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

10. Integration of Salt & Water Balance – REVIEW ARTICLE
11. Clinical Correlation – Dr. Credo – 9 am - HANDOUT

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 10
Integration of Salt & Water Balance
Chapter 6 & 10 Koeppen & Stanton Physiology
Review Article: Renal Renin Angiotensin System

1. Regulation ECFV
2. RAS & Control of Renin Secretion
3. SNS, ANP, AVP
4. Response to Δ ECFV
5. Kidney Diseases
Control System

Rates subject to *physiological control*

KIDNEY - Δ rate of filtration, reabsorption, and/or secretion to maintain *homeostasis*

Integration of Salt and Water Balance

Important to regulate ECFV to maintain BP – tissue perfusion

- Regulation ECF Volume = monitor ‘*effective circulating volume*’ = functional blood volume evidenced by fullness or pressure w/i blood vessels, NOT ECFV
- Adjust total-body content **NaCl**
- *Modulate urinary Na*⁺ *excretion*
Integration of Salt and Water Balance

- Regulation ECF Osmolality – hypotonic or hypertonic = ∆ cell volume – alter cell function – brain
- modulate urinary $H_2O$ excretion
- manifest $\Delta P_{Osm}$

Regulation of Na$^+$ Excretion

HEMODYNAMICS

ALDOSTERONE

ANP

SYMPATHETICS

ANGIOTENSIN II

RENNIN
# ECF Volume Receptors Table 6-1

<table>
<thead>
<tr>
<th>Vascular sensors</th>
<th>* Low-pressure *</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sense effective circulating volume</strong></td>
<td>Cardiac atria</td>
</tr>
<tr>
<td></td>
<td>Pulmonary vasculature</td>
</tr>
<tr>
<td></td>
<td>High-pressure - arterial</td>
</tr>
<tr>
<td></td>
<td>Carotid sinus</td>
</tr>
<tr>
<td></td>
<td>Aortic arch</td>
</tr>
<tr>
<td></td>
<td>JGA – afferent arteriole</td>
</tr>
<tr>
<td><strong>Sensors in CNS</strong></td>
<td>CSF, arteriole [Na⁺]</td>
</tr>
<tr>
<td><strong>Sensors in Liver</strong></td>
<td>Pressure, [Na⁺]</td>
</tr>
</tbody>
</table>

## Regulation of ECFV

<table>
<thead>
<tr>
<th>What is sensed?</th>
<th>Effective Circulating Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sensors</strong></td>
<td>Carotid sinus, aortic arch, renal afferent arteriole, atria</td>
</tr>
<tr>
<td><strong>Efferent pathway</strong></td>
<td>RAS, SNS, AVP, ANP</td>
</tr>
<tr>
<td><strong>Effector</strong></td>
<td>Short term: Heart, blood vessels</td>
</tr>
<tr>
<td></td>
<td>Long term: <strong>Kidney</strong></td>
</tr>
<tr>
<td><strong>What is Affected?</strong></td>
<td>Short term: Blood pressure</td>
</tr>
<tr>
<td></td>
<td>Long term: <strong>Na⁺ excretion</strong></td>
</tr>
</tbody>
</table>
Control Renal Sodium and Water Excretion

Table 6-2

Effective circulating volume affects 4 systems:

1. RAS
2. SNS
3. AVP
4. ANP

Regulation of Osmolality

<table>
<thead>
<tr>
<th>What is sensed?</th>
<th>Plasma Osmolality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensors</td>
<td>Hypothalamic Osmoreceptors</td>
</tr>
<tr>
<td>Efferent pathways</td>
<td>AVP</td>
</tr>
<tr>
<td>Effector</td>
<td>Kidney</td>
</tr>
<tr>
<td>Effector</td>
<td>Thirst</td>
</tr>
<tr>
<td>Effector</td>
<td>Brain-drinking</td>
</tr>
<tr>
<td>What is Affected?</td>
<td>H₂O excretion</td>
</tr>
<tr>
<td></td>
<td>H₂O intake</td>
</tr>
</tbody>
</table>
Stimuli for ADH Release

** Osmolality of Plasma **

- **Osmoreceptors**
  - $\uparrow P_{Osm} 1\%$
  - steep slope $P[ADH]$ for 280-300 mOsm/kg H$_2$O
  - $\uparrow$ ADH – *most sensitive*

- **Baroreceptors**
  - $\downarrow$ pressure > 10% fall BV or BP
  - $\uparrow$ ADH – *most powerful*

Renal Physiology Lecture 10

1. Regulation ECFV
2. RAS & Control of Renin
3. SNS, ANP, AVP
4. Response to $\Delta$ ECFV
5. Kidney Diseases
**RAS Fig 6-1**

1. **RENIN**
   - **Rate limiting**
   - \( \downarrow \text{Na}^+ \ & \text{H}_2\text{O} \text{ Excretion} \)

2. **AngII**
   - **ACE**
   - **Lung**
   - **Adrenal**
   - **Kidney**

3. **Brain**
   - **ADH**

4. **Na\(^+\) & H\(_2\)O Excretion**

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**Actions of Angiotensin II**

- **ANG II in plasma**
  - **Arterioles**
    - **Vasoconstrict**
    - **Cardiovascular response**
  - **Cardiovascular control center in medulla oblongata**
  - **Hypothalamus**
    - **Vasopressin**
    - **Thirst**
    - **Na\(^+\) reabsorption**
  - **Adrenal cortex**
    - **\(\uparrow\) Aldosterone**
  - **Blood pressure**
    - **Volume and maintain osmolarity**
**Control of RENIN Release pg 96**

Production of renin - *rate limiting* step AngII formation

≡ importance of regulation

1. **Perfusion pressure** -
   Intrarenal baroreceptors - afferent arterioles

2. **Sympathetic** nerves – input to JG cells

3. **Delivery NaCl** to Macula densa cells

---

**Control of RENIN Release**

1. **“Renal” baroreceptors** –
   JG cells afferent arteriole

   • ↑ RAP  ↑ stretch
   ↓ renin release

   • ↓ RAP  ↓ stretch  ↓ Ca$^{2+}$
   ↑ renin release
Renal Artery Stenosis – pg 41, 94

1. "Renal" baroreceptors – JG cells
   afferent arteriole detect ↓ pressure
   - Constriction aorta above renal arteries = stenosis (narrowing of renal artery) due to atherosclerosis (90%)
   - Stenosis of preglomerular arteries or arterioles by fibrosis
   - = Renal hypertension ↑ renin
   - Treat patient w/ ACE inhibitor or ARB with or w/o diuretic and a statin

Control of RENIN Release

2. Influence of sympathetic nerves on JG cells
   • ↑ activity of nerves
     ↑ renin secretion
   • ↓ activity of nerves
     ↓ renin secretion
Control of RENIN Release

3. Influence of distal delivery of NaCl

- ↑ NaCl
  - ↓ renin secretion
- ↓ NaCl
  - ↑ renin secretion
  - ↑ AngII
  - ↑ BP - maintain tissue perfusion

Hemodynamic Actions AngII

↑ Rₐa & ↑↑ Rₑa

↓ GFR

↑ Thick ascending limb resistance
↓ Vasa recta blood flow
↑ Peritubular capillary hydrostatic pressure
↑ Proximal Na⁺ resorption
↓ Na⁺ excretion
↓ H₂O excretion

↑ Renal blood flow
↑ Filtration fraction
↑ Peritubular capillary oncotic pressure
↑ Loop Na⁺ reabsorption
↓ MBF

↑ [Urea] in medullary interstitium
↑ Gradient for passive NaCl resorption by the thin ascending limb of Henle
**Tubular Actions AngII – 4-2, 10**

1. Enhance Na\(^+\)-H\(^+\) exchanger PT & TAL = \(\uparrow\) Na\(^+\) reabsorption

2. Enhance NCC in DT & ENaC in CD = \(\uparrow\) Na\(^+\) reabsorption

3. \(\uparrow\) TGF Sensitivity

Net effect = \(\downarrow\) Na\(^+\) excretion

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**Renal Physiology Lecture 10**

1. Regulation ECFV
2. RAS & Control of Renin
3. SNS, ANP, AVP
4. Response to Δ ECFV
5. Kidney Diseases
2. SNS Activity

1. AA & EA renal vascular resistance = GFR
2. Renin release = AngII
3. Tubular Na⁺ reabsorption - PT *
   Activity during low Na⁺ intake, hemorrhage

Net effect = Na⁺ excretion

3. Actions AVP = ADH

1. H₂O retention - distal nephron - AQP2
2. Na/K/Cl cotransporter TAL
3. ENaC open probability - CD

Generation of hypertonic medullary interstitium
low Na⁺ intake, hemorrhage

Net effect = Na⁺ excretion
4. Actions ANP

1. ↑ ANP (atria) & BNP (ventricle)
2. Dilation of AA = Renal vasodilation - ↑ CBF, ↑ GFR, ↑ MBF – medullary washout interstitium
3. ↓ Renin & Aldosterone
4. ↑ Na⁺ load to PT & TAL = ↑ Na⁺ excretion
5. ↓ NaCl reabsorption by ENaC in CD
6. ↓ ADH secretion = ↑ H₂O excretion
7. Net effect = ↑ Na⁺ & H₂O excretion

BUT REMEMBER:

1. ↓ effective circulating volume
2. ↓ ANP/BNP release
3. Net effect = ↓ Na⁺ excretion
Renal Physiology Lecture 10

1. Regulation ECFV
2. RAS & Control of Renin
3. SNS, ANP, AVP
4. Response to Δ ECFV
5. Kidney Diseases

Volume Expansion - ↑ Effective Circulating Volume

Fig 6-4

- Volume expansion
- SNS
- ANP
- ADH
- AngII
- Aldo
- Renin
- Heart
- Urodiol
- Lung
- Adrenal gland
- Na⁺, H₂O excretion
- Aldosterone
Volume Expansion - \( \uparrow \) Effective Circulating Volume

Fig 6-4

\( \uparrow \) ANP & BNP

\( \downarrow \) SNS

\( \downarrow \) Renin

\( \downarrow \) AngII

\( \downarrow \) ADH

\( \downarrow \) ANP

\( \downarrow \) AngII

\( \uparrow \) UNaV = \( \uparrow \) GFR X PNa\(^+\) \( \downarrow \) Reabsorption

\( \Delta \) hemodynamics & transport

\( \Delta \) Effective circulating volume affects 4 systems:

1. \( \downarrow \) RAS = \( \downarrow \) Renin \( \downarrow \) AngII \( \downarrow \) Aldosterone

2. \( \downarrow \) SNS

3. \( \downarrow \) AVP

4. \( \uparrow \) ANP & BNP
Volume Expansion

1. \(\uparrow\) GFR = \(\uparrow\) filtered load Na\(^+\)
2. \(\downarrow\) PT & loop of Henle Na\(^+\) reabsorption
3. \(\uparrow\) Na\(^+\) delivery to distal nephron = \(\downarrow\) Na\(^+\) reabsorption

Net effect:
\[= \uparrow\text{ Na}^+ \& \text{H}_2\text{O excretion}\]

Volume Contraction - \(\downarrow\) Effective Circulating Volume

Fig 6-5

- \(\downarrow\) ANP
- \(\uparrow\) ADH
- \(\uparrow\) Renin
- \(\uparrow\) AngII
- \(\uparrow\) Aldo
Volume Contraction - ↓ Effective Circulating Volume

Fig 6-5

Δ Effective circulating volume affects 4 systems:

1. ↑ RAS = ↑ Renin ↑ AngII
   Aldosterone↑

2. ↑ SNS

3. ↑ AVP

4. ↓ ANP & BNP
**Volume Contraction**

1. \( \downarrow \text{GFR} = \downarrow \) filtered load \( \text{Na}^+ \)
2. \( \uparrow \) PT & loop of Henle \( \text{Na}^+ \) reabsorption
3. \( \downarrow \) \( \text{Na}^+ \) delivery to distal nephron = \( \uparrow \) \( \text{Na}^+ \) reabsorption

Net effect

\( \Rightarrow \downarrow \text{Na}^+ \) & \( \text{H}_2\text{O} \) excretion

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**CHF**

*Fig 6-6*

- Myocardial dysfunction
  - \( \downarrow \text{BP} \)
  - \( \downarrow \text{CO} \)

  - Vascular volume sensitiveness
    - \( \uparrow \) RAAS
      - \( \uparrow \) Sympathetic nerve activity
      - \( \uparrow \) ADH

  - \( \text{NaCl} \) and \( \text{H}_2\text{O} \) retention by kidneys

- U\( \text{NaCl} \) does not reflect ECFV; Reflects vascular volume

- Treatment
  - \( \downarrow \) \( \text{Na}^+ \) Intake
  - + Diuretics

- \( \uparrow \) fluid movement into interstitium

  - \( \uparrow \) lymph flow

  - \( \uparrow \) lymph flow capacity is exceeded

- \( \text{EDEMA} \)
What Does a Nephrologist Expect a Medical Student to Know?

1. What is GFR?
   - How is it determined?
   - How is it estimated?
2. Body Fluid Compartments
3. Regulation of Sodium and Water Balance
4. Potassium Homeostasis
5. Acid/Base Physiology

Renal Physiology Lecture 10

1. Regulation ECFV
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** Renal Failure Patient **

<table>
<thead>
<tr>
<th>Patient Data</th>
<th>$\Delta$ Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{Plasma}_{K^+}$</td>
<td>$\uparrow$</td>
</tr>
<tr>
<td>$P_{\text{Urea}}$</td>
<td>$\uparrow$</td>
</tr>
<tr>
<td>BP</td>
<td>$\uparrow$</td>
</tr>
<tr>
<td>$P_{\text{PO}_4^{-}}$</td>
<td>$\uparrow$</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>$\downarrow$</td>
</tr>
<tr>
<td>$P_{\text{HCO}_3^{-}}$</td>
<td>$\downarrow$</td>
</tr>
<tr>
<td>$P_{\text{pH}}$</td>
<td>$\downarrow$</td>
</tr>
<tr>
<td>$P_{\text{Ca}^{2+}}$</td>
<td>$\downarrow$</td>
</tr>
</tbody>
</table>

Renal Disease

- **Anemia**
  - $\downarrow$ Secretion of erythropoietin
  - Treatment:
    - recombinant human erythropoietin (epoetin alpha; Epogen – Amgen) iv/sc injection
    - Oral or iv iron supplements
Renal Disease

- **Uremia**
  - retention of excessive by-products of protein metabolism in the blood
  - toxic condition
- **Kidney stones**
  - block ureter
  - tubular pressure increases

ESRD
End Stage Renal Disease

ESRD - < 10% total glomerular filtration renal function

- **Normal Patient**
  - GFR = 125 ml/min
- **ESRD**
  - GFR = 10 - 20 ml/min
<table>
<thead>
<tr>
<th>Segment</th>
<th>Apical Na⁺ Transporter</th>
<th>Drugs (Chapter 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal tubule PT</td>
<td>Na⁺ cotransporter (glucose, amino acids, phosphate, sulfate, etc) Na⁺/H⁺ exchanger (NHE3)</td>
<td>carbonic anhydrase inhibitor (Acetazolamide)</td>
</tr>
<tr>
<td>Thick ascending limb TAL</td>
<td>Na⁺/K⁺/2Cl⁻ cotransporter (NKCC2)</td>
<td>Loop Diuretics (Furosemide, Lasix, Bumetanide)</td>
</tr>
<tr>
<td>Distal tubule DT</td>
<td>Na⁺/Cl⁻ cotransporter (NCC)</td>
<td>Thiazides (Hydrochlorothiazide)</td>
</tr>
<tr>
<td>Collecting duct CD</td>
<td>Epithelial Na⁺ channel (ENaC)</td>
<td>(Amiloride, Triamterene)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Apical Transporter</th>
<th>Loss of Function</th>
<th>Gain of Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>NKCC2 TAL</td>
<td>Bartter’s Syndrome</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Salt wasting</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Hypokalemia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Alkalosis</td>
<td></td>
</tr>
<tr>
<td>NCC Distal tubule</td>
<td>Gitelman’s Syndrome</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Salt wasting</td>
<td></td>
</tr>
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<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>• Alkalosis</td>
<td></td>
</tr>
<tr>
<td>ENaC Collecting duct</td>
<td>Pseudohypoaldosteronism (type 1)</td>
<td>Liddle’s Syndrome</td>
</tr>
<tr>
<td></td>
<td>• Salt wasting</td>
<td>• Salt retention</td>
</tr>
<tr>
<td></td>
<td>• Hyperkalemia</td>
<td>• Early onset severe hypertensive</td>
</tr>
<tr>
<td></td>
<td>• Acidosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Hypotension</td>
<td></td>
</tr>
</tbody>
</table>

LSU Medical Physiology 2010
What Did We Learn Today

1. Kidneys are very important for maintaining ECFV

2. Thank you kidneys for allowing us to eat at McDonalds.

3. KIDNEY IS AN AMAZING ORGAN!

Renal Physiology Problem Sets Review on
Monday, May 9th @ 9 am

EXAM IV REVIEW
on
Monday, May 9th @ 10 am
Good Luck on the Exam!
Clinical Correlation Tomorrow