Objectives

1. Understand the roles of the kidney
2. Understand the structure of the kidney, and how this structure facilitates its function
3. Begin to appreciate the inter-dependence of regulatory mechanisms

Readings

- Rose and Rennke, pages 1-15
- Rennke and Denker, pages 1-17

I. Roles of the Kidney

The primary roles of the kidney are to maintain an internal milieu that allows optimal cellular function, and to remove toxins that are generated by metabolism or ingested with a diet. The careful monitoring of the internal milieu, and the adjusting of excretory patterns for perturbations from intake, endogenous production, external losses, or metabolic consumption is called **homeostasis**. The removal of toxins is called **clearance**. Additional responsibilities of the kidney include maintaining systemic hemodynamics and producing several important endocrine molecules.

A. Homeostasis is the response to changes in intake, losses, and metabolic demands in order to maintain a relatively constant extra-cellular environment. The kidney balances intake and production against losses and consumption.

   1. Sodium – extra-cellular fluid volume
      a. Filtration
         i. Filtration is directly related to glomerular perfusion pressure. The glomerular perfusion pressure is determined by systemic blood pressure, as well as afferent and efferent arteriolar tone.
         ii. Angiotensin II (AII) stimulates glomerular mesangial cell contraction. This contraction results in reductions in both the glomerular surface area and the filtration fraction.
      b. Proximal reabsorption – AII up-regulates proximal Na\(^+\) reabsorption. The bulk of Na\(^-\) is reabsorbed in the proximal tubule and the loop of Henle. Proximal sodium reabsorption is also highly dependent on tubular flow rate.
c. Aldosterone-dependent collecting tubule reabsorption – The renin/angiotensin/aldosterone cascade (RAA) facilitates Na\(^+\) reabsorption in the collecting tubule by increasing the activity of Na\(^+\) channels in the luminal membrane. Fine regulation of Na\(^+\) reabsorption occurs at the level of the collecting tubule via this mechanism.

<table>
<thead>
<tr>
<th>Tubule Segment</th>
<th>% Na Reabsorbed</th>
<th>Mode of Reabsorption</th>
<th>Regulatory Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal Tubule</td>
<td>50-55%</td>
<td>Na(^+)/H(^-)-exchanger</td>
<td>AII, Norepinephrine, GFR</td>
</tr>
<tr>
<td>Loop of Henle</td>
<td>35-40%</td>
<td>Na(^+)/K(^+)/2Cl(^-)-co-transport</td>
<td>Flow-dependent</td>
</tr>
<tr>
<td>Distal Tubule</td>
<td>5-8%</td>
<td>Na(^+)/Cl(^-)-co-transport</td>
<td>Flow-dependent</td>
</tr>
<tr>
<td>Collecting Tubule</td>
<td>2-3%</td>
<td>Na(^+)-Channels</td>
<td>Aldosterone, ANP</td>
</tr>
</tbody>
</table>

2. Water – osmolality

a. Countercurrent multiplier of the loop of Henle is responsible for creating a hypertonic medulla.

b. Distal convoluted tubule achieves a maximally dilute filtrate by reabsorbing solute without water.

c. The presence or absence of Anti-Diuretic Hormone (ADH)-sensitive water channels regulates water reabsorption down an osmotic gradient in the cortical and medullary collecting duct. This determines whether a concentrated or dilute urine is produced.

3. Acid-Base – pH control

a. Bicarbonate (HCO\(_3\)\(^-\)) reabsorption in the proximal convoluted tubule is linked to Na\(^+\) reabsorption.

b. Hydrogen ion (H\(^+\)) secretion occurs in the collecting tubule. This process is enhanced by aldosterone, which both up-regulates H\(^+\)-ATPase activity and creates a more negative lumen charge by reabsorbing Na\(^+\).

c. Ammonia (NH\(_3\)) genesis – Ammonia diffuses into the tubular lumen and combines with H\(^+\), creating NH\(_4\)\(^+\). NH\(_4\)\(^+\), now charged and unable to diffuse out of the tubular lumen, excretes additional protons without lowering the urinary pH below a maximum acidification.
4. Electrolytes – Potassium, Calcium, Phosphate
   a. Aldosterone-dependent sodium reabsorption leads to potassium excretion in the collecting tubule.
   b. Vitamin D and PTH-dependent Ca\(^{++}\) reabsorption occurs in the distal convoluted tubule.

B. Clearance
   1. Filtration – charge and size selective barrier
   2. Secretion – i.e. creatinine secretion by proximal tubule
   3. Reabsorption – i.e. urea reabsorption by the proximal tubule

C. Hemodynamics
   1. Vascular Tone – Renin-stimulated AII activity results in arteriolar vasoconstriction.
   2. Sodium Retention
      a. AII induces proximal tubular sodium reabsorption.
      b. Aldosterone stimulates collecting tubule sodium reabsorption.
      c. Atrial Natriuretic Peptide (ANP) blocks sodium reabsorption in the collecting tubule.
   3. Pressure Natriuresis – At times of high kidney perfusion and increased GFR, tubular flow rate is increased and more filtered Na\(^+\) is excreted. This is due to an inability of the tubules to reabsorb all of the filtered Na\(^+\).
   4. Water Retention – Sympathetic nervous system activation from chronic hypotension at the carotid bodies results in ADH release from the posterior pituitary.

D. Endocrine Function
   1. Renin
      a. Renin is released from the juxta-glomerular apparatus (JGA) after stimulation from the macula densa of the distal tubule. The macula densa senses decreased luminal chloride delivery as an indicator of slow tubular flow, increased proximal reabsorption, and volume depletion.
b. Also released by direct $\beta_1$ sympathetic receptor activity

c. Stimulates conversion of angiotensinogen to angiotensin I (AI) with downstream increases in vascular tone, tubular sodium reabsorption, and aldosterone release mediated by AII

Figure 1
2. Erythropoietin
   a. Produced by the medullary interstitial cells in response to hypoxia (anemia)
   b. Stimulates erythropoiesis in the bone marrow
3. Vitamin D
   a. Hydroxylation by the kidney converts 25-hydroxycholecalciferol (25-Vitamin D) to 1,25-dihydroxycholecalciferol (1,25-Vitamin D) in response to parathyroid hormone (PTH) and hypophosphatemia
   b. 1,25-Vitamin D results in:
      i. Decreased calcium and phosphate excretion by the kidney
      ii. Calcium and phosphate absorption from the small intestine
      iii. Increased osteoclast activity and bone turnover (via PTH)
II. Structure of the Kidney

The structure of the kidney, and the nephron in particular, is uniquely designed to accomplish the functions outlined above. Sodium, water, electrolyte, and H+ ion handling, as well as hormone production, are performed by specific tubular segments that are suited to each task.
A. Kidney Blood Flow

1. The kidneys are in intimate contact with the circulation
2. Receive 20% of the cardiac output.
3. Utilizes large amounts of energy/oxygen

B. Glomerular Blood Flow – the kidneys have the ability to maintain glomerular filtration despite wide fluctuations in systemic hemodynamics so that kidney function is not jeopardized.

1. Afferent Arteriole – Prostaglandin dependent vasodilation preserves glomerular perfusion despite falls in kidney blood flow. Vasoconstriction at times of high pressure protects the delicate glomerular capillary architecture downstream.
2. Glomerular Capillary – highly specialized membrane
3. Efferent Arteriole – AII dependent vasoconstriction increases intra-glomerular pressure and filtration, even with falls in kidney blood flow

C. Glomerulus

1. Clearance
   a. Glomerular Capillary – highly porous
   b. Glomerular Basement Membrane – size and charge selective barrier
   c. Mesangial Cells – control glomerular surface area and filtration fraction

D. Proximal Convoluted Tubule (PCT)

1. Volume Regulation – bulk (55%) of Na\(^+\) reabsorption takes place in the proximal tubule in an isotonic, iso-electric manner.
   a. Na\(^+\) reabsorption is up-regulated by reduced tubular flow, AII, and norepinephrine. At high tubular flow, a reduced fraction of filtered Na\(^+\) is capable of being absorbed, leading to pressure natriuresis.
   b. Na\(^+\) reabsorption is powered by the Na\(^+\)/K\(^+\)-ATPase on the basolateral membrane, which keeps intracellular Na\(^+\) concentrations low and maintains a negative intracellular charge (3 Na\(^+\) out and 2 K\(^+\) in). This provides an electrical and chemical gradient across the luminal membrane for Na\(^+\) transport
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c. Na\(^+\)-H\(^+\)-counter-transport maintains electro-neutrality and facilitates HCO\(_3^-\) reabsorption (see below)

d. Na\(^+\) is also co-transported with amino acids, glucose, phosphates, and other organic acids

2. Acid/Base Balance

a. HCO\(_3^-\) reabsorption is a product of intracellular carbonic anhydrase (CA) generating H\(^+\) and HCO\(_3^-\) from H\(_2\)O and CO\(_2\). H\(^+\) is secreted across the luminal membrane by the Na\(^+\)/H\(^+\)-counter-transport and HCO\(_3^-\) is returned to the circulation across the basolateral membrane. The secreted H\(^+\) combines with filtered HCO\(_3^-\) to produce H\(_2\)O and CO\(_2\) in the lumen, under the enzymatic activity of additional CA located on the brush border of the tubular cells. The net effect is transport of a HCO\(_3^-\) molecule from the filtrate to the interstitial space.

b. NH\(_4^+\) Genesis (occurs in all tubular segments)

i. Conversion of glutamine to NH\(_4^+\) and \(\alpha\)-ketoglutarate results in excretion of additional H\(^+\) without lowering the urine pH (raising the H\(^+\) concentration)

ii. Can be up-regulated in the setting of acidemia

C. Clearances
1. Many small molecules (i.e. urea) are reabsorbed in the proximal tubule by solvent drag as water iso-osmotically follows Na\(^+\) reabsorption across trans-cellular and para-cellular routes.

2. Other molecules are secreted by known and unknown transporters.

E. Loop of Henle (LOH)

1. Volume Regulation – Na\(^+\) reabsorption is again powered by the Na\(^+\)/K\(^+\)-ATPase on the basolateral membrane. Luminal transport occurs iso-electrically via Na\(^+\)/K\(^+\)/2Cl\(^-\)-co-transport.

![Diagram of Loops of Henle](image)

Figure 5

2. Water Balance

   a. The descending limb of the LOH is freely permeable to water, and water is absorbed iso-osmotically.

   b. The ascending limb of the LOH contains tight junctions that do not allow water reabsorption. This leads to the creation of a dilute filtrate (200 mOsm/L) and a concentrated medullary interstitium (1200 mOsm/L). Remember the magical counter-current multiplier?

3. Electrolyte Homeostasis – K\(^+\) back-leak into the lumen (down gradient from high intracellular K\(^+\) concentration) causes the lumen to be positively charged in relation to the interstitium. This drives Ca\(^{++}\), Mg\(^{++}\), and additional Na\(^+\) reabsorption via para-cellular routes.
4. Endocrine – Erythropoietin is produced by the interstitial cells in the deep medulla. This very hypoxic region is sensitive to small changes in the oxygen carrying capacity of the blood.

F. Distal Convoluted Tubule (DCT)

1. Volume Regulation - Again, the Na\(^+\)/K\(^+\)-ATPase on the basolateral membrane drives Na\(^+\) reabsorption. A Na\(^+\)/Cl\(^-\)-co-transporter is responsible for iso-electric luminal movement.

![Diagram of Na\(^+\)/Cl\(^-\)-co-transporter](image)

Figure 6

2. Water Balance - The distal tubule remains impermeable to water. Continued electrolyte reabsorption without water results in reduction of filtrate osmolality to 50 mOsm/L.

3. Hemodynamics

   a. Luminal Cl\(^-\) delivery is sensed by the macula densa of the DCT.

   b. At times of low kidney perfusion, reduced glomerular filtration, and sluggish tubular flow, the PCT and LOH deplete the filtrate of Na\(^+\) and Cl\(^-\). Low Cl\(^-\) at the macula densa stimulates release of renin from the JGA.

4. Electrolyte Homeostasis

   a. Ca\(^{++}\) enters cells of the DCT via Ca\(^{++}\) channels on the luminal membrane down an electro-chemical gradient due to low intra-cellular Ca\(^{++}\) levels and a net negative intra-cellular charge.
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b. Ca\(^{++}\) binds a Vit D-dependent Ca\(^{++}\) binding protein for shuttling across the cytosol.

c. Ca\(^{++}\) is actively transported across the basolateral membrane by a Ca\(^{++}\)-ATPase and a Na\(^{+}/Ca^{++}\)-exchanger. This maintains intracellular Ca\(^{++}\) at low levels and drives luminal transport.

G. Collecting Tubule/Duct

1. Volume regulation
   a. Aldosterone
      i. Aldosterone is released from the zona glomerulosa of the adrenal gland after stimulation by AII
      ii. Aldosterone increases the activity of Na\(^{+}\) channels in the luminal membranes of principal cells
      iii. The activation of Na\(^{+}\) channels increased Na\(^{+}\) reabsorption down its gradient
      iv. This is regulated by volume status (renin ➔ AII ➔ aldosterone)
   b. Atrial Natriuretic Peptide (ANP)
      i. Released from cardiac myocytes under conditions of chamber dilation
      ii. Inactivates Na\(^{+}\) channels leading to Na\(^{+}\) excretion

2. Water Balance
   a. Anti-Diuretic Hormone (ADH) is released from the posterior pituitary in response to a rise in serum osmolality sensed by the hypothalamus, or sympathetic nervous activity from the carotid body
   b. ADH results in incorporation of pre-formed water channels in the luminal membrane of the medullary collecting duct
   c. Water channels facilitate water reabsorption (down the gradient towards medullary interstitial osmolality of 1200 mOsm/L), and results in tubular/urinary concentration

3. Acid/Base Balance
   a. Hydrogen ions are secreted by a H\(^{+}\)-ATPase and a H\(^{+}/K^{+}\)-exchanger on the luminal membrane of the intercalated cells
b. $H^+$ secretion is enhanced by aldosterone, which up-regulates activity of the $H^+$-ATPase. Also, by facilitating $Na^+$ reabsorption, aldosterone creates a more lumen negative charge and facilitates proton excretion.

c. This is where urinary acidification takes place

4. Electrolyte Homeostasis

a. $K^+$ excretion occurs at the principal cells of the collecting tubule in response to aldosterone

b. Aldosterone stimulates $Na^+$ reabsorption down an electro-chemical gradient. This creates a lumen-negative force for $K^+$ excretion

c. $K^+$ excretion cannot take place without $Na^+$ reabsorption by the principal cells (i.e. distal delivery of $Na^+$ and presence of aldosterone)

III. Self-Assessment Problems (solutions found on TUSK)

A 44-year-old woman presents to the emergency department with 1 week of nausea, vomiting, and abdominal pain. Her symptoms have been so severe that she has been unable to hold down fluids or feedings for three days. She has had no fever or chills, and no blood in her vomit or stool. She describes feeling faint upon rising from a sitting to a standing position.

On physical exam, her heart rate is 108 and her blood pressure is 110/60 while lying down. When upright, her heart rate is 144 and her blood pressure is 85/60. Her mucous membranes are dry and her JVP is appreciable only when she is lying flat. Her heart is tachycardic and regular, with no murmur. Her lungs are clear. Her abdomen has mild diffuse tenderness, but no rebound or guarding. Bowel sounds are present. Her extremities have no edema, her distal pulse are weak, and nail-bed capillary refill is greater than 2 seconds.

Laboratory data reveals:

<table>
<thead>
<tr>
<th>Electrolyte</th>
<th>Value</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>137 mEq/L</td>
<td>135-145 mEq/L</td>
</tr>
<tr>
<td>Potassium</td>
<td>5.6 mEq/L</td>
<td>3.5-5.0 mEq/L</td>
</tr>
<tr>
<td>Chloride</td>
<td>97 mEq/L</td>
<td>96-115 mEq/L</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>33 mEq/L</td>
<td>21-27 mEq/L</td>
</tr>
<tr>
<td>BUN</td>
<td>60 mg/dL</td>
<td>8-25 mg/dL</td>
</tr>
<tr>
<td>Creatinine</td>
<td>2.2 mg/dL</td>
<td>0.6-1.5 mg/dL</td>
</tr>
<tr>
<td>GFR</td>
<td>30 ml/min/1.73 m²</td>
<td></td>
</tr>
</tbody>
</table>

1) What is the most likely clinical scenario for this presentation?

2) What hemodynamic compensation is triggered by volume depletion?
3) Why are the BUN and creatinine elevated? Why might the BUN rise greater (3 fold higher) than the creatinine (2 fold higher)?

4) Despite intact homeostatic pathways, why has this patient developed a metabolic alkalosis with a $\text{HCO}_3^-$ of 33?

5) Why has the $\text{K}^+$ risen to 5.6 if all homeostatic pathways are intact?