Renal Physiology - Lectures

✓ Physiology of Body Fluids – PROBLEM SET, RESEARCH ARTICLE
✓ Structure & Function of the Kidneys
✓ Renal Clearance & Glomerular Filtration – PROBLEM SET
✓ Regulation of Renal Blood Flow - REVIEW ARTICLE
✓ Transport of Sodium & Chloride – TUTORIAL A & B
✓ Transport of Urea, Glucose, Phosphate, Calcium & Organic Solutes
✓ Regulation of Potassium Balance
✓ Regulation of Water Balance
9. Transport of Acids & Bases
10. Integration of Salt & Water Balance
11. Clinical Correlation – Dr. Credo
12. **PROBLEM SET REVIEW – May 9, 2011 at 9 am**
13. **EXAM REVIEW – May 9, 2011 at 10 am**
14. **EXAM IV – May 12, 2011**

Renal Physiology Lecture 9

Transport of Acids & Bases

Chapter 8 Koeppen & Stanton Renal Physiology

1. Excreting Nonvolatile Acids ~70 mmoles/day - CRUCIAL
2. Bicarbonate Handling
   - Reclaims ~ ALL Filtered Bicarbonate
   - Generates NEW Bicarbonate
3. Hydrogen Ion Regulation
   - Titrates Filtered Non-HCO_3^- Buffers
   - Titrates Endogenously Produced Ammonia
4. Acid-Base Disorders

** Renal Failure Patient **

Patient Data	Δ Normal
$Plasma_{K+}$	⇑
P_{Urea}	⇑
BP	⇑
P_{PO4-}	⇑
Hematocrit	⇓
P_{HCO3-}	⇓
P_{pH}	⇓
P_{Ca2+}	⇓

REVIEW - Filtration & Reabsorption

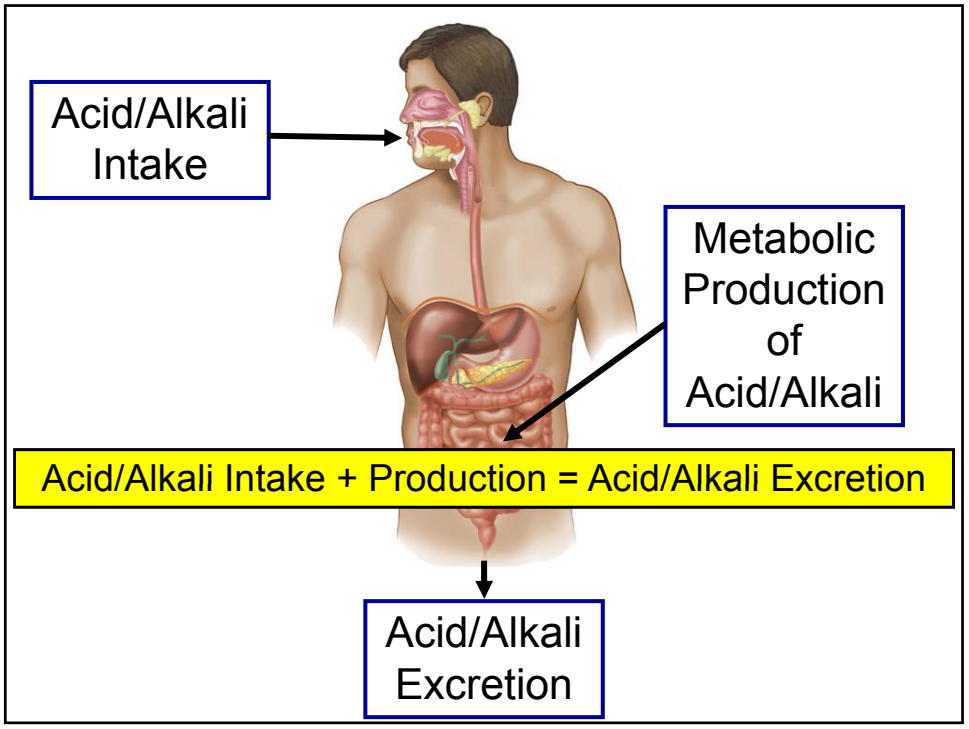
	Amount FILTER/d	Amount EXCRETE/d	% REABSORB
√ Water (L)	**180**	**1.8**	**99.0**
√ K^+ (mEq)	**720**	**100**	**86.1**
√ Ca^{2+} (mEq)	**540**	**10**	**98.2**
HCO_3^- (mEq)	**4,320**	**2**	**99.9 ++**
√ Cl^- (mEq)	**18,000**	**150**	**99.2**
√ Na^+ (g)	**25,500**	**150**	**99.5**
√ Glucose (mmol)	**800**	**0**	***100***
√ Urea (g)	**56**	**28**	***50***

Role of Kidney in Acid Base Balance

- Virtually all cellular, tissue, & organ processes sensitive to pH
- Acid & alkali ingested diet
- Cellular metabolism produces substances impact pH

Hydrogen Ion

- $[H^+]$ low compared to other ions
- pH = 7.4 $P[H^+]$ = 40 nM
- P_{Na+} 3,000,000 X > P_{H+}
- 140 mEq/L vs 40 nEq/L (0.00004mEq/L)
- pH = -log $[H^+]$



You Are What You Eat!

Food Acid/Alkali Impact

Fruit	Alkali
Vegetables	Alkali
Meat	Acid
Grains	Acid
Dairy Products	Acid

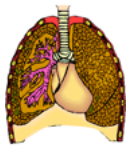




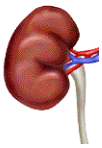
"Typical" American Diet Results in Net Endogenous Acid Production (**NEAP**)

Regulatory Systems – Acid Base Balance of Body

1. Independently control 2 major buffering systems



- CO_2



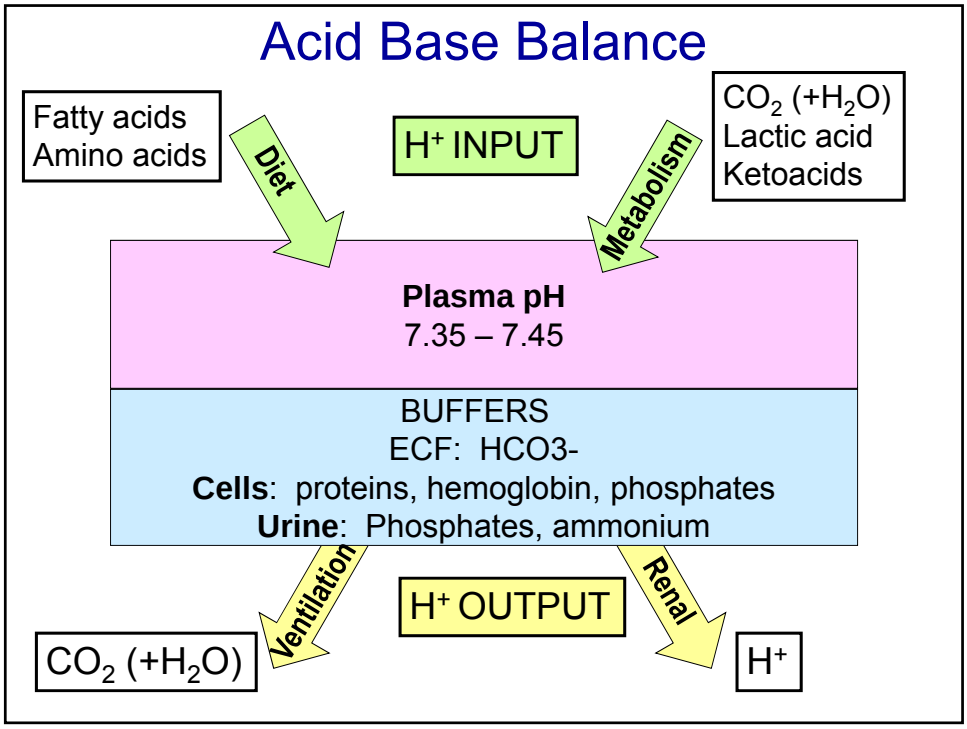
- HCO_3^-

2. Regulate $[H^+]$ body fluids prevent
   - acidosis
   - alkalosis

Role of Kidney in Acid Base Balance

- Normal pH body fluids
  - ***7.35 - 7.45***

- Alkalosis
  - H^+ loss exceeds gain
  - ⇓ arterial plasma $[H^+]$ pH > 7.45
- Acidosis
  - H^+ gain exceeds loss
  - ⇑ arterial plasma $[H^+]$ pH < 7.35



Henderson-Hasselbalch Eq 8-3

$$pH = 6.1 + \log \frac{HCO_3^-}{P_{CO2}}$$

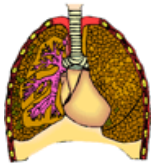
Regulation of ratio of concentration of $[HCO_3^-]$ to $[CO_2]$ in plasma = maintenance normal pH

Volatile Acid Production

Volatile Acid 

$$\boxed{CO_2} + H_2O \overset{\text{(-CA)}}{\underset{\text{slow}}{\Leftrightarrow}} H_2CO_3 \overset{\text{fast}}{\Leftrightarrow} HCO_3^- + H^+$$

15,000 mmol CO_2 produced/day – oxidation carbohydrates, fats, amino acids



Lungs eliminate CO_2

NONvolatile Acid Production

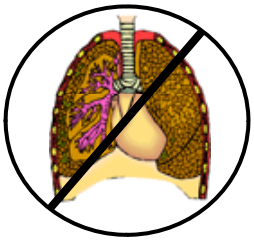
Organic, inorganic acid produced - **NOT CO_2**

- Phosphoric, sulfuric, lactic acid
- Metabolism protein, phospholipids, amino acids

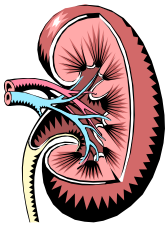
Acid **NOT** excreted lungs

Derived from metabolism, diet, intestinal losses

NOT easily converted CO_2



Renal Mechanisms



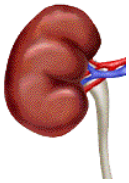
Nonvolatile acid production =

70 mmol/day

- Neutralized by HCO_3^- in ECF
- *Kidneys* must replenish lost HCO_3^-
- Plasma = 25 mEq/L HCO_3^-
- ECF = 14 L
- Total HCO_3^- buffering 350 mEq H^+
  (25 mEq/L HCO_3^- X 14 L)
- Deplete HCO_3^- in 5 days if not replenished

Renal Mechanisms

- HCO_3^- freely filtered glomerulus
  - 180 L/day X 24 mmol/L = 4,320 mmole/d
    - 70 mmol/d HCO_3^- to buffer nonvolatile acid production
- Must reabsorb > 99.9% filtered HCO_3^-
- Produce 70 mmol/d NEW HCO_3^-
- Rely on **H^+ secretion**
- Usually **NO** HCO_3^- urine



NET Urinary Acid Excretion pg 132

Net urinary acid excretion (NAE)

EQUALS

Excreted H^+ bound phosphate (as HPO_4^{2-}, divalent),$H_2PO_4^-$, (monovalent), creatinine, uric acid = *titratable acid*

PLUS

Excreted H^+ bound NH_3 (as NH_4^+)

MINUS

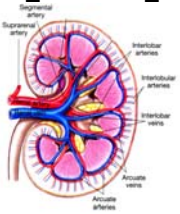
Excretion filtered HCO_3^-

Renal Handling of H^+

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

*

$$NaHCO_3^- + HCl \Leftrightarrow NaCl + CO_2 + H_2O$$

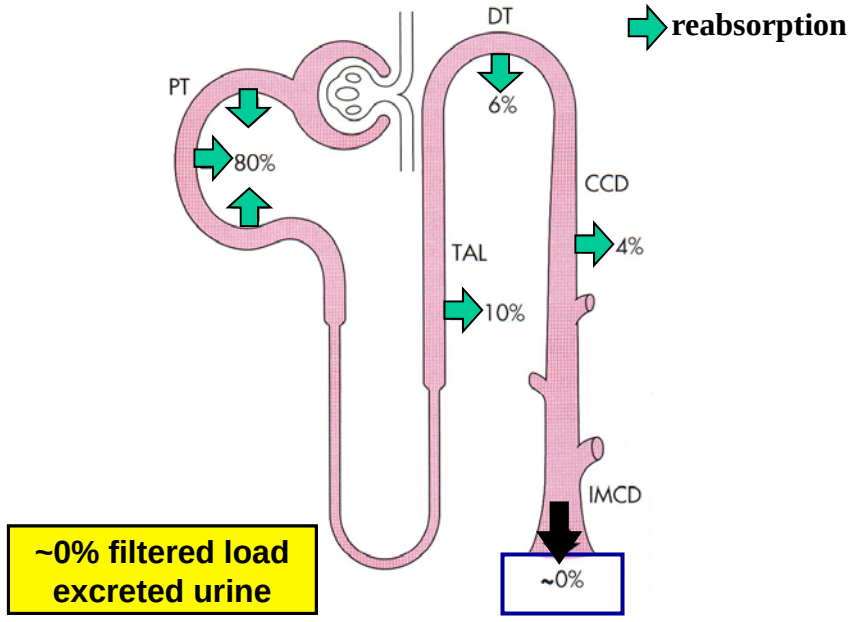


- H^+ load
- HCO_3^- consumed by H^+
- CO_2 excreted by lungs
- Kidneys <u>regenerate</u> HCO_3^- by **making** 70 mmol/d new HCO_3^- to neutralize nonvolatile acids

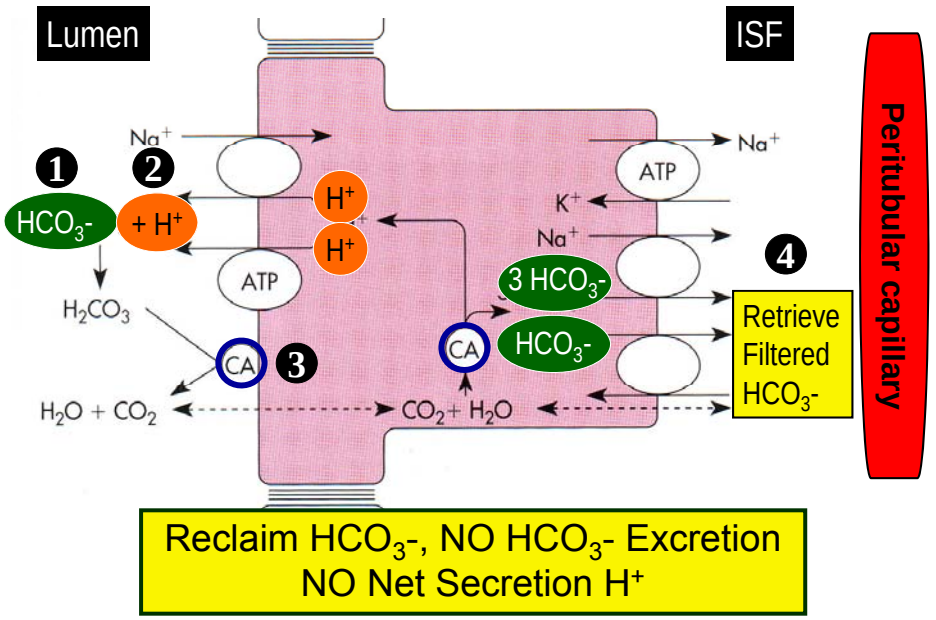
Renal Physiology Lecture 9

1. Excreting Nonvolatile Acids
2. Bicarbonate Handling
3. Hydrogen Ion Regulation
4. Acid-Base Disorders

Bicarbonate Handling by Nephron Fig 8-1



PT REABSORPTION Bicarbonate Fig 8-2



Reabsorption of Bicarbonate

1. H^+ secreted + filtered $HCO_3^- \Rightarrow H_2CO_3$
2. $H_2CO_3 \Rightarrow CO_2 + H_2O$
   - carbonic anhydrase *apical* membrane
3. $CO_2 + H_2O$
   - rapidly reabsorbed
   - tubule highly permeable
4. Net effect
   - HCO_3^- removed tubule lumen
   - HCO_3^- appears peritubular blood
5. 180 L/d x 24 mmol/L = 4,320 mmol/d HCO_3^- filtered = 4,320 mmol/d H^+ secretion

What happens if you take a drug that blocks CA = acetazolamide *(Diamox)*?

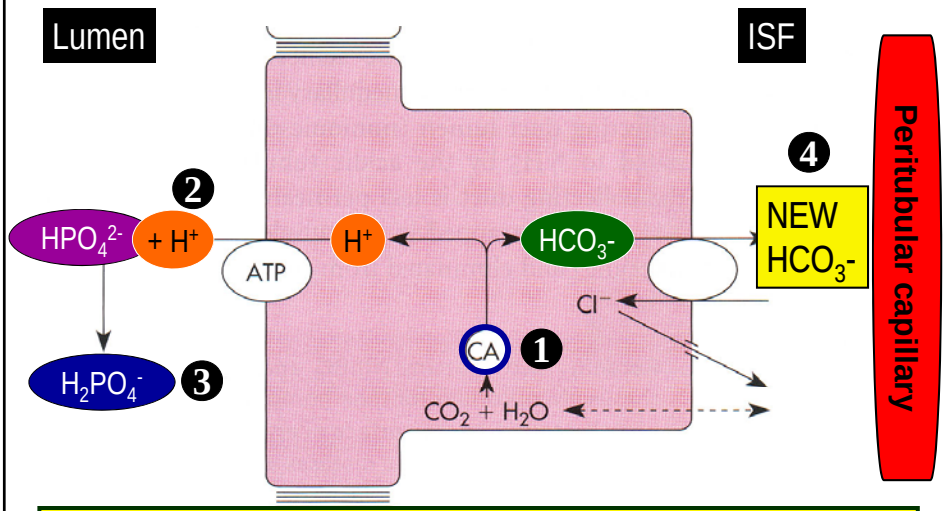
Weak Diuretic

- Inhibits apical, intracellular, basolateral carbonic anhydrases
- Inhibits HCO_3^- reabsorption
- Reduces Na^+ reabsorption
- Slows acid secretion
- Excretion of alkaline urine
- May cause metabolic acidosis

Treatment

- glaucoma, epilepsy, fluid retention in CHF, mountain sickness

Formation Titratable Acid – Intercalated Cell
Titrate non-NH_3, non-HCO_3- Fig 8-4



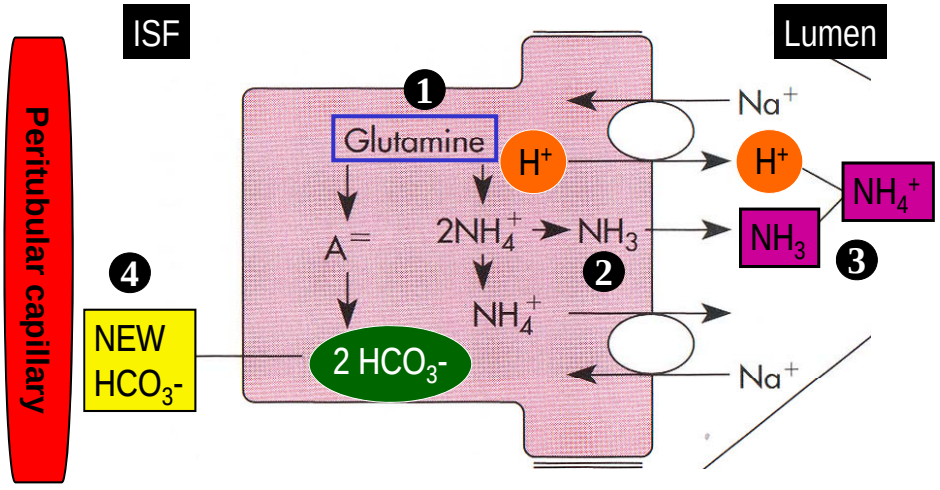
Protonate Divalent Phosphate, Net Secretion H^+
NEW HCO_3^- Added Plasma

Titratable Acid = Generation of New Bicarbonate

- Secreted H^+ in lumen + filtered urinary buffers (HPO_4^{2-}; divalent phosphate) <u>other than</u> HCO_3^-
  - **NEW** HCO_3^- added plasma
- Occurs <u>only</u> after filtered HCO_3^- removed lumen
- H^+ excreted as $H_2PO_4^-$ (monovalent phosphate)

Filtered Phosphate – Primary Urinary Buffers

PT Ammonium Excretion Fig 8-5



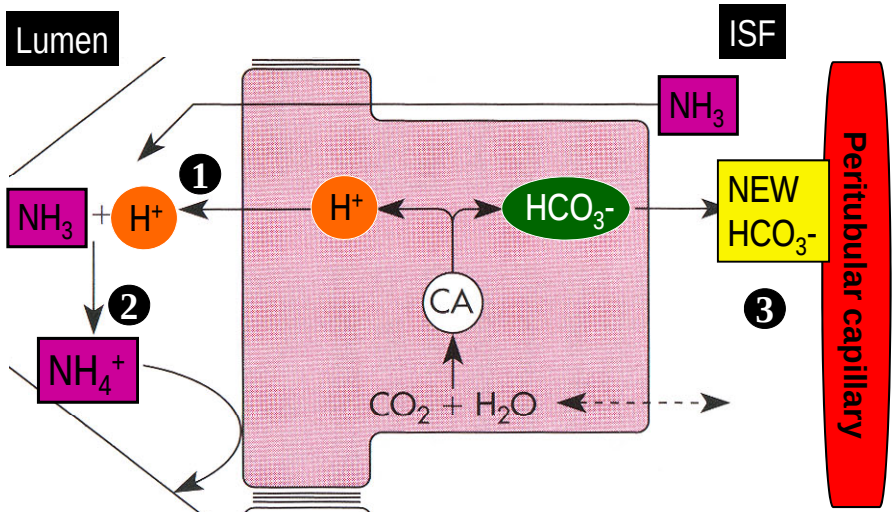
Protonate Ammonia, NET Secretion H^+
New HCO_3^- Added Plasma

Ammoniagenesis – Generation of New Bicarbonate

- Stimulated by acidosis
- PT takes up glutamine & metabolized to NH_4^+ (ammonium)
- NH_4^+ dissociates to NH_3 + H^+
- NH_3 diffuses to lumen, H^+ secreted = NH_4^+ lumen
- HCO_3^- moves into peritubular capillaries
- Acidify the urine by excreting NH_4^+

Addition Of A NEW Bicarbonate To Plasma

CD Ammonium Excretion Fig 8-5



Protonate Ammonia, Net Secretion H^+
NEW HCO_3^- Added Plasma

Renal Physiology Lecture 9

1. Excreting Nonvolatile Acids
2. Bicarbonate Handling
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H^+ Secretion – Proximal Tubule Fig 38-4AB

1. Na^+/H^+ exchanger = 2/3 (major *NHE3*)
2. H^+ ATPase = 1/3 (pump)

80% Filtered HCO_3^- Reabsorbed in PT

H+ Secretion – TAL & CD Fig 38-4CD

1. Na^+/H^+ exchanger (major *NHE3*)
2. H^+ ATPase (pump)
3. H^+/K^+ ATPase (pump)

~ 20% Filtered HCO_3^- Reabsorbed in TAL, DCT, CD

Hydrogen Ion Secretion – Apical

1. Na^+/H^+ exchanger (major *NHE3*) - *all* PCT, TAL, DCT
2. H^+ ATPase (pump) – *mainly* intercalated cells CD; also PT, TAL, DCT ~ *everywhere*
3. H^+/K^+ ATPase (exchange pump) - CD

Bicarbonate Reabsorption – Basolateral

1. Na^+/HCO_3^- cotransporter (1:3, *NBC1*)
2. Cl^-/HCO_3^- exchanger (anion exchanger, *AE*)

Secreted H^+ From Blood to Lumen

Titrate:

1. Filtered Bicarbonate
2. Filtered Phosphate (or other buffers)
3. Ammonia (secreted + filtered)

Acid/Base Regulation

Net acid excretion (NAE)

- **Acidosis**

$\uparrow\uparrow NAE = \uparrow U_{NH_4^+} V + \uparrow U_{TA} V - \downarrow U_{HCO_3^-} V$

- **Alkalosis**

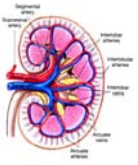
$\downarrow\downarrow NAE = \downarrow U_{NH_4^+} V + \downarrow U_{TA} V - \uparrow U_{HCO_3^-} V$

Renal Handling of H+

- Acid load handled by "dividing" 70 mmol/d of carbonic acid (H_2CO_3)
  - excrete 70 mmol/d H^+ into urine

  AND
  - 70 mmol/d NEW HCO_3^- into blood

  THEREFORE
  - NEW HCO_3^- neutralizes daily load 70 mmol nonvolatile acid



Sole Effective Route For Neutralizing Nonvolatile Acids

Renal Physiology Lecture 9

1. Excreting Nonvolatile Acids
2. Bicarbonate Handling
3. Hydrogen Ion Regulation
4. Acid-Base Disorders

Primary Acid/Base Disturbances

Metabolic Acidosis

1. Uncontrolled diabetes mellitus
2. Renal failure
3. Severe diarrhea
4. Ingestion of antifreeze

Metabolic Alkalosis

1. Vomiting
2. Nasogastric drainage
3. Antacids

Primary Acid/Base Disturbances

Respiratory Acidosis

1. Chronic pulmonary disease
2. Pulmonary edema
3. Sedative overdosage
4. Obstruction of airway

Respiratory Alkalosis

1. High altitude
2. Anxiety, pain, fear hyperventilation
3. Gram-negative sepsis

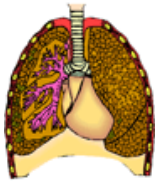
Compensatory Responses by *Lungs*

Metabolic Acidosis

- ⇓ P_{CO2} by *hyper*ventilation

Metabolic Alkalosis

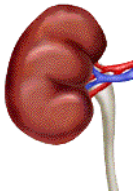
- ⇑ P_{CO2} by *hypo*ventilation



Compensation Almost Instantaneous

Compensatory Responses by *Kidneys*

Respiratory Acidosis



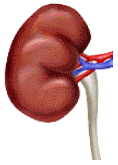
- ⇑ renal H^+ excretion = ⇑ production NEW HCO_3^- via NH_4^+ excretion
- Acute ⇑ P_{CO2} – ⇑ H^+ secretion
- Chronic ⇑ P_{CO2} – upregulate apical Na^+-H^+ exchanger, H^+ pump & basolateral Cl^--HCO_3^- exchanger

Respiratory Alkalosis

- Opposite occurs + ⇑ HCO_3^- secretion

Compensation Takes Several DAYS

Compensatory Responses by *Kidneys*



Metabolic Acidosis

- ⇑ excretion of titratable acid & NH_4^+ = ⇑ production NEW HCO_3^-
- Alterations in numbers and activities of acid-base transporters (H^+, HCO_3^- & NH_4^+)

Metabolic Alkalosis

- ⇑ excretion HCO_3^-
- Net acid excretion is *negative*

Compensation Takes Several DAYS

Fig 8-6

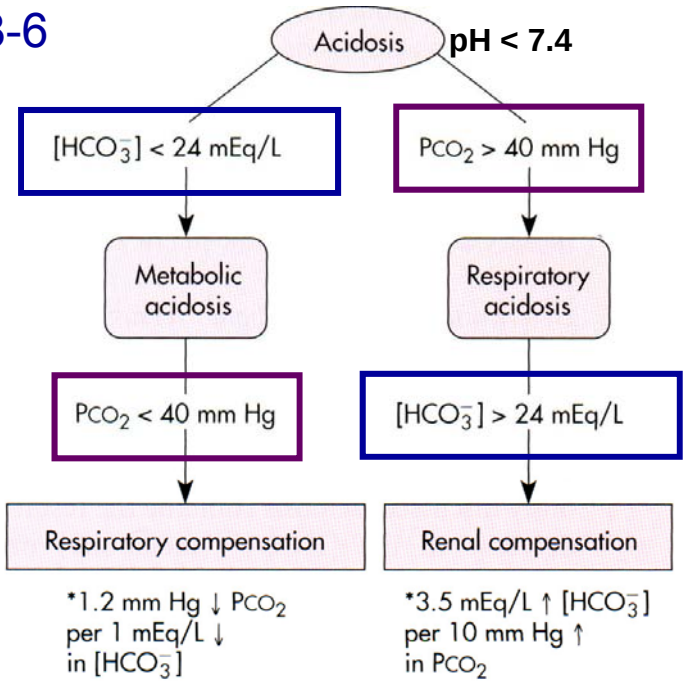
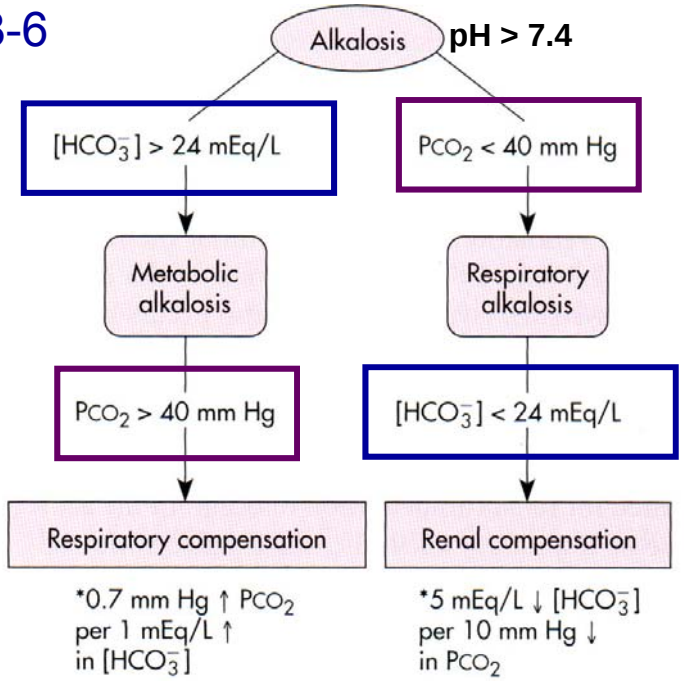
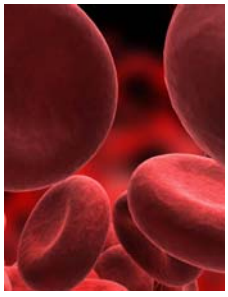


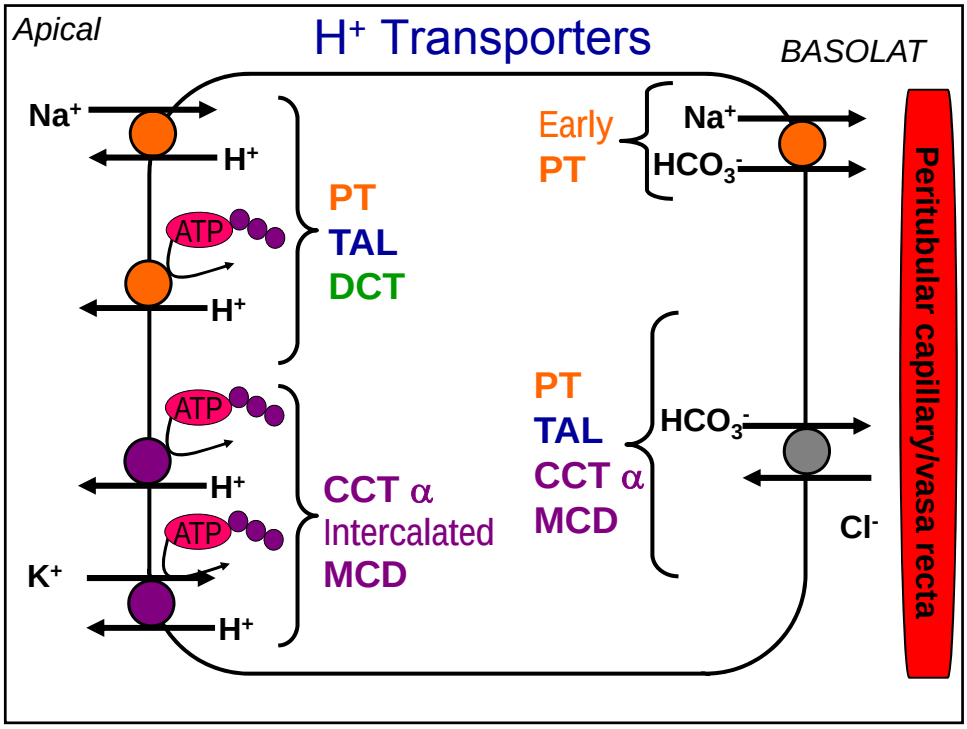
Fig 8-6



Role of Kidney in Acid Base Balance

- Preservation of HCO_3^- stores
  - H^+ secretion reabsorb virtually ALL filtered HCO_3^-
  - Formation NEW HCO_3^- in renal cells, add to blood
- Net excretion of H^+
  - Excretion of divalent phosphate
  - Ammonium excretion





What Did We Learn Today

1. Kidneys Play an Important Role in Acid Base Balance
2. Kidneys MUST Excrete Non-Volatile Acids
3. Reabsorb ALL Filtered HCO_{3-}
4. Excretion of Fixed H^+
   - $H_2PO_4^-$ (titratable acid)
   - NH_4^+
5. GOAL - Net secretion of H^+ & net reabsorption of NEWLY synthesized HCO_3^-