Overview of The Kidney and Body Fluids

Introduction

- The maintenance of volume and a stable composition of body fluids is essential for homeostasis
- The kidneys are key players that control many functions
  - Overall regulation of body fluid volume
  - Regulation of the constituents of extracellular fluid
  - Regulation of acid-base balance
  - Control of fluid exchange between extracellular and intracellular compartments
Balance of Fluid Intake and Fluid Output

Introduction

- Water intake comes from two sources
  - Ingested in the form of liquids or within food
  - Synthesized as a result of the oxidation of carbohydrates

- Water loss occurs in many forms
  - Insensible water loss
    - Evaporation through skin
    - Humidification of inspired air
  - Sweat
  - Feces
  - Urine
    - The kidneys are a critical mechanism of controlling water loss

<table>
<thead>
<tr>
<th>Intake</th>
<th>Normal</th>
<th>Exercise</th>
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<table>
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<tr>
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<tr>
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Body Fluid Compartments

- Total body fluid is divided between extracellular fluid, transcellular fluid, and intracellular fluid
  - Extracellular fluid is again divided between blood plasma and interstitial fluid
  - Transcellular fluid includes fluid in the synovial, peritoneal, pericardial, and intraocular space
- A 70 kg person contains approximately 42 liters of water (60%) and varies with significant physical parameters
  - Age
  - Sex
  - Obesity
Balance of Fluid Intake and Fluid Output

Body Fluid Compartments

- About 28 liters are inside the 75 trillion cells of the body and thus are part of the intracellular fluid
  - Despite the vast differences in cell functions, the composition of most cells is relatively similar
- About 14 liters are extracellular
  - Three quarters of this water is interstitial
  - One quarter of this water is plasma
- About 5 liters are blood, 3 liters of which are plasma
  - Plasma is 60%, RBCs is 40%

Composition of Plasma and Interstitial Fluid

- Since the plasma and interstitial fluids are separated by highly permeable capillary membranes, their compositions are quite similar
- However, due to low protein permeability, the interstitial spaces of most tissues have low protein concentrations
- Donnan Ion Effect
  - Proteins are mostly impermeable through the capillary wall
  - Plasma proteins are negatively charged and therefore bind cations (Na\(^+\) and K\(^+\)) as well as repel anions
  - Thus, the concentration of cations is slightly greater in the plasma than in the interstitial fluid
Balance of Fluid Intake and Fluid Output

<table>
<thead>
<tr>
<th></th>
<th>Plasma (mOsm/l H2O)</th>
<th>Interstitial (mOsm/l H2O)</th>
<th>Intracellular (mOsm/l H2O)</th>
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<td>Corrected Osmolar</td>
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<td>281.0</td>
<td>281.0</td>
</tr>
</tbody>
</table>

Balance of Fluid Intake and Fluid Output

Measurement of Fluid Volumes

- **Total Body Water**
  - Add a bolus of radioactive water and measure concentration after a few hours
- **Extracellular Fluid Volume**
  - Add a bolus of radioactive sodium and measure concentration after a few hours
- **Intracellular Fluid Volume**
  - Equals total body water minus extracellular fluid volume
- **Plasma Volume**
  - Add a bolus of radioactive serum albumin and measure concentration after a few hours
- **Interstitial Fluid Volume**
  - Equals extracellular fluid volume minus plasma volume
- **Total Blood Volume**
  - Equals plasma volume / (1 - hematocrit*)
  - *Here hematocrit is total blood cell volume*
Balance of Fluid Intake and Fluid Output

Osmosis and Osmotic Pressure

- Osmosis is the diffusion of water, through a selectively permeable membrane, from a region of low solute concentration to high solute concentration
  - Water moves to try to equilibrate solute concentration on either side of the membrane

- An osmole is the total number of particles in solution that are establishing an osmotic gradient
  - Osmoles are identical to moles, if the particle does not dissociate
    - However, if a particle does dissociate, then an osmole equals the number of moles multiplied by the number of dissociating particles
  - Osmolality = osmoles / kg solution
  - Osmolarity = osmoles / liter solution

- The pressure applied to one side of a selectively permeable pressure which stops osmosis is called osmotic pressure
  - Osmotic pressure is proportional to its osmolarity
    - Molecular size is not relevant here, rather the number of osmotically active molecules is the critical parameter
  - Osmotic Pressure, $\Pi = CRT$
    - $C$ = Concentration of solutes in osmoles per liter (osmolarity)
    - $R$ = Ideal gas constant
    - $T$ = absolute temperature (K)
  - Example: $C = 1.0 \text{ mOsm/l}$ and $T = 310 \text{ K}$, $\Pi = 19.3 \text{ mmHg}$
    - Thus, for each mOsm concentration gradient of an impermeable solute molecule, about 19.3 mmHg osmotic pressure is exerted across the separating membrane
Balance of Fluid Intake and Fluid Output

Osmosis and Osmotic Pressure

- Basic osmotic pressure calculation: a 0.9% sodium chloride solution
  - 0.9% = 0.9 gm/100 mL or 9.0 gm/l
  - Molecular weight of sodium chloride = 58.5 gm/mol
  - Molarity of the solution = 9 gm/l / 58.5 gm/mol = 0.154 mol/l
  - Osmolarity of the solution = 2 x 0.154 mol/l = 0.308 Osm/l = 308 mOsm/l
  - Osmotic pressure = 308 mOsm/l x 19.3 mmHg/mOsm/l = 5944 mmHg

- Note that sodium chloride does not completely dissociate, thus the true osmotic pressure is less
  - An osmotic coefficient is thus used as a correction factor
  - Osmotic coefficient for sodium chloride is 0.93
  - Thus, osmolality = 0.93 x 308 mOsm/l = 286 mOsm/l

Balance of Fluid Intake and Fluid Output

Osmosis Equilibrium

- Relatively small changes in concentration of impermeable solutes in the extracellular fluid can cause tremendous changes in cell volume

- If a cell is placed in a solution with normal osmolarity (280 mOsm/l), the cell will neither shrink or swell - the solution is isotonic
  - Isotonic solutions include 0.9% sodium chloride and 5% glucose

- If a cell is placed in a solution with less osmolarity (hypotonic), the cell will swell as it tries to dilute its solutes

- If a cell is placed in a solution with more osmolarity (hypertonic), the cell will shrink as it tries to concentrate its solutes

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Fluid Regulation in Abnormal States

Introduction

- Abnormalities of the composition and volumes of body fluids are among the most common and important of clinical problems and are of concern for almost all seriously ill

- Factors that augment extracellular and intracellular volumes include
  - Ingestion of water
  - Dehydration
  - Intravenous infusions
  - Loss of fluid from the gastrointestinal tract
  - Loss of fluid from sweating
  - Loss of fluid through the kidneys

- Two basic principles guide our discussion
  - Water moves rapidly across the cell membrane, thus the osmolarities of intracellular and extracellular fluids are almost exactly equal
  - Cell membrane is almost completely impermeable to many solutes, thus the number of osmoles in the extracellular and intracellular fluid remains constant unless directly added / removed

Example: Patient in Water Deficit

- A patient has an osmolarity of 320 mOsm/l, so how much water should be administered to reduce this to 280 mOsm/l?

- Assume
  - Extracellular volume is 20% body weight, 14 liters
  - Intracellular volume is 40% body weight, 28 liters

- Thus
  - Extracellular osmolarity = 320 mOsm/l x 14 liters = 4,480 mOsm
  - Intracellular osmolarity = 320 mOsm/l x 28 liters = 8,960 mOsm
  - Total body fluid osmolarity = 320 mOsm/l x 42 liters = 13,440 mOsm

- We want an osmolarity of 280 mOsm/l, thus the necessary volume should be
  - Extracellular volume = 4,480 mOsm / 280 mOsm/l = 16 liters
  - Intracellular volume = 8,960 mOsm / 280 mOsm/l = 32 liters
  - Total body fluid volume = 13,440 mOsm / 280 mOsm/l = 48 liters

- Thus, 6 liters need to be administered
Fluid Regulation in Abnormal States

Example: Patient in Water Deficit

- **If an isotonic saline solution is administered**
  - The osmolarity of the extracellular fluid does not change
  - No osmosis through the cell membrane occurs
  - The effect is an increase in extracellular fluid volume

- **If a hypertonic solution is administered**
  - The osmolarity of the extracellular fluid increases
  - Osmosis pushes water out of the cell and into the extracellular space
  - The effect is a large increase in extracellular fluid volume and a decrease in intracellular fluid volume

- **If a hypotonic solution is administered**
  - The osmolarity of the extracellular fluid decreases
  - Osmosis pushed water into the cell and out of the extracellular space
  - The effect is an increase in extracellular fluid volume and a larger increase in intracellular fluid volume

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**Fluid Regulation in Abnormal States**

Example: Patient in Water Deficit

- What is the effect on extracellular and intracellular fluid volumes when 2 liters of a hypertonic 2.9% sodium chloride solution is administered to a 70 kg patient with an initial osmolarity of 280 mOsm/liter

  - Using the basic assumptions
    - Extracellular osmolarity = 280 mOsm/l x 14 liters = 3,920 mOsm
    - Intracellular osmolarity = 280 mOsm/l x 28 liters = 7,840 mOsm
    - Total body fluid osmolarity = 280 mOsm/l x 42 liters = 11,760 mOsm
  - Next, 2 liters of a 29 g/l sodium chloride (58 g/mol) solution provides 1 mole or 2 osmoles (2,000 mOsm) of sodium chloride
    - The instantaneous change would be
      - Extracellular concentration = (3,920 + 2,000) mOsm / 16 liters = 370 mOsm/l
      - Intracellular concentration remains constant = 280 mOsm/l
    - The long term change would be
      - Total body fluid concentration = 13,760 mOsm / 44 liters = 312.7 mOsm/l
      - Extracellular volume = 5,920 mOsm / 312.7 mOsm/l = 18.9 liters
      - Intracellular volume = 7,840 mOsm / 312.7 mOsm/l = 25.1 liters
Fluid Regulation in Abnormal States

Hyponatremia and Hypernatremia

- Rather than measuring plasma osmolarity, plasma sodium concentration is easier and therefore more commonly measured.

- Normal sodium concentration is 142 mEq/liter.

- Hyponatremia: Reduced sodium levels
  - Results from loss of sodium chloride from the extracellular fluid or the addition of excess water to the extracellular fluid.
  - May result from diarrhea, vomiting, overuse of diuretics, or excess water retention.

- Hypernatremia: Elevated sodium levels
  - Results from loss of water from the extracellular fluid or an excess of sodium in the extracellular fluid.

Fluid Regulation in Abnormal States

Edema

- Edema is the presence of excess fluid in the body, typically in the extracellular fluid space but sometimes involving the intracellular fluid space.

- Intracellular Edema
  - Two conditions lead to intracellular swelling
    - Depression of metabolic systems of the tissues.
    - Inadequate nutrient delivery to the cell.

- Extracellular Edema
  - Much more predominant.
  - Two general conditions lead to extracellular edema
    - Abnormal leakage of fluid from the plasma through the capillary wall and into the interstitial space.
    - Failure of the lymphatics to return fluid from the interstitium back into the blood.
Fluid Regulation in Abnormal States

Edema

- Capillary filtration may be described by
  \[ \text{Filtration} = K_f \times (P_c - P_f - \pi_c + n_c) \]
  where
  - \( K_f \): capillary filtration coefficient
  - \( P_c \): capillary hydrostatic pressure
  - \( P_f \): interstitial fluid hydrostatic pressure
  - \( n_c \): capillary osmotic pressure
  - \( n_f \): interstitial osmotic pressure

- Thus, capillary filtration may be increased by
  - Increased capillary filtration coefficient
  - Increased capillary hydrostatic pressure
  - Decreased capillary osmotic pressure

Causes of Extracellular Edema

- Increased capillary pressure
  - Excessive kidney retention of salt and water
  - Acute or chronic kidney failure
  - Mineralocorticoid excess
  - High venous pressure and venous constriction
  - Heart failure
  - Venous obstruction
  - Failure of venous pumps
    - Paralysis of muscles
    - Immobilization of parts of the body
    - Failure of venous valves
  - Decreased arteriolar resistance
  - Excessive body heat
  - Insufficiency of sympathetic nervous system
  - Vasodilator drugs

- Decreased plasma proteins
  - Loss of proteins in urine (nephrotic syndrome)
  - Loss of protein from denuded skin areas
    - Burns
    - Wounds
  - Failure to produce proteins
    - Liver disease (e.g., cirrhosis)
    - Serious protein or caloric malnutrition

- Increased capillary permeability
  - Immune reactions that cause release of histamine and other immune products
  - Toxins
  - Bacterial infections
  - Vitamin deficiency, especially vitamin C
  - Prolonged ischemia
  - Burns
  - Blockage of lymph return
  - Cancer
  - Infections (e.g., filaria nematodes)
  - Surgery
  - Congenital absence or abnormality of lymphatic vessels

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Fluid Regulation in Abnormal States

Edema Caused by Heart Failure

- In heart failure, the heart fails to pump blood normally
- As a result, venous pressure rises and capillary pressure rises - and therefore causing more capillary filtration
- Renal Effects
  - Additionally, arterial pressure falls, decreasing water and salt excretion by the kidneys, increasing blood volume and further increasing capillary pressure
  - Also, diminished blood flow stimulates renin secretion, causing additional salt and water retention
- In pulmonary edema, blood cannot easily leave the pulmonary veins due to heart damage, increasing pulmonary capillary pressure and therefore water retention - death can occur rapidly

Edema Caused by Salt and Water Retention

- In some kidney failures, salt and water excretion is diminished
- Salt and water build in the blood and leak into the interstitial space, causing
  - Increased in interstitial fluid volume
  - Hypertension due to increase blood volume

Edema Caused by Decreased Plasma Proteins

- A decrease in plasma proteins increases capillary filtration and extracellular edema
- Causes include
  - Renal abnormalities which allow proteins to leave through the urine
  - Cirrhosis of the liver where fibrous tissue in the liver produces increased plasma protein levels
Fluid Regulation in Abnormal States

Prevention of Edema

- Three major safety factors prevent fluid accumulation in the interstitial space
  - Low compliance of the interstitium when interstitial fluid pressure is negative
  - The ability of the lymph flow to increase 10 to 50 fold
  - Washdown of interstitial fluid protein

- Low Compliance of the Interstitium
  - Interstitial fluid hydrostatic pressure is slightly negative, about -3 mmHg
  - Once interstitial fluid pressure rises above 0 mmHg, compliance increases and fluids rapidly accumulate
  - Safety factor is about 3 mmHg

- Increased Lymph Flow
  - The ability of the lymphatics to dramatically increase their flow allows a release mechanism for fluids retained within the interstitial space
  - Increase lymph flow occurs in response to increased capillary filtration and therefore preventing increased interstitial pressure
  - Safety factor is about 7 mmHg

- Washdown of Interstitial Fluid Protein
  - As increased fluids are filtered into the interstitium, interstitial fluid pressure increases, and causing increased lymph flow
  - This increased lymph flow, washes out protein concentration
  - Safety factor is about 7 mmHg

- Total safety factor preventing edema is approximately 17 mmHg
  - Capillary pressure in a peripheral tissue can rise approximately 17 mmHg, or double its normal level, without significant edema
Fluid Regulation in Abnormal States

Effusion

- Edema can occur in tissues adjacent to other volumes - potential spaces - that can also collect fluid
  - Pleural cavity
  - Pericardial cavity
  - Peritoneal cavity
  - Synovial cavities

- Potential spaces are "filled" by capillaries and "drained" by lymphatics in a manner similar to other tissues

- When edema occurs with fluid collection in a potential space, it is called effusion

Kidneys: Glomerular Filtration

Introduction

- The kidneys act to both rid the body of waste as well as to control the volume and composition of bodily fluids

- The kidneys perform their functions by filtering the plasma and removing substances from the filtrate, with the rate of removal depending upon the current needs of the body
  - Cleared substances are excreted in the urine
  - Needed substances are returned to the blood

- Specific functions of the kidney include
  - Regulation of water and electrolyte balance
  - Regulation of osmolality and electrolyte concentration
  - Regulation of acid-base balance
  - Excretion of waste products
  - Regulation of arterial pressure
  - Secretion of hormones
  - Gluconeogenesis
Kidneys: Glomerular Filtration

Introduction

- Regulation of water and electrolyte balance
  - Excretion of water and electrolytes must match their intake
  - Increased salt intake causes an increase in salt excretion by the kidneys
    - Salt intake (typically 10 mEq/day) can increase or decrease by 1 order of magnitude with little change in plasma sodium concentration or extracellular fluid volume
  - Changes in chloride, potassium, calcium, hydrogen, magnesium, and phosphate ions can all be balanced by renal functions

- Excretion of waste products
  - Excretion of waste products must match their production and intake
  - Excreted metabolic products include urea, creatinine, uric acid, bilirubin, and metabolites from various hormones
  - Excreted toxins include pesticides, drugs, and food additives

- Regulation of arterial pressure
  - Regulation occurs by excreting variable amounts of salt and water as well as through systems such as renin production

- Regulation of acid-base balance
  - Regulation occurs by excreting acids and controlling buffering capabilities

- Regulation of erythrocyte production
  - Kidneys secrete nearly all endogenous erythropoietin, which stimulates RBC production under both normal and hypoxic conditions

- Regulation of 1,25-dihydroxy vitamin D
  - Kidneys produce the active form of vitamin D

- Glucose synthesis
  - Kidneys synthesize glucose from amino acids and other precursors during long periods of fasting
Kidneys: Glomerular Filtration

Physiological Anatomy of the Kidneys

- The two kidneys lie on the posterior wall of the abdomen, outside the peritoneal cavity
- Each weighs about 150 gm and is about the size of a clenched fist
- Medial side contains an indented region known as the hilum, allowing passage of a number of structures
  - Renal artery and vein
  - Lymphatics
  - Nerve supply
  - Ureter, which carries urine out of the kidney to the bladder

A coronal section of the kidney shows two regions
- Outer cortex
- Inner medulla

Medulla is divided into renal pyramids, whose bases originate at the border with the cortex and whose apex terminates in the papilla, which projects into the renal pelvis

Urine from the tubules of each papilla is then collected into the minor and major calices

Walls of the calices, pelvis, and ureter are contractile, allowing the movement of urine to the bladder
Physiological Anatomy of the Kidneys

- Blood flow to the kidneys is normally 21% of cardiac output (1200 ml/min)

- Blood enters the kidney through the renal artery, and then branches progressively to form interlobar arteries, arcuate arteries, interlobular arterioles, and afferent arterioles

- Afferent arterioles lead to the glomerular capillaries, which then coalesce to form efferent arterioles, and then the peritubular capillaries
  - Glomerular capillaries are the site of fluid and solute filtration
  - Efferent arterioles regulate pressure

- Peritubular capillaries empty into the venous system which run in parallel to the arteriolar vessels
  - Peritubular capillaries are the site of reabsorption

- Peritubular capillaries coalesce into the interlobular vein, arcuate vein, interlobar vein, and renal vein

- Thus, two capillary beds exist: glomerular capillaries and the peritubular capillaries
  - High hydrostatic pressure in the glomerular capillaries allows rapid filtration
  - Low hydrostatic pressure in the peritubular capillaries allows rapid reabsorption
Kidneys: Glomerular Filtration

Nephron, the Function Unit of the Kidney

- Each kidney contains about 1 million nephrons, which form urine
- In renal disease, there is a decline in the number of functional nephrons
  - After age 40, total nephron function falls 10% every 10 years
- Each nephron has two major components
  - Glomerulus through which large amounts of fluid are filtered from the blood
  - Tubule in which the fluid is converted into urine on its way to the pelvis of the kidney

- The glomerulus is composed of a network of branching capillaries have a high hydrostatic pressure (60 mmHg)
- Glomerular capillaries are covered by epithelial cells
- Entire glomerulus is encased in Bowman’s capsule
- Fluid flows from the glomerular capillaries into Bowman’s capsule, into the proximal tubule, into the loop of Henle
  - Loop of Henle consists of a descending and ascending limb
Kidneys: Glomerular Filtration

Nephron, the Function Unit of the Kidney

- Fluid flow continues past the Macula densa, into the distal tubule, connecting tubule, the cortical collecting tubule, and the cortical collecting duct.

- Approximately 8 to 10 cortical collecting ducts join to form a larger duct, which runs downward to become the medullary collecting duct and ultimately the collecting duct.

- Each kidney contains about 250 large collecting ducts, each of which collects from approximately 4000 nephrons.

Kidneys: Glomerular Filtration

Nephron, the Function Unit of the Kidney

- Nephrons differ depending upon the location within the kidney.

- Nephrons whose glomeruli are located in the outer cortex are called cortical nephrons and possess short loops of Henle:
  - Entire tubular system is surrounded by peritubular capillaries.

- Nephrons whose glomeruli are located deep in the renal cortex are called juxtamedullary nephrons and possess long loops of Henle:
  - Tubular system is surrounded by vasa recta capillaries which lie side by side to the loop of Henle.
Kidneys: Glomerular Filtration

Urine Formation

- The rate of at which substances are excreted into the urine depends upon three factors
  - Glomerular filtration
  - Reabsorption of substances from the renal tubules into the blood
  - Secretion of substances from the blood into the renal tubules

- Urinary excretion rate = filtration rate - reabsorption rate + secretion rate

Urine formation begins with filtration from the glomerular capillaries into Bowman’s capsule
- Here a large amount of fluid, which is protein-free, is collected
- Substances are freely filtered, so that their concentration are nearly the same in Bowman’s capsule as in the plasma - with the exception of proteins

As fluid leaves Bowman’s capsule, water and specific solutes are reabsorbed back into the blood
- Also, other substances are also secreted from the blood into the filtrate

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Kidneys: Glomerular Filtration

A few notes about filtration, reabsorption, and secretion

- Reabsorption is quantitatively more important than secretion
- Most substances cleared from the blood (urea, creatinine, uric acid, and urates) are poorly reabsorbed and therefore cleared in the urine
- Electrolytes (sodium, chloride, and bicarbonate ions) are highly reabsorbed, so they appear little in the urine
- Amino acids and glucose are completely reabsorbed and do not appear in the urine
- Filtration, reabsorption, and secretion are regulated by the needs of the body
Kidneys: Glomerular Filtration

Glomerular Filtration

- Glomerular filtration rate (GFR), the rate of fluid extraction from the glomerular capillaries into Bowman’s capsule, is approximately 180 liter/day

- GFR is largely determined by
  - The balance of hydrostatic and colloid osmotic forces acting across the capillary membrane
  - The capillary filtration coefficient (Kf), which is determined by the permeability and the filtering surface area of the capillaries

- The fraction of renal plasma flow that is filtered (filtration fraction) averages about 0.2, where about 20% of the plasma flowing through the kidney is filtered by the glomerular capillaries
  - Filtration fraction = GFR / renal plasma flow

Kidneys: Glomerular Filtration

Glomerular Filtration

- Glomerular capillary membranes are similar to other capillary membranes, except that it has three major layers (remember, most have only two)
  - The endothelium of the capillary
  - A basement membrane
  - A layer of epithelial cells (podocytes) surrounding the outer surface of the capillary basement membrane

- The endothelium is perforated by thousands of small holes (fenestrae) allowing for free transport, even for proteins

- The basement membrane consists of collagen and negatively charged proteoglycans, preventing protein filtration

- Podocytes, although not continuous, present large processes (“feet”) separated by gaps that allow glomerular filtrate transport
Kidneys: Glomerular Filtration

Glomerular Filtration

- Glomerular filtration is a function of molecular size and electrical charge
  - Sodium, glucose, and inulin are filtered as freely as water
  - Myoglobin is filtered 75% as rapidly as water; albumin 0.5% as water

- In general, negatively charged large molecules are filtered less easily than equally sized positively charged molecules

<table>
<thead>
<tr>
<th>Molecular Weight (Da)</th>
<th>Filtration Rate (gm/ml / gm/ml H2O)</th>
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<tbody>
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<tr>
<td>Sodium</td>
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</tr>
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<td>Glucose</td>
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</tr>
<tr>
<td>Inulin</td>
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</tr>
<tr>
<td>Myoglobin</td>
<td>17,000</td>
</tr>
<tr>
<td>Albumin</td>
<td>69,000</td>
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Determinants of Glomerular Filtration

- The GFR is determined by net filtration pressure and capillary filtration coefficient, such that
  \[ \text{GFR} = K_f \times \text{net filtration pressure} \]

- Net filtration pressure
  - Favored by glomerular hydrostatic pressure \( (P_G) \) and Bowman’s capsule colloid osmotic pressure \( (\pi_B) \)
    - Typically, \( \pi_B \approx 0 \)
  - Opposed by glomerular capillary colloid osmotic pressure \( (\pi_C) \) and Bowman’s capsule hydrostatic pressure \( (P_B) \)
  - Net filtration pressure \( = P_G - P_B - \pi_C + \pi_B \)
  - Thus, \( \text{GFR} = K_f \times (P_G - P_B - \pi_C + \pi_B) \)
Kidneys: Glomerular Filtration

Determinants of Glomerular Filtration

- $K_f$ is the product of hydraulic conductivity and the surface area of the glomerular capillaries

- From before
  - $K_f = \frac{GFR}{(P_G - P_B - \pi_G + \pi_B)}$
  - $K_f = \frac{GFR}{\text{net filtration pressure}}$

- Typically, $GFR = 125 \text{ ml/min}$ and net filtration pressure $= 10 \text{ mmHg}$
  - Thus $K_f = 12.5 \text{ ml/min/mmHg}$

- On the basis of kidney mass
  - $K_f = 4.2 \text{ ml/min/mmHg per 100 g}$
  - This is approximately 400 times the values of the typical capillary

- Changes in $K_f$ are not a primary mechanism of regulation, but do occur in some pathologies

Hydrostatic pressure in Bowman’s capsule ($P_B$) is roughly 18 mmHg under normal conditions
- Increasing $P_B$ does reduce GFR, however this is not a primary regulatory mechanism
- Again, pathologies, such as kidney stones, can increase $P_B$ by obstructing outflow of the urinary tract

Glomerular capillary colloid osmotic pressure ($\pi_G$)
- As blood passes through the glomerular capillaries, protein concentration increases as water is filtered out, and thus glomerular capillary colloid osmotic pressure increases
- Two factors determine glomerular capillary colloid osmotic pressure
  - Arterial plasma colloid osmotic pressure
    - Increase in colloid osmotic pressure decreases GFR
  - Fraction of plasma filtered by the glomerular capillaries (filtration fraction)
    - As blood flow increases, GFR increases
Kidneys: Glomerular Filtration

Determinants of Glomerular Filtration

- Changes in glomerular hydrostatic pressure are the primary mechanism for the physiological regulation of GFR
  - Increases in glomerular hydrostatic pressure cause an increase in GFR
  - Glomerular hydrostatic pressure is determined by
    - Arterial pressure
      - Increased arterial pressure increases glomerular hydrostatic pressure and thus increases GFR
    - Afferent arteriolar resistance
      - Increased resistance reduces glomerular hydrostatic pressure and thus decreases GFR
    - Efferent arteriolar resistance
      - Increased resistance (up to a point!) reduces glomerular capillary outflow, increases glomerular hydrostatic pressure and thus increases GFR

Kidneys: Glomerular Filtration

Renal Blood Flow

- A 70 kg person sees a total renal blood flow of 1200 ml/min, or 21% of cardiac output
  - Blood flow provides nutrients to renal tissues
  - Blood flow also supplies enough plasma for high GFR necessary for bodily homeostasis
  - Renal blood flow is determined by the pressure gradient across the renal vasculature, divided by the total renal vascular resistance
    - Renal blood flow = \( \frac{(\text{renal arterial pressure} - \text{renal venous pressure})}{\text{total renal vascular resistance}} \)
Kidneys: Glomerular Filtration

Physiological Control of GFR and Renal Blood Flow

- Control over GFR is primarily exerted by changes in glomerular hydrostatic pressure and glomerular capillary colloid osmotic pressure - both of which lie under the control of the sympathetic nervous system, hormones, autacoids, and other kidney feedback control systems

- Sympathetic nervous system
  - Strong activation constricts renal arterioles, lowers blood flow, and lowers GFR
  - Only activated under short term, severe disturbances

- Hormonal and autacoid control systems
  - Norepinephrine and epinephrine (adrenal medulla) and endothelin (vascular endothelial cells of kidney or other tissues) restrict renal blood vessels and lower GFR
  - Angiotensin II (autocrine and paracrine) is a powerful renal vasconstrictor acting upon efferent arterioles, thus prevents decreases in GFR
  - Endothelial derived nitric oxide decreases renal vascular resistance and increases GFR

Kidneys: Glomerular Filtration

Autoregulation of GFR and Renal Blood Flow

- The kidneys themselves contain intrinsic mechanisms that keep GFR and renal blood flow relatively constant despite external disturbances
  - Blood perfused kidneys, removed from the body, still posses functional mechanisms to regulate GFR and renal blood flow
  - This inherent ability is known as autoregulation

- Typically, autoregulation provides sufficient nutrition to the cells of a particular tissue

- In the kidneys, where blood flow far exceeds nutritional needs, autoregulation acts to maintain GFR and renal excretion of water and solutes

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Kidneys: Glomerular Filtration

Autoregulation of GFR and Renal Blood Flow

- In the absence of autoregulation, small changes in blood pressure could result in huge changes in urine output, quickly depleting blood volume
- Tubuloglomerular Feedback
  - Changes in sodium chloride concentration causes changes in the macula densa, that then control renal arteriolar resistance
  - Two components are at work here
    - An afferent arteriolar feedback mechanism
    - An efferent arteriolar feedback mechanism
  - A decrease in sodium chloride concentration initiates a signal from the macula densa that decreases resistance of the afferent arterioles (raising glomerular hydrostatic pressure) and increases renin release that constricts efferent arterioles (also raising glomerular hydrostatic pressure)

Kidneys: Tubular Processing of Glomerular Filtrate

Reabsorption and Secretion by the Renal Tubules

- As the glomerular filtrate enters the renal tubules, it flows through the proximal tubule, loop of Henle, distal tubule, collecting tubule, and the collecting duct
- During this flow, some substances are selectively reabsorbed from the tubules back into the blood and other substances are secreted from the blood into the filtrate
- Urine composition results from these regulated processes:
  - \( \text{Urinary excretion rate} = \text{filtration rate} - \text{reabsorption rate} + \text{secretion rate} \)
- Reabsorption is generally much more important than secretion, however, depending upon the substance secretion can play a significant role

<table>
<thead>
<tr>
<th>Substance</th>
<th>Amount Filtered (gm/day)</th>
<th>Amount Reabsorbed (gm/day)</th>
<th>Amount Excreted (gm/day)</th>
<th>Percent Filtered Reabsorbed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose</td>
<td>180</td>
<td>180</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>4,320</td>
<td>4,318</td>
<td>2</td>
<td>100.0</td>
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<tr>
<td>Sodium</td>
<td>25,560</td>
<td>25,410</td>
<td>150</td>
<td>99.4</td>
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<tr>
<td>Chloride</td>
<td>19,440</td>
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<td>Urea</td>
<td>47</td>
<td>23</td>
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<tr>
<td>Creatinine</td>
<td>2</td>
<td>0</td>
<td>2</td>
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</table>
Kidneys: Tubular Processing of Glomerular Filtrate

Reabsorption and Secretion by the Renal Tubules

- The processes of glomerular filtration and tubular reabsorption are quantitatively very large relative to urinary excretion
  - A small change in glomerular filtration or tubular reabsorption can potentially cause a large change in urinary excretion

- While glomerular filtration is relatively nonselective, tubular reabsorption is highly selective
  - Glucose and amino acids are almost entirely reabsorbed
  - Ions are highly reabsorbed, but the reabsorption is regulated to meet the needs of the body
  - Urea and creatinine are poorly reabsorbed

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<td>2</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
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Kidneys: Tubular Processing of Glomerular Filtrate

Tubular Reabsorption

- Reabsorption requires transport across the tubular epithelial membrane into the renal interstitial fluid and through the peritubular capillary membrane back into the blood
  - Transport can be conductive, involving both active and passive mechanisms
  - Transport can be transcellular (through cells) and paracellular (between cells)
  - Transport can be convective, involving hydrostatic and osmotic pressure
Kidneys: Tubular Processing of Glomerular Filtrate

Tubular Reabsorption

- Primary active transport through the tubular membrane is linked to the hydrolysis of ATP so as to move solutes against their electrochemical gradient
  - Sodium-potassium ATPase
  - Hydrogen ATPase
  - Hydrogen-potassium ATPase
  - Calcium ATPase

- For example, sodium-potassium ATPase actively transports Na⁺ from the tubular epithelial cells and into the blood, while thus driving Na⁺ diffusion from the tubular lumen into the tubular epithelial cells

Secondary active transport involves the unidirectional movement of two molecules across a membrane, where the energy generated by the transport of one molecule drives the transport of the other molecule
- ATP is not consumed, but generated energy is consumed
- For example, a sodium gradient allows Na⁺ transport, which drive glucose transport against its concentration gradient
- Note, however, that a sodium-potassium pump, which is consuming energy, is required to establish the sodium gradient
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Tubular Reabsorption

• Secondary active secretion is similar to secondary active transport, however the direction of the transported molecules opposes one another.

• For example, the transport of $\text{Na}^+$ into the cell, down its concentration gradient, is utilized to drive $\text{H}^+$ transport out of the cell against its concentration gradient.
  - Transport is mediated by a specific protein in the brush border of the luminal membrane.

• Active transport has a maximum limit.
  - For example, the transport maximum for glucose is about 320 mg/min, where loads above this limit cause filtered glucose to not be reabsorbed and thus excreted in the urine.
  - The threshold for glucose transport is 220 mg/min (lower than the maximum), as individual nephrons become saturated.
  - All nephrons are saturated at the 320 mg/min limit.
  - Plasma glucose only reaches this limit in pathological states, primarily diabetes.
Kidneys: Tubular Processing of Glomerular Filtrate

Tubular Reabsorption

- Passive transport has NO limit
- Active transport requires a carrier system that can become saturated
- Passive transport is determined by
  - Electrochemical gradient
  - Membrane permeability
  - Fluid retention time within the tubule
- If a carrier in an active transport system has a capacity that is dramatically above the observed loads, then the active transport system can essentially behave as a passive system and display no physiological limits

Kidneys: Tubular Processing of Glomerular Filtrate

Tubular Reabsorption

- Sodium transport drives water reabsorption by osmosis
- As sodium is transported out of the tubule, its concentration increases in the renal interstitium and decreases in the tubule
- Thus water, due to the osmotic pressure to dilute sodium concentration, is transported in the same direction as sodium - but regulated by water permeability
  - The proximal tubule is highly permeable to water, and allows significant water transport
    - Despite tight junctions, water and small molecule permeation occurs
    - Water transport also “drags” along other small ions and solutes
  - Tight junctions in the loop of Henle and collecting tubule are considerably more “tight” and thus prevent water reabsorption as well as its effects
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Tubular Reabsorption

- Reabsorption of chloride and urea

- Chloride is reabsorbed by a number of different mechanisms
  - Sodium transport induces an electrical gradient, driving chloride transport through the paracellular pathway
  - Sodium transport induces water transport, which concentrates chloride ions and thus induces their diffusion
  - Secondary active transport along with sodium

- Urea is also passively reabsorbed due to sodium induce water transport, however urea permeability is low and thus about one half of urea is excreted

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Reabsorption and Secretion Along the Nephron

- About 65% of the filtered load of sodium, chloride, and water are reabsorbed by the proximal tubule before reaching the loop of Henle

- The proximal tubule contains
  - Epithelial cells that are highly metabolic and support potent active transport processes
  - Brush border as well as intercellular and basal channels that provide extensive membrane surface area for rapid transport
  - Brush border loaded with protein carrier molecules that move sodium as well as amino acids and glucose in a co-transport mechanism
    - First half of the proximal tubule, sodium moves with amino acids and glucose
    - Second half of the proximal tubule, sodium moves with chloride

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Reabsorption and Secretion Along the Nephron

- The concentration of molecules along the nephron are a result of both the individual molecules’ transport as well as the transport of water

- Sodium is highly transported, but its concentration does not change as water is also highly removed

- Glucose concentration falls dramatically, as it is transported much more quickly than water

- Creatinine and urea increase in concentration

- Toxic substances are highly filtered and secreted, and little reabsorption occurs

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Reabsorption and Secretion Along the Nephron

- The loop of Henle contains three functionally distinct segments

  - Descending thin segment
    - Highly permeable to water and moderately permeable to urea and sodium
    - Allows for simple diffusion, primarily water
    - Water is mostly reabsorbed here, diluting the downstream fluid

  - Ascending thin segment
    - Lower reabsorptive capacity than thick segment

  - Thick ascending segment
    - Thick epithelial cells capable of active reabsorption of sodium, chloride, and potassium
    - Approximately 25% of these filtered molecules are reabsorbed here
    - Movement of sodium across the luminal membrane is mediated primarily by a 1-sodium, 2-chloride, 1-potassium cotransporter
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Reabsorption and Secretion Along the Nephron

- Distal Tubule, Late Distal Tubule, and Cortical Collecting Tubule
- The distal tubule contains the juxtaglomerular complex which provides feedback control of GFR and blood flow in this same nephron
- The distal tubule, like the thick segment of the loop of Henle, reabsorbs most ions including sodium, potassium and chloride, but is impermeable to water and urea
- The late distal tubule and cortical collecting tubule contain two cell types
  - Principal cells, which reabsorb sodium and water as well as secrete potassium
  - Intercalated cells, which reabsorb potassium and secrete hydrogen

Summary of Tubular Reabsorption and Secretion

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Regulation of Tubular Reabsorption

- A basic regulation mechanism - glomerulotubular balance - is the intrinsic ability of the tubules to increase their reabsorption rate in response to increased tubular load.

- For example, if GFR increases from 125 to 150 ml/min, proximal tubular reabsorption increases from 81 ml/min to 97.5 ml/min.

- Note that proximal tubular reabsorption remains 65% of GFR.

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Regulation of Tubular Reabsorption

- Hydrostatic and colloid osmotic forces also govern the rate of reabsorption across the peritubular capillaries.

- More than 99% of the water and most solutes are reabsorbed.
  - Normal rate of reabsorption is 124 ml/min.

- Reabsorption = $K_r \times \text{net reabsorption force}$
  - Net reabsorption force results from:
    - Peritubular hydrostatic pressure ($P_c$).
    - Renal interstitium hydrostatic pressure ($P_i$).
    - Peritubular colloid osmotic pressure ($\pi_c$).
    - Renal interstitium colloid osmotic pressure ($\pi_i$).
  - $Reabsorption = K_r \times (-P_c + P_i + \pi_c - \pi_i)$.
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Regulation of Tubular Reabsorption

- Peritubular capillary hydrostatic pressure is influenced by
  - Arterial pressure
    - An increase in arterial pressure, increases hydrostatic pressure, and decreases reabsorption
  - Resistance of the afferent and efferent arterioles
    - Increase of either resistance, increases hydrostatic pressure, and decreases reabsorption

- Peritubular colloid osmotic pressure is influenced by
  - Systemic plasma colloid osmotic pressure
    - Increase of systemic osmotic pressure, increases peritubular colloid osmotic pressure, and increases reabsorption
  - Filtration fraction
    - Increase in filtration fraction, increases plasma filtration, increases plasma protein concentration, and increases reabsorption

Effect of Arterial Pressure on Urine Output

- When arterial pressure is regulated between 75 and 160 mmHg, arterial pressure has only a slight effect on renal blood flow and GFR
- When GFR autoregulation is impaired, as occurs in kidney disease, increases small changes in arterial pressure can cause large increases in GFR and an even greater effect on sodium and water excretion
Kidneys: Tubular Processing of Glomerular Filtrate

Hormonal Control of Tubular Reabsorption

- **Aldosterone**
  - Site of Action: Collecting tubule and duct
  - Result: Increases NaCl reabsorption, increases H$_2$O reabsorption, increases K$^+$ secretion

- **Angiotensin II**
  - Site of Action: Proximal tubule
  - Result: Increases NaCl reabsorption, increases H$_2$O reabsorption, increases H$^+$ secretion

- **Antidiuretic hormone**
  - Site of Action: Distal tubule/collecting tubule and duct
  - Result: Increases H$_2$O reabsorption

- **Atrial natriuretic peptide**
  - Site of Action: Distal tubule/collecting tubule and duct
  - Result: Decreases NaCl reabsorption

- **Parathyroid hormone**
  - Site of Action: Proximal tubules, thick ascending loop of Henle, distal tubules
  - Result: Decreases PO$_4^{2-}$ reabsorption, increases Ca$^{2+}$ reabsorption