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
- Transport of Acids & Bases
- Integration of Salt & Water Balance
- 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

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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-HCO₃⁻ Buffers
   • Titrates Endogenously Produced Ammonia
4. Acid-Base Disorders
** Renal Failure Patient **

<table>
<thead>
<tr>
<th>Patient Data</th>
<th>△ Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma_K⁺</td>
<td>↑</td>
</tr>
<tr>
<td>P_Urea</td>
<td>↑</td>
</tr>
<tr>
<td>BP</td>
<td>↑</td>
</tr>
<tr>
<td>P_PO4⁻</td>
<td>↑</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>↓</td>
</tr>
<tr>
<td>P_HCO₃⁻</td>
<td>↓</td>
</tr>
<tr>
<td>PₚH</td>
<td>↓</td>
</tr>
<tr>
<td>P_Ca²⁺</td>
<td>↓</td>
</tr>
</tbody>
</table>

** REVIEW - Filtration & Reabsorption**

<table>
<thead>
<tr>
<th></th>
<th>Amount FILTER/d</th>
<th>Amount EXCRETE/d</th>
<th>% REABSORB</th>
</tr>
</thead>
<tbody>
<tr>
<td>√ Water (L)</td>
<td>180</td>
<td>1.8</td>
<td>99.0</td>
</tr>
<tr>
<td>√ K⁺ (mEq)</td>
<td>720</td>
<td>100</td>
<td>86.1</td>
</tr>
<tr>
<td>√ Ca²⁺ (mEq)</td>
<td>540</td>
<td>10</td>
<td>98.2</td>
</tr>
<tr>
<td>HCO₃⁻ (mEq)</td>
<td>4,320</td>
<td>2</td>
<td>99.9 ++</td>
</tr>
<tr>
<td>√ Cl⁻ (mEq)</td>
<td>18,000</td>
<td>150</td>
<td>99.2</td>
</tr>
<tr>
<td>√ Na⁺ (g)</td>
<td>25,500</td>
<td>150</td>
<td>99.5</td>
</tr>
<tr>
<td>√ Glucose (mmol)</td>
<td>800</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>√ Urea (g)</td>
<td>56</td>
<td>28</td>
<td>50</td>
</tr>
</tbody>
</table>
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
- \(\text{pH} = 7.4 \quad P[H^+] = 40 \text{ nM}\)
- \(P_{Na^+} 3,000,000 \times > P_{H^+}\)
- 140 mEq/L vs 40 nEq/L (0.00004mEq/L)
- \(\text{pH} = -\log [H^+]\)
Acid/Alkali Intake + Production = Acid/Alkali Excretion

You Are What You Eat!

Food Acid/Alkali Impact

<table>
<thead>
<tr>
<th>Food</th>
<th>Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fruit</td>
<td>Alkali</td>
</tr>
<tr>
<td>Vegetables</td>
<td>Alkali</td>
</tr>
<tr>
<td>Meat</td>
<td>Acid</td>
</tr>
<tr>
<td>Grains</td>
<td>Acid</td>
</tr>
<tr>
<td>Dairy Products</td>
<td>Acid</td>
</tr>
</tbody>
</table>

“Typical” American Diet Results in Net Endogenous Acid Production (NEAP)
Regulatory Systems – Acid Base Balance of Body

1. Independently control 2 major buffering systems
   - CO₂
   - HCO₃⁻

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
Acid Base Balance

**H+ INPUT**
- Fatty acids
- Amino acids
- CO₂ (+H₂O)
- Lactic acid
- Ketoacids

**Plasma pH**
7.35 – 7.45

**BUFFERS**
- ECF: HCO₃⁻
- Cells: proteins, hemoglobin, phosphates
- Urine: Phosphates, ammonium

**H+ OUTPUT**
- CO₂ (+H₂O)
- H⁺
- Ventilation
- Renal

**Henderson-Hasselbalch Eq 8-3**

\[
pH = 6.1 + \log \frac{[HCO_3^-]}{[CO_2]}
\]

Regulation of ratio of concentration of [HCO₃⁻] to [CO₂] in plasma = maintenance normal pH
Volatile Acid Production

Volatile Acid

\[
\text{CO}_2 + H_2O \underset{\text{slow}}{\overset{\text{fast}}{\rightleftharpoons}} H_2CO_3 \rightleftharpoons HCO_3^- + H^+
\]

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 $HCO_3^-$

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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 regenerate $HCO_3^-$ 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

~0% filtered load excreted urine

reabsorption
Reabsorption of Bicarbonate

1. $\text{H}^+\text{ secreted} + \text{filtered } \text{HCO}_3^- \Rightarrow \text{H}_2\text{CO}_3$

2. $\text{H}_2\text{CO}_3 \Rightarrow \text{CO}_2 + \text{H}_2\text{O}$
   - carbonic anhydrase *apical* membrane

3. $\text{CO}_2 + \text{H}_2\text{O}$
   - rapidly reabsorbed
   - tubule highly permeable

4. Net effect
   - $\text{HCO}_3^-$ removed tubule lumen
   - $\text{HCO}_3^-$ appears peritubular blood

5. $180 \text{ L/d} \times 24 \text{ mmol/L} = 4,320 \text{ mmol/d}$
   - $\text{HCO}_3^-$ filtered = 4,320 mmol/d $\text{H}^+$ secretion
What happens if you take a drug that blocks CA = acetazolamide (Diamox)?

Weak Diuretic
- Inhibits apical, intracellular, basolateral carbonic anhydrases
- Inhibits $\text{HCO}_3^-$ reabsorption
- Reduces $\text{Na}^+$ 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
Titrates non-NH₃, non-HCO₃⁻ Fig 8-4

Protonate Divalent Phosphate, Net Secretion H⁺
NEW HCO₃⁻ Added Plasma

Titratable Acid = Generation of New Bicarbonate

- Secreted H⁺ in lumen + filtered urinary buffers (HPO₄²⁻; divalent phosphate) other than HCO₃⁻
  - NEW HCO₃⁻ added plasma
- Occurs only after filtered HCO₃⁻ removed lumen
- H⁺ excreted as H₂PO₄⁻ (monovalent phosphate)

Filtered Phosphate – Primary Urinary Buffers
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
Renal Physiology Lecture 9

1. Excreting Nonvolatile Acids
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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 HCO₃⁻ 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 HCO₃⁻ 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⁺/HCO₃⁻ cotransporter (1:3, NBC1)
2. Cl⁻/HCO₃⁻ exchanger (anion exchanger, AE)
Secreted H\(^+\) From Blood to Lumen

Titrate:

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

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Acid/Base Regulation

Net acid excretion (NAE)

\[ \text{\textbullet\ Acidosis} \]

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

\[ \text{\textbullet\ Alkalosis} \]

\[ \downarrow\downarrow NAE = \downarrow U_{NH_4^+} V + \downarrow U_{TA} V - \uparrow U_{HCO_3^-} V \]
Renal Handling of H+

- Acid load handled by “dividing” 70 mmol/d of carbonic acid (H$_2$CO$_3$)
  - 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
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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

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### 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
• $\downarrow P_{CO_2}$ by hyperventilation

Metabolic Alkalosis
• $\uparrow P_{CO_2}$ by hypoventilation

Compensation Almost Instantaneous

Compensatory Responses by Kidneys

Respiratory Acidosis
• $\uparrow$ renal $H^+$ excretion = $\uparrow$ production NEW $HCO_3^-$ via $NH_4^+$ excretion
• Acute $\uparrow P_{CO_2}$ – $\uparrow H^+$ secretion
• Chronic $\uparrow P_{CO_2}$ – upregulate apical $Na^+$-$H^+$ exchanger, $H^+$ pump & basolateral $Cl^-$-$HCO_3^-$ exchanger

Respiratory Alkalosis
• Opposite occurs + $\uparrow HCO_3^-$ secretion

Compensation Takes Several DAYS
Compensatory Responses by Kidneys

Metabolic Acidosis

– ↑ excretion of titratable acid & NH₄⁺ = ↑ production NEW HCO₃⁻
– Alterations in numbers and activities of acid-base transporters (H⁺, HCO₃⁻ & NH₄⁺)

Metabolic Alkalosis

– ↑ excretion HCO₃⁻
– Net acid excretion is negative

Compensation Takes Several DAYS

Fig 8-6

Acidosis pH < 7.4

- [HCO₃⁻] < 24 mEq/L
- PCO₂ > 40 mm Hg

Metabolic acidosis
- PCO₂ < 40 mm Hg
- Respiratory compensation
  - *1.2 mm Hg ↓ PCO₂ per 1 mEq/L ↓ in [HCO₃⁻]

Respiratory acidosis
- [HCO₃⁻] > 24 mEq/L
- Renal compensation
  - *3.5 mEq/L ↑ [HCO₃⁻] per 10 mm Hg ↑ in PCO₂
Role of Kidney in Acid Base Balance

- **Preservation of HCO₃⁻ stores**
  - H⁺ secretion reabsorb virtually ALL filtered HCO₃⁻
  - Formation NEW HCO₃⁻ 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$_2$PO$_4^-$ (titratable acid)
   - NH$_4^+$
5. GOAL - Net secretion of H$^+$ & net reabsorption of NEWLY synthesized HCO$_3^-$