO_4 ⇒ met acidosis

Buffering (secs)

- serum buffering of H+:
  - ↓serum buffers ie ↓Hb-, ↓Prot-, ↓HCO3-
  - HCO3 & H+ ⇒ H_2CO_3 ⇒ H20 & CO2
    ↳uncompensated met acidosis

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 H_2SO_4 added:

$$2NaHCO_3 + H_2SO_4 \Rightarrow NaSO_4 + 2H_2CO_3$$

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

$$Na_2SO_4 + 2H_2CO_3 \Rightarrow 2NaHCO_3 + 2H^+ + SO_4^{2-}$$

- H+ & SO_4^{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