Study Guide for Exam II
Clinical Chemistry I, CHM 651/751

A. Chapter 6: Mechanisms of Sodium and Water Reabsorption

1. Know that it is the amount of sodium in the body (exchangeable) not the concentration of sodium in the ECF that dictates the body’s water volume status.

2. Know the sodium excretion equation
   \[ E_{Na} = F_{Na} - R_{Na} = GFR \times [Na^+]_{plasma} - R_{Na} \]
   
   a) Control of Na\(^+\) excretion is accomplished through the second term (R, reabsorption) since GFR and [Na\(^+\)] are unchanged normally
   
   b) The first F term (filtration) becomes a factor in disease in which GFR changes lead to changes in sodium excretion (usual circumstance is there is ↓ GFR leading to body retaining Na\(^+\))

3. Know the osmolarity changes that occur in the various tubular segments (in comparison to the previous segment):
   a. Proximal tubule – isoosmotic (no change, same as plasma)
   b. Loop of Henle –
      1’. Thin Descending Limb – hyperosmotic
      2’. Thin Ascending Limb – decreased osmolarity from the thin descending limb, having progressively less osmolarity as the fluid approaches the thick ascending limb
      3’. Thick Ascending Limb – hypoosmotic (further decrease in osmolarity from thin ascending limb)
   c. Distal Convoluted Tubule – hypoosmotic (further decrease in osmolarity from thick ascending limb)
   d. Collecting Ducts (both cortical and medullary)
      1’. ADH present – hyperosmotic (greater than plasma)
      2’. ADH absent - hyposmotic (further decrease in osmolarity from distal convoluted tubule)

4. Know the approximate percentage of the original sodium load that is filtered at the glomerulus that are reabsorbed by the tubular sections:
   a. By tubular section
      1’. Proximal Tubule - 65%
      2’. Loop of Henle – 25%
      3’. Distal Tubule and Connecting Segment – 8-9%
      4’. Collecting ducts – 1-2%
   b. Under aldosterone control - 2%

5. Know substances that are completely reabsorbed by the proximal tubule and thus should not be present in urine (proteins, glucose, amino acids)
6. Know the osmolarity values of plasma (300 mosm/L) and at the papilla of the medulla (1200 – 1400 mosm/L) and that there is a gradient in osmolarity in the medulla in going from the outer medulla (starts at 300 mosm/L) to the papilla.

7. Know that HCO$_3^-$ and Cl$^-$ are both reabsorbed by the proximal tubule but that HCO$_3^-$ is preferentially reabsorbed leading to a decreased [HCO$_3^-$] but increased [Cl$^-$] in the tubular fluid in the proximal tubule compared to the ECF (plasma). Note that [Cl$^-$] increases even with some reabsorption of Cl$^-$ in the proximal tubule because there is considerable water reabsorption in the proximal tubule leading to the increase.

8. Be able to list and summarize the principal 4 mechanisms of sodium reabsorption in the proximal tubule (electrochemical gradient, electrogenic, passive NaCl, solvent drag).


10. For electrochemical gradient mechanism of sodium reabsorption know that there are three transport proteins on the luminal side of the membrane that are needed for Na$^+$ to pass into the proximal tubule cell:
   a. Na$^+$/H$^+$ counter transport protein
   b. Na$^+$/glucose co-transport protein
   c. Na$^+$/ amino acid co-transport protein

11. For the Na$^+$/H$^+$ counter transport protein be able to go into detail about the mechanism by which Na$^+$ HCO$_3^-$ is reabsorbed into the peritubular capillaries: with H$^+$ being exchange with Na$^+$ by the counter transport protein, HCO$_3^-$ getting into the proximal tubule cell as CO$_2$ (formed from H$_2$CO$_3$ by carbonic anhydrase on the luminal membrane of the tubular cell, which is formed by the combination of H$^+$ and HCO$_3^-$) and then being converted into H$_2$CO$_3$ by carbonic anhydrase present in the tubular cell cytosol which combines CO$_2$ and H$_2$O, which then dissociates into H$^+$ and HCO$_3^-$ (regenerating the H$^+$ which can then be used by the counter transport protein again). The HCO$_3^-$ and the Na$^+$ reabsorbed into the proximal tubular cell is then transferred through the peritubular side of the cell membrane by a Na$^+$/ HCO$_3^-$ co-transport protein.

12. Explain how the cell has a negative potential (-2 mv) in the beginning of the proximal tubule and a positive potential (+2 mv) for the rest of the proximal tubule.

13. Explain how an increase in the concentration of solute (such as glucose) in the tubular fluid leads to increased urine volume.

14. What is glomerular tubular balance?
15. Be able to give all the steps of the two mechanisms by which glomerular tubular balance occurs:
   a. Starling forces [changed GFR leads to appropriate changes in P(peritubular capillaries) and π (peritubular capillaries)]
   
   b. Bicarbonate mechanism (increase in GFR causes causes less HCO$_3^-$ reabsorption and thus increased HCO$_3^-$ in the tubular fluid, which then stimulates the Na$^+$/H$^+$ counter transport protein leading to increased Na$^+$ reabsorption. For decrease in GFR the opposite effects occur)

16. Know the Na$^+$ and water permeability characteristics and the details of the mechanism(s) of Na$^+$ reabsorption of each of the segments of the Loop of Henle.

17. Know for each segment what membrane proteins on the tubular cell are involved in Na$^+$ reabsorption, as given below. Note: for the most part, all Na$^+$ reabsorption into the tubular cell is passive going down its concentration gradient, the protein allows for passage through the membrane
   a) proximal tubule -
      i. Na$^+$/H$^+$ counter transport protein
      ii. Na$^+$/glucose co-transport protein
      iii. Na$^+$/ amino acid co-transport protein
   b) thick ascending limb of Loop of Henle – Na$^+$.K$^+$.2Cl$^-$ carrier protein
   c) distal convoluted tubule - Na$^+$/Cl$^-$ cotransporter protein
   d) connecting segment –
      i. Na$^+$/Cl$^-$ co-transporter protein
      ii. Na$^+$ channels
   e) cortical collecting tubule (principal cells only) - Na$^+$ channels
   f) medullary collecting tubule (principal cells only) - Na$^+$ channels

18. Know the permeability characteristics of the tubular cell membrane of the distal convoluted tubule (permeable to sodium NOT water) and the details of the mechanism of Na$^+$ reabsorption in the distal convoluted tubule (via concentration gradient utilizing Na/Cl cotransporter).

19. Know the permeability characteristics of the tubular cell membrane of the connecting segment (permeable to sodium NOT water) and the details of the mechanism of Na$^+$ reabsorption in the connecting segment
   a. Via concentration gradient utilizing Na$^+$/Cl$^-$ cotransporter
   b. Via concentration gradient through Na$^+$ channels being opened by aldosterone

20. Know the permeability characteristics of the cortical and medullary collecting [permeable to sodium (principal cells only) and NOT water except in the presence of ADH, where cells are also permeable to water and the details of the mechanism of Na$^+$ reabsorption (via concentration gradient through Na$^+$ reabsorption being
opened by aldosterone (for principal cells in both cortical and medullary collecting tubules) or closed by ANP (inner medullary collecting tubule only).

21. Know the mechanism by which aldosterone works in Na\(^+\) reabsorption (opens up Na\(^+\) down concentration gradient and K\(^+\) secretion).

22. Which tubular segments are specifically acted upon by the following hormones and what are the physiologic results of the hormones acting on these segments:
   a. aldosterone
   b. antidiuretic hormone (ADH)
   c. atrial natriuretic peptide (ANP)

23. Mechanisms of by which diuretics thiazide and amiloride prevent Na\(^+\) reabsorption and thus lead to increased urine volume.

24. Mechanism of Na\(^+\) reabsorption in principal cells of the cortical collecting tubule (aldosterone opening Na\(^+\) channels) and either reabsorption of Na\(^+\) by the principal cells of the medullary collecting tubules (aldosterone opening Na\(^+\) channels) in low ECF volume conditions or excretion of Na\(^+\) (ANP closing Na\(^+\) channels) in high ECF volume conditions.

B. Chapter 7 Renal Regulation of Extracellular Fluid Volume Through Sodium Reabsorption and Excretion

1. What are the consequences of severe ECF volume increase or severe ECF volume decrease?
   - Congestive heart failure and edema with ↑ ECF volume
   - Insufficient blood flow to tissues with ↓ ECF volume

2. What are the compartments in which sodium is present in the body? What compartments are exchangeable and what percentage of the body’s sodium is exchangeable? What is the significance of the exchangeable sodium?

3. What is the normal daily output of urine? What is the highest osmolarity that a urine can be?

4. List the various normal non-renal sources of loss of water and the amount lost daily for each of these sources. For all but the GI sources know the relative amount of electrolytes that are also lost.

5. List two hormonal factors that cause Na\(^+\) reabsorption and three hormonal factors that lead to Na\(^+\) excretion (as well as cause vasodilation).
6. Know three mechanisms by which a decrease in ECF volume causes a decrease in GFR (note: a decrease in GFR thus causes Na\(^+\) retention because less Na\(^+\) is filtered)

1. ↑\(\pi_{\text{plasma}}\)
2. ↓ arterial pressure (plasma)
3. ↓ stretch receptor signal
   - vasoconstriction of afferent arteriole (less inhibitory signal from stretch receptor to nerve that is connected to afferent arteriole)

7. Know the three factors that lead to release of aldosterone from the adrenal glands
   - ↑ angiotensin II
   - low [Na\(^+\)] in plasma
   - high [K\(^+\)] in plasma

8. Know the mechanisms by which renin is released by ↓ ECF volume
   - ↓ renal arterial pressure effect on juxtaglomerular cells of afferent arteriole causing a release of renin
   - ↓ GFR → ↓Na\(^+\) load to macula densa cells → release of renin
   - decreased inhibition of renal nerve by stretch receptors and baroreceptors (in high ECF volume states stretch receptors and baroreceptors are firing, which inhibits the renal nerve)

9. List the ways angiotensin II increases Na\(^+\) reabsorption
   a) Effect on renal hemodynamics dynamics (Starling Forces)
      1’) Constriction of efferent arteriole (in cortical nephrons) eventually leading to:
         ↑\(\pi_{\text{peritubular capillaries}}\) and ↓\(P_{\text{peritubular capillaries}}\) which causes ↑ water (salt) reabsorption (see notes for full explanation). This occurs in the proximal tubule.
      2’) Constriction of efferent arteriole (in juxtaglomerular nephrons) leading to ↓ medullary blood flow (vasa recta) leading to ↑ sodium reabsorption due to ↓ medullary washout (see Figure 8 in Chapter 7 for full explanation).
         This occurs in the Loop of Henle
   b) Release of aldosterone from adrenal glands. Aldosterone acts in the Connecting segment and the cortical and medullary collecting tubules
   c) Direct effect on proximal tubule

10. For angiotensin II’s effect on renal hemodynamics given above know each of the steps of the mechanism
11. Be able to list the four physical and hemodynamic mechanisms controlling Na\(^+\) reabsorption:
   - Starling forces (see first point in point 9 above)
   - Medullary Blood Flow
   - Renal Interstial Hydrostatic Pressure
   - Pressure Natriuresis

12. You **DO NOT** have to memorize the various mechanisms by which pressure natriuresis occurs.

13. Be able to explain how an increase or decrease in ECF volume affects medullary blood flow which eventually affects Na\(^+\) reabsorption. Be able to give a complete mechanism of all the steps (i.e., know Fig 8 in chapter 7)

14. Be able to state how and by what mechanism a change in ECF volume changes the renal interstitial hydrostatic pressure to affect Na\(^+\) reabsorption

15. Know that stimulation of renal nerves causes Na\(^+\) retention and three of the ways that it accomplishes this:
   a) Renin release
   b) Vasoconstriction of afferent arteriole leading to ↓ GFR and ↓ RBF – leading to less Na\(^+\) excretion due to decrease in GFR
   c) Direct stimulation of several tubular segments (proximal tubule and Loop of Henle) causing ↑ Na\(^+\) reabsorption

C. Control of ECF Osmolarity

1. List three ways ECF osmolarity is controlled:
   - Intake of water controlled by thirst
   - Output of water by the kidneys controlled by release of ADH
   - Shift of water between ECF and ICF

2. List and know the following details of the four mechanisms by which thirst sensation is stimulated:
   - High ECF osmolarity (solute not permeable to thirst receptor cells) draws water out of thirst receptor cells in the hypothalamus causing receptors to shrink, causing them to send thirst sensation
   - Receptors in left atrium of heart and pulmonary veins are stimulated with significant ECF volume loss (> 10% volume loss)
   - Excessive loss of potassium by the body causes cells (including thirst receptor cells) to shift potassium out of the cells to the ECF to maintain potassium concentration in the blood which causes the thirst receptor cells to shrink (Why?) and thus send a thirst signal
   - Direct action of angiotensin II on the third ventricle of the brain has been shown to give a thirst sensation
3. **DO NOT** need to know the structure of ADH (vasopressin) other than it is a 9 amino acid peptide

4. Know the two factors that cause ADH release and know when each factor predominates in its control of ADH release

5. Know the mechanism (step by step) by which an increase in ECF osmolarity causes a release of ADH by the pituitary gland. Know the same for a decrease in ECF osmolarity.

6. Know that ECF volume control of ADH release is through the stretch receptors in the atria of the heart and the baroreceptors (aortic arch and carotid arteries). Note that for the stretch receptors that it is a decrease in an inhibitory signal sent to the hypothalamus in conditions of ↓ ECF volume (> 10%) which leads to increase signal sent from the hypothalamus to the pituitary gland to release ADH.

7. Know the following about the mechanism of ADH action:
   1. The tubular segments acted upon
   2. The action that it causes
      - it increases the permeability of the luminal cell wall to water
   3. The molecular mechanism
      - ADH binds to receptor on peritubular side of the collecting duct cell which activates adenylate cyclase causing the conversion of ATP to cAMP, which ultimately leads to ↑ in protein kinase, which causes alteration of luminal cell wall of the collecting duct cell (phosphorylation of proteins in the luminal cell wall?) increasing its permeability to water
      - Note: you **DO NOT** need to know the various chemical factors that inhibit or enhance this process, as given in Fig 9 of the slides, however you should know that certain renal diseases cause the tubular cell to be less responsive to ADH by either affecting the cell wall response to the protein kinase or altering the biochemical reaction pathway given above.

8. The mechanism of ADH release and thirst is controlled by ECF osmolarity except in conditions of significant hypovolemia (> 10% volume loss) in which case the volume mechanisms of ADH release and thirst are operative.

D. **Disorders of Sodium Depletion** (Negative Sodium Balance)

1. Disorders of sodium depletion occur when sodium losses exceed sodium intake. Normally any reduction in intake will be compensated for by the kidney decreasing its excretion rate of sodium. It does take 3 days however for the kidney
to completely readjust its rate of excretion to match its new intake level, leading to some loss of sodium from the body.

2. Any loss of sodium from the body from its normal level (remember that ECF volume is maintained at a constant level for a healthy individual) will be compensated for by a decrease in body water volume as the body maintains ECF osmolarity. However in cases of chronic sodium loss the volume will begin to be conserved (i.e., the body cannot lose too much water volume otherwise there will be circulatory insufficiency) and the osmolarity of the ECF will decrease.

3. Know that two categories of conditions of negative sodium balance:
   • Extrarenal (normal kidney function, losses of $\text{Na}^+$ due to other pathways other than the kidney: GI tract or through skin)
   • Renal (either diseased kidney or normal kidney but abnormal conditions or factors acting on the normal kidney to cause increased excretion of sodium)

4. Know the following content of GI tract fluids:
   - Gastric – $[\text{H}^+]$ - 33 mEq/L; $[\text{K}^+]$ - 13 mEq/L (plasma – 3.5 to 5 mEq/L)
   - Intestinal – varies depending on section but higher $[\text{K}^+]$ and higher $[\text{HCO}_3^-]$ than ECF (plasma)

5. Know that loss of GI tract fluid will lead to:
   • No change in ECF osmolarity
   • Hypokalemia
   • Changed acid status depending on where fluid is lost from
     1. metabolic alkalosis – loss of gastric fluid (vomiting)
     2. metabolic acidosis – loss of intestinal fluid (diarrhea)
   Note: Know the reason for hypokalemia and changed acid status (see point 4)

6. Cutaneous losses include:
   • Excess sweat (leads to $\uparrow$ ECF osmolarity)
   • Burns

7. For burns know the cause of water loss from body (skin barrier compromised so body water evaporates) and loss of vascular water volume (because of body water volume lost due to there not being a skin barrier present; and because of damage to capillaries which leads to water, sodium, protein loss from vasculature, the protein loss leads to additional vascular volume loss, as less water is osmotically retained in the vasculature).

8. Know the renal causes for negative sodium balance in which a normal kidney is acted upon by factors to cause $\uparrow$ excretion of $\text{Na}^+$:
   • Osmotic diuresis
   • Diuretics
   • Primary Adrenal Insufficiency (Addison’s Disease)
9. For osmotic diuresis know the general mechanism by which this causes \( \text{Na}^+ \) excretion as given below:

Water retained in proximal tubule due to osmotic pull of excess solute in the tubular fluid

\[ \downarrow \]

\( \downarrow [\text{Na}^+] \) in tubular fluid entering Loop of Henle

\[ \downarrow \]

Decreased reabsorption of \( \text{Na}^- \) in thin and thick ascending limb of Loop of Henle (because reabsorption in these sections are governed by secondary active mechanisms driven by a concentration gradient)

\[ \downarrow \]

Increased \( \text{Na}^+ \) load to distal tubule segments (distal tubule, connecting segment, collecting ducts) which overloads the capacity for these segments to reabsorb \( \text{Na}^+ \)

\[ \uparrow \]

\( \uparrow \text{Na}^+ \) excretion

10. For nonreabsorbable anion diuresis the mechanism of 9 above applies, as well as the fact that the anion causes \( \text{Na}^+ \) (as well as \( \text{K}^+ \)) to be retained in the tubular fluid due to electrostatic interaction and thus this leads to both excretion of \( \text{Na}^+ \) and \( \text{K}^+ \)

11. Primary Adrenal Insufficiency (Addison’s Disease) is a disease in which function of adrenal gland is diminished. Thus it does not produce adequate amounts of aldosterone, which will lead to sodium excretion. However this is normally compensated for by increased dietary consumption in \( \text{Na}^+ \) thus the volume depletion is not that great. This shows itself clinically when there is an extra renal loss compounding the Primary Adrenal Insufficiency, which shows a considerable water loss with this extra cause for water (\( \text{Na}^+ \)) loss.

12. Be able to explain the laboratory urine test differences for [\( \text{Na}^+ \)], volume, and [\( \text{K}^+ \)] for extrarenal verses renal losses of sodium.

13. Explain why gastric fluid loss (such as vomiting) does not follow the pattern of point 12 in terms of urine test. [What test(s) are different and why?].

14. You DO NOT have to know the signs and symptoms of ECF volume depletion.

15. You DO NOT have to know the kidney diseases that cause sodium depletion.
E. **Conditions of Sodium Excess (Positive Sodium Balance)**

1. List the various conditions that causes a hypervolemic state (positive sodium balance)
   a) Congestive Heart Failure
   b) Cirrhosis-Protein Deficiency States
   c) Lymphatic Obstructions
   d) Conditions of Increased Aldosterone

2. For conditions a-d above (point 1) there is a consistent cause for persistent Na\(^+\) and water retention resulting from decreased blood volume as given below:

3. For conditions b-d in point 1 know how each condition leads to decreased blood volume so that the diagram in point 2 can be applied to the particular condition

4. How does the congestive heart failure condition fit into the diagram in point 2?

5. You **DO NOT** have to know the kidney diseases that cause sodium excess.
F. **Potassium Physiology**

1. What are the two major functions of potassium in the body?

2. What physiological effect does changing $K^+$ concentration:
   - In the ECF (one major effect)
   - In the ICF (two effects)

3. Know the following:
   - 98% of body’s potassium is intracellular
   - Two routes of excretion of $K^+$
     1. urine – 90 mEq/day
     2. feces – 10 mEq/day

4. Know the two ways in which the body regulates $[K^+]$ in the ECF:
   - Renal excretion
   - Uptake or release of $K^+$ by cells

5. Know that there are both reabsorption and or secretion mechanisms for $K^+$ in every tubular segment (except distal convoluted tubule) however the tubular segments where potassium excretion is controlled is in the connecting segment, the cortical collecting duct, and the medullary collecting duct (outer) (where $K^+$ secretion takes place). You **DO NOT** have to know what particular $K^+$ transfer process (i.e., reabsorption or secretion) takes place in each segment **EXCEPT** for the effect of aldosterone on the connecting segment, the cortical collecting duct, and the medullary collecting duct (outer) causing potassium secretion into the tubular segment.

6. Know the timing in which an increased $K^+$ is corrected for by the kidneys (hours) and a decreased $K^+$ is corrected for by the kidneys (days). In general know that the kidney is much more efficient in dealing with excess $K^+$ (since the regulation of $K^+$ level is through a secretion mechanism) than in conserving $K^+$.

7. Know the **general principles** that causes increased secretion of $K^+$ by tubular cells [connecting segment, cortical collecting duct, and medullary collecting duct (outer)]:
   - a) $\uparrow$ $[K^+]$ in tubular cell (increased $K^+$ concentration gradient between tubular cell ICF and lumen causes $K^+$ secretion into lumen)
   - b) $\downarrow$ $[K^+]$ in lumen (increased $K^+$ concentration gradient between tubular cell ICF and lumen causes $K^+$ secretion)
   - c) $\uparrow$ negative charge in lumen or $\uparrow$ positive charges in the tubular cell (moves positively charged $K^+$ into the lumen, i.e. $K^+$ secretion into lumen)

8. Know the **general mechanisms** that causes the three effects given in point 7
   - a) Mechanisms 1-3 (see below) which $\uparrow$ $[K^+]$ in the tubular cell (point 7a)
   - 1’) Mechanism 1

11
↑ [Na\(^+\)] in tubular cell → ↑ Na,K ATPase activity → ↑ [K\(^+\)] in tubular cell

2') Mechanism 2

↑ [K\(^+\)] in ECF → ↑ Na,K ATPase activity → ↑ [K\(^+\)] in tubular cell

3') Mechanism 3

↑ pH in ECF → exchange of H\(^+\) going out of cell into the ECF with K\(^+\) going into the cell from the ECF → ↑ [K\(^+\)] in all cells (including the tubular cell)

b) Mechanism 4 which causes decreased [K\(^+\)] in lumen (point 7b)

↓ [K\(^+\)] in lumen (increased K\(^+\) concentration gradient between ICF of the tubular cell and the lumen, driving K\(^+\) through the K\(^+\) channels in the tubular cell into the lumen from the tubular cell)

c) Electrostatic Mechanisms (point 7c)

1') Mechanism 5

↑ non-reabsorbed anions [keeps positive counterions (K\(^+\) and Na\(^+\)) in lumen ]

2') Mechanism 6

↑ [Na\(^+\)] \(_{\text{tubular cell}}\) → increased positivity (less negativity) of the tubular cell, leading to K\(^+\) being driven out of the tubular cell into the lumen through the K\(^+\) channels

9. Know the specific factors employing one or more of the mechanisms in point 8 leading to K\(^+\) secretion. Know the mechanism in point 8 that applies for this factor.

- ↑ aldosterone
  Process – aldosterone opens up sodium channels in connecting segment and collecting ducts causing more sodium to enter the tubular cell via concentration gradient effect → mechanisms 1,6

- ↑ Na delivery to distal tubule segments (connecting segment, collecting ducts)
  Process – increases the concentration of Na\(^+\) present in the tubular fluid; since the mechanism of Na\(^+\) reabsorption in these latter segments is secondarily active (i.e., is driven by concentration gradient in Na\(^+\) through Na\(^+\) channels)→ causes more sodium to enter the tubular cell via concentration gradient effect → mechanism 1,6

- ↑ poorly reabsorbable anions
  mechanism 5

- alkaline pH
  mechanism 3

- ↑ urine flow
  mechanism 4 (increased volume of water in tubular system dilutes [K\(^+\)] in lumen) and 1,6 (more Na\(^+\) delivered to later tube segments, leading to increased Na\(^+\) concentration gradient causing Na\(^+\) entering the tubule cell through the Na\(^+\) channels)

- hyperkalemia
  mechanism 2
mechanisms 1,6 (increased [K+] in plasma causes release of aldosterone, see discussion of effect of ↑ aldosterone on K+ secretion above)

- volume expansion mechanisms 1,6 (body responds by causing more sodium to reach later tubular segments to lower ECF volume, more Na+ delivered to later tubule segments, leading to increased Na+ concentration gradient causing Na+ entering the tubule cell through the Na+ channels)

mechanism 4 (volume expansion leads to increased volume of water in tubular system dilutes [K+] in lumen)

10. Know what factors causes K+ to move into cells
   - ↑ insulin
   - ↑ pH of ECF

11. Know that ↑ ECF osmolarity causes K+ to go from the cells to the ECF via a solvent drag effect

12. Be able to give the reason why [K+] in the ECF increases as ECF pH decreases and [K+] in the ECF decreases as ECF pH increases

13. **DO NOT** need to know the mechanism by which insulin affects K+ uptake by cells

14. Know that hyperkalemia, in addition to its effects given in point 9, causes the release of insulin, which causes cells to take up K+

**G. Hypokalemia, Hyperkalemia**

1. Know the normal range [K+] in plasma (serum) is 3.5 to 5.0 mEq/L. Above 5.0 is hyperkalemia and below 3.5 is hypokalemia.

2. Know the clinical manifestations of hypokalemia and the reason for these manifestations:
   - Neuromuscular – weak ([K+]plasma at 2.5 mEq/L) to paralysis ([K+]plasma at <2.0 mEq/L) (reason is decreased excitability of muscles and nerves)
   - GI symptoms – nausea, vomiting, anorexia (reason is impaired GI motility due to decreased excitability of muscles in GI tract)
   - Renal – polyuria from mild to severe correlated with how much K+ is lost (reason thought to be either decreased osmolarity of medulla or decreased ADH effectiveness) (Note: **DO NOT** need to know how much loss of K+ loss is associated with mild or severe polyuria)
• Cardiac – arrhythmias (i.e., irregular heart beats) from decreased excitability of heart muscle cells and conductive fibers and S/A node

3. **DO NOT NEED TO KNOW THIS MECHANISM FOR THE TEST** Know the mechanistic steps by which S/A node cells generate a periodic + signal, which is then transmitted down the connective fibers and heart muscle cells leading to a contraction. This includes knowing the following steps:
   a. Why the cell’s potential rises (becomes progressively less negative) from its resting membrane potential to a threshold potential (Na⁺ slowly leaks into the cell through Na⁺ leak channels because of the concentration gradient between ISF and the cell)
   b. What happens at the threshold potential [voltage gated Na⁺/Ca²⁺ channels open up (due to the protein of the ion channel going through a rapid conformation change) which leads to a “rush” of Na⁺/Ca²⁺ into the SA node cell (due to concentration gradient) which establishes a positive charge in the cell due to positive Na⁺/Ca²⁺ ions but not counter charges entering the cell (or a positive balance of positive charges leaving the cell)]
   c. Know why the potential of the cell then drops back to the resting potential shortly after this [At the threshold potential there is a simultaneous slow conformation change in another part of the protein lining the voltage-gated Na⁺/Ca²⁺ channels which slowly closes these channels (simultaneous to the rapid conformation change discussed in “b” above). Also there is a slow opening of K⁺ voltage-gated channels (through a conformation change of the protein) which causes K⁺ to reestablish the resting potential through its concentration gradient.
   d. This K⁺ channel protein then goes through another conformation change to close these channels so that the leak channels are once again slowly making the cell potential less negative perpetuating the cycle.

4. Know why a change in K⁺ concentration in the ECF leads to either bradycardia (decreased heart rate) for hypokalemia and tachycardia (increased heart rate) for hyperkalemia (**DO NEED TO KNOW THIS FOR TEST**).

5. Be able to list the causes for hypokalemia (need to know only those listed below):
   • Loop diuretics and thiazide
   • GI losses
   • Primary hyperaldosteronism
   • Hyperrenism
   • Increased ACTH conditions (Cushing’s Disease, ectopic ACTH production, 11 β-hydroxylase deficiency, 17 α-hydroxylase deficiency)
- Insulin therapy
- Alkalosis
- Decreased potassium intake

6. Know why loop diuretic and thiazide lead to hypokalemia, but the sodium channel inhibitor amiloride does not.

7. Know why gastric fluid losses lead to a more severe hypokalemia than diarrhea losses (be able to explain this in a stepwise fashion as given below) (see Figure 13 in slides). Again this mechanism for hypokalemia only applies for vomiting, not diarrhea. Note also there are 2 other mechanisms listed in point 8 below that apply to both vomiting and diarrhea

Vomiting

↓
Loss of HCl from stomach

↓
H⁺ enters stomach from ISF (replacing H⁺ lost from stomach)

↓
H⁺ enters ISF from cells (replacing H⁺ transferred to stomach)

↓
K⁺ enters cells to replace leaving H⁺ (positive charge exchange)

↓
All cells in the body take up K⁺, leads decrease of [K⁺] in the ECF (hypokalemia)

↓
Renal tubular cells involved in K⁺ secretion have ↑ ICF [K⁺], due to the shift to ICF in K⁺ into the tubular cells, leading ↑ secretion through K⁺ channels due to ↑ K⁺ concentration gradient between tubular cell and lumen, leading to loss of K⁺ from the body due to kaliuresis (hypokalemia)

8. Know the two additional mechanisms for hypokalemia for both vomiting and diarrhea GI tract fluid loss (see Figure 13 in slides)
   a. Loss of KCl: a loss of GI tract fluid will lead to K⁺ and water being sequestered from the ECF into the GI tract, with a greater amount of K⁺ being sequestered since GI tract fluid has higher [K⁺] than ECF, thus ↓ [K⁺] in the ECF (i.e. hypokalemia)
b. Loss of NaCl, which leads to ↓ in ECF volume, which leads to ↑ in renin, which leads to ↑ in angiotensin II, which leads to ↑ in aldosterone, which leads to ↑ secretion of K⁺ by the tubular cells, which leads to kaliuresis

9. Know that primary aldosteronism is a disease of the adrenal glands in which there is an increased number of adrenal cells (for the test you need to know only that it is a condition of increased number of cells, you do not need to know how to distinguish between an adenoma, hyperplasia, or tumor) which will produce more aldosterone than normal.

10. For hyperrenism know how this leads to hypokalemia (↑ renin leads to ↑ ang II leads to ↑ aldosterone leads to ↑ K⁺ secreted by the tubular cells). You **DO NOT** need to know the conditions that cause hyperrenism.

11. For ACTH production diseases know the following:
   - The normal hypothalamic-pituitary axis that leads to cortisol production and how there is a negative feedback loop controlling this process (hypothalamus produces CRF which acts on the pituitary gland to produce ACTH which is released into the blood and acts upon the adrenal gland to produce cortisol; cortisol then acts upon the hypothalamus in a negative feedback loop to turn off CRF production)
   - Know what each of the increased ACTH diseases (Cushing’s Disease, Ectopic ACTH production, 11β-hydroxylase deficiency, 17α-hydroxylase deficiency) is and how each leads to a disconnect of the negative feedback loop leading to continual ACTH production
   - Memorize the chemical pathway for cortisol and aldosterone synthesis on the slide (including enzymes that are involved in the steps). Know how a deficiency in an enzyme will alter the pathway of the reaction leading to the buildup of intermediates or aldosterone that have mineralocorticoid activity (know which intermediates or compounds have mineralocorticoid activity).
   - Know for Cushing’s Disease and Ectopic ACTH production that increased ACTH production drives the synthesis of both cortisol (which has mineralocorticoid activity) and aldosterone leading to K⁺ secretion into the tubular fluid

12. You **DO NOT** need to know the treatment regimen for hypokalemia

13. Know the following for clinical manifestations of hyperkalemia:
   - There is not a progression of symptoms as [K⁺] rises, like in the case of hypokalemia where there is a progression of muscle weakness as the [K⁺] falls, thus life threatening arrhythmias can develop with little pre-warning
• Manifestations:
  a) Non-specific neuromuscular manifestions may or may not be present
  b) Hyperexcitability of heart beat leading arrhythmias

14. Know the causes for hyperkalemia and how they lead to $\uparrow [K^+]$ in the plasma:
• Acute renal failure (retention of $K^+$ because of decreased kidney function)
• Chronic renal failure with additional factors (substantial increase in $K^+$ intake, $\downarrow$ aldosterone, drugs that decrease $K^+$ secretion)
• End stage chronic renal failure (kidney function decreased to such an extent that $K^+$ retained)
• Adrenal Insufficiency Conditions ($\downarrow$ aldosterone)
  a) Addison’s Disease
  b) 21-hydroxylase deficiency (why does this lead to $\downarrow$ mineralocorticoid compounds?)
  c) hypopituitarism (leads to decrease ACTH)
  d) adrenalectomy (removal of adrenal glands, no aldosterone)
• Hyporeninemic hypoaldosteronism (DO NOT have to know conditions causing this) ($\downarrow$ renin leads to $\downarrow$ ang II leads to $\downarrow$ aldosterone leads to $\downarrow$ $K^+$ secreted by the tubular cells)
• Acidosis (Why does this lead to hyperkalemia?)
• Conditions leading to massive release of $K^+$ from cells (know several examples)
• Several drugs (know amiloride, but do not need to know others)

15. Know what pseudohyperkalemia is (artifactual rise in $K^+$ due to laboratory processing of sample) and how it can appear:
  a. Hemolysis
  b. Conditions of increased platelets or leukocytes (WBCs) in which blood clotting causes a portion of these cells to be damaged to release cellular contents (including $K^+$)
  c. Tourniquet with vigorous fist action

16. DO NOT need to know treatment regimens for hyperkalemia.