Lecture Outline for Integrated Basic Health Sciences for Pharmacy

Physiology Component of Module : Renal

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Fluid Compartments

- *Total body water = 40 L*
  1. Intracellular fluid (ICF) compartment: 2/3 or 25 L in cells
  2. Extracellular fluid (ECF) compartment: 1/3 or 15 L
     - Plasma: 3 L
     - Interstitial fluid (IF): 12 L in spaces between cells
     - Other ECF: lymph, CSF, humors of the eye, synovial fluid, serous fluid, and gastrointestinal secretions

Extracellular and Intracellular Fluids

- *Each fluid compartment has a distinctive pattern of electrolytes*
- *ECF*
  - All similar, except higher protein content of plasma
    - Major cation: Na^+
    - Major anion: Cl^-

Extracellular and Intracellular Fluids

- *ICF:*
  - Low Na^+ and Cl^-
  - Major cation: K^+
  - Major anion HPO_4^{2-}

Extracellular and Intracellular Fluids

- *Proteins, phospholipids, cholesterol, and neutral fats make up the bulk of dissolved solutes*
  - 90% in plasma
  - 60% in IF
  - 97% in ICF

Fluid Movement Among Compartments

- *Regulated by osmotic and hydrostatic pressures*
- *Water moves freely by osmosis; osmolalities of all body fluids are almost always equal*
- *Two-way osmotic flow is substantial*
- *Ion fluxes require active transport or channels*
- *Change in solute concentration of any compartment leads to net water flow*

Water Balance and ECF Osmolality

- *Water intake = water output = 2500 ml/day*
- *Water intake: beverages, food, and metabolic water*
- *Water output: urine, insensible water loss (skin and lungs), perspiration, and feces*

Regulation of Water Intake

- *Thirst mechanism is the driving force for water intake*
- *The hypothalamic thirst center osmoreceptors are stimulated by*
  - ↓ Plasma osmolality of 2–3%
  - Angiotensin II or baroreceptor input
  - Dry mouth
  - Substantial decrease in blood volume or pressure

Regulation of Water Intake

- *Drinking water creates inhibition of the thirst center*
- *Inhibitory feedback signals include*
  - Relief of dry mouth
  - Activation of stomach and intestinal stretch receptors

Regulation of Water Output

- *Obligatory water losses*
  - Insensible water loss: from lungs and skin
  - Feces
  - Minimum daily sensible water loss of 500 ml in urine to excrete wastes
- *Body water and Na^+ content are regulated in tandem by mechanisms that maintain cardiovascular function and blood pressure*

Regulation of Water Output: Influence of ADH

- *Water reabsorption in collecting ducts is proportional to ADH release*
- *↓ ADH → dilute urine and ↓ volume of body fluids*
- *↑ ADH → concentrated urine*

Regulation of Water Output: Influence of ADH

- *Hypothalamic osmoreceptors trigger or inhibit ADH release*
- *Other factors may trigger ADH release via large changes in blood volume or pressure, e.g., fever, sweating, vomiting, or diarrhea; blood loss; and traumatic burns*

Disorders of Water Balance: Dehydration

- *Negative fluid balance*
  - ECF water loss due to: hemorrhage, severe burns, prolonged vomiting or diarrhea, profuse sweating, water deprivation, diuretic abuse
  - Signs and symptoms: thirst, dry flushed skin, oliguria
  - May lead to weight loss, fever, mental confusion, hypovolemic shock, and loss of electrolytes

Disorders of Water Balance: Hypotonic Hydration

- *Cellular overhydration, or water intoxication*

- *Occurs with renal insufficiency or rapid excess water ingestion*
- *ECF is diluted → hyponatremia → net osmosis into tissue cells → swelling of cells → severe metabolic disturbances (nausea, vomiting, muscular cramping, cerebral edema) → possible death*

Disorders of Water Balance: Edema

- *Atypical accumulation of IF fluid → tissue swelling*
- *Due to anything that increases flow of fluid out of the blood or hinders its return*
  - ↑ Blood pressure
  - ↑ Capillary permeability (usually due to inflammatory chemicals)
  - Incompetent venous valves, localized blood vessel blockage
  - Congestive heart failure, hypertension, ↑ blood volume

Edema

- *Hindered fluid return occurs with an imbalance in colloid osmotic pressures, e.g., hypoproteinemia (↓ plasma proteins)*
  - Fluids fail to return at the venous ends of capillary beds
  - Results from protein malnutrition, liver disease, or glomerulonephritis

Edema

- *Blocked (or surgically removed) lymph vessels*
  - Cause leaked proteins to accumulate in IF
  - ↑ Colloid osmotic pressure of IF draws fluid from the blood
  - Results in low blood pressure and severely impaired circulation

Kidney Functions

- *Removal of toxins, metabolic wastes, and excess ions from the blood*
- *Regulation of blood volume, chemical composition, and pH*
- *Gluconeogenesis during prolonged fasting*
- *Endocrine functions*
  - Renin: regulation of blood pressure and kidney function
  - Erythropoietin: regulation of RBC production
- *Activation of vitamin D*

Kidney Physiology: Mechanisms of Urine Formation

- *The kidneys filter the body's entire plasma volume 60 times each day*
- *Filtrate*
  - Blood plasma minus proteins
- *Urine*
  - <1% of total filtrate
  - Contains metabolic wastes and unneeded substances

Mechanisms of Urine Formation

1. *Glomerular filtration*
2. *Tubular reabsorption*

- Returns all glucose and amino acids, 99% of water, salt, and other components to the blood

3. *Tubular secretion*
   - Reverse of reabsoprtion: selective addition to urine

Glomerular Filtration

- *Passive mechanical process driven by hydrostatic pressure*
- *The glomerulus is a very efficient filter because*
  - Its filtration membrane is very permeable and it has a large surface area
  - Glomerular blood pressure is higher (55 mm Hg) than other capillaries
- *Molecules >5 nm are not filtered (e.g., plasma proteins) and function to maintain colloid osmotic pressure of the blood*

Net Filtration Pressure (NFP)

- *The pressure responsible for filtrate formation (10 mm Hg)*

Net Filtration Pressure (NFP)

- *Determined by*
  - Glomerular hydrostatic pressure (HP_g) the chief force
  - Two opposing forces:
    - Colloid osmotic pressure of glomerular blood (OP_g)
    - Capsular hydrostatic pressure (HP_c)

$$NFP = HP_g - (OP_g + HP_c)$$

Glomerular Filtration Rate (GFR)

- *Volume of filtrate formed per minute by the kidneys (120–125 ml/min)*
- *Governed by (and directly proportional to)*
  - Total surface area available for filtration
  - Filtration membrane permeability
  - NFP

Regulation of Glomerular Filtration

- *GFR is tightly controlled by two types of mechanisms*
- *Intrinsic controls (renal autoregulation)*
  - Act locally within the kidney
- *Extrinsic controls*
  - Nervous and endocrine mechanisms that maintain blood pressure, but affect kidney function

Intrinsic Controls

- *Maintains a nearly constant GFR when MAP is in the range of 80–180 mm Hg*
- *Two types of renal autoregulation*
  - Myogenic mechanism (Chapter 19)
  - Tubuloglomerular feedback mechanism, which senses changes in the juxtaglomerular apparatus

Intrinsic Controls: Myogenic Mechanism

- *$\uparrow$ BP $\rightarrow$ constriction of afferent arterioles*

- Helps maintain normal GFR
- Protects glomeruli from damaging high BP

• *↓ BP → dilation of afferent arterioles*
- Helps maintain normal GFR

Intrinsic Controls: Tubuloglomerular Feedback Mechanism

• *Flow-dependent mechanism directed by the macula densa cells*

• *If GFR increases, filtrate flow rate increases in the tubule*

• *Filtrate NaCl concentration will be high because of insufficient time for reabsorption*

Intrinsic Controls: Tubuloglomerular Feedback Mechanism

• *Macula densa cells of the JGA respond to ↑NaCl by releasing a vasoconstricting chemical that acts on the afferent arteriole → ↓ GFR*

• *The opposite occurs if GFR decreases.*

Extrinsic Controls: Sympathetic Nervous System

• *Under normal conditions at rest*
- Renal blood vessels are dilated
- Renal autoregulation mechanisms prevail

Extrinsic Controls: Sympathetic Nervous System

• *Under extreme stress*
- Norepinephrine is released by the sympathetic nervous system
- Epinephrine is released by the adrenal medulla
- Both cause constriction of afferent arterioles, inhibiting filtration and triggering the release of renin

Extrinsic Controls: Renin-Angiotensin Mechanism

• *Triggered when the granular cells of the JGA release renin*

angiotensinogen (a plasma globulin)

renin → ↓

angiotensin I

angiotensin converting enzyme (ACE) → ↓

angiotensin II

Effects of Angiotensin II

1. *Constricts arteriolar smooth muscle, causing MAP to rise*
2. *Stimulates the reabsorption of Na^+*
   - Acts directly on the renal tubules
   - Triggers adrenal cortex to release aldosterone
3. *Stimulates the hypothalamus to release ADH and activates the thirst center*

Effects of Angiotensin II

4. *Constricts efferent arterioles, decreasing peritubular capillary hydrostatic pressure and increasing fluid reabsorption*
5. *Causes glomerular mesangial cells to contract, decreasing the surface area available for filtration*

Extrinsic Controls: Renin-Angiotensin Mechanism

- *Triggers for renin release by granular cells*
  - Reduced stretch of granular cells (MAP below 80 mm Hg)
  - Stimulation of the granular cells by activated macula densa cells
  - Direct stimulation of granular cells via β1-adrenergic receptors by renal nerves

Other Factors Affecting GFR

- *Prostaglandin E_2*
  - Vasodilator that counteracts vasoconstriction by norepinephrine and angiotensin II
  - Prevents renal damage when peripheral resistance is increased

Other Factors Affecting GFR

- *Intrarenal angiotensin II*
  - Reinforces the effects of hormonal angiotensin II
- *Adenosine*
  - A vasoconstrictor of renal vasculature

Tubular Reabsorption

- *A selective transepithelial process*
  - All organic nutrients are reabsorbed
  - Water and ion reabsorption are hormonally regulated
- *Includes active and passive process*
- *Two routes*
  - Transcellular
  - Paracellular

Tubular Reabsorption

- *Transcellular route*
  - Luminal membranes of tubule cells
  - Cytosol of tubule cells
  - Basolateral membranes of tubule cells
  - Endothelium of peritubular capillaries

Tubular Reabsorption

- *Paracellular route*
  - Between cells
  - Limited to water movement and reabsorption of Ca^{2+}, Mg^{2+}, K^{+}, and some Na^{+} in the PCT where tight junctions are leaky

Sodium Reabsorption

- *Na^{+} (most abundant cation in filtrate)*
  - Primary active transport out of the tubule cell by

Na^+-K^+ ATPase in the basolateral membrane

- Na^+ passes in through the luminal membrane by secondary active transport or facilitated diffusion mechanisms

Sodium Reabsorption

- *Low hydrostatic pressure and high osmotic pressure in the peritubular capillaries*
- *Promotes bulk flow of water and solutes (including Na^+)*

Reabsorption of Nutrients, Water, and Ions

- *Na+ reabsorption provides the energy and the means for reabsorbing most other substances*
- *Organic nutrients are reabsorbed by secondary active transport*
  - Transport maximum (Tm) reflects the number of carriers in the renal tubules available
  - When the carriers are saturated, excess of that substance is excreted

Reabsorption of Nutrients, Water, and Ions

- *Water is reabsorbed by osmosis (obligatory water reabsorption), aided by water-filled pores called aquaporins*
- *Cations and fat-soluble substances follow by diffusion*

Reabsorptive Capabilities of Renal Tubules and Collecting Ducts

- *PCT*
  - Site of most reabsorption
    - 65% of Na^+ and water
    - All nutrients
    - Ions
    - Small proteins

Reabsorptive Capabilities of Renal Tubules and Collecting Ducts

- *Loop of Henle*
  - Descending limb: H_2O
  - Ascending limb: Na^+, K^+, Cl^-

Reabsorptive Capabilities of Renal Tubules and Collecting Ducts

- *DCT and collecting duct*
  - Reabsorption is hormonally regulated
    - Ca^{2+} (PTH)
    - Water (ADH)
    - Na^+ (aldosterone and ANP)

Reabsorptive Capabilities of Renal Tubules and Collecting Ducts

- *Mechanism of aldosterone*
  - Targets collecting ducts (principal cells) and distal DCT
  - Promotes synthesis of luminal Na^+ and K^+ channels
  - Promotes synthesis of basolateral Na^+-K^+ ATPases

Tubular Secretion

- *Reabsorption in reverse*

- K^+, H^+, NH_4^+, creatinine, and organic acids move from peritubular capillaries or tubule cells into filtrate

- *Disposes of substances that are bound to plasma proteins*

Tubular Secretion

- *Eliminates undesirable substances that have been passively reabsorbed (e.g., urea and uric acid)*
- *Rids the body of excess K^+*
- *Controls blood pH by altering amounts of H^+ or HCO_3^- in urine*

Regulation of Urine Concentration and Volume

- *Osmolality*
  - Number of solute particles in 1 kg of H_2O
  - Reflects ability to cause osmosis

Regulation of Urine Concentration and Volume

- *Osmolality of body fluids*
  - Expressed in milliosmols (mOsm)
  - The kidneys maintain osmolality of plasma at ~300 mOsm, using countercurrent mechanisms

Countercurrent Mechanism

- *Occurs when fluid flows in opposite directions in two adjacent segments of the same tube*
  - Filtrate flow in the loop of Henle (countercurrent multiplier)
  - Blood flow in the vasa recta (countercurrent exchanger)

Countercurrent Mechanism

- *Role of countercurrent mechanisms*
  - Establish and maintain an osmotic gradient (300 mOsm to 1200 mOsm) from renal cortex through the medulla
  - Allow the kidneys to vary urine concentration

Countercurrent Multiplier: Loop of Henle

- *Descending limb*
  - Freely permeable to H_2O, which passes out of the filtrate into the hyperosmotic medullary interstitial fluid
  - Filtrate osmolality increases to ~1200 mOsm

Countercurrent Multiplier: Loop of Henle

- *Ascending limb*
  - Impermeable to H_2O
  - Selectively permeable to solutes
    - Na^+ and Cl^- are passively reabsorbed in the thin segment, actively reabsorbed in the thick segment
  - Filtrate osmolality decreases to 100 mOsm

Urea Recycling

- *Urea moves between the collecting ducts and the loop of Henle*
  - Secreted into filtrate by facilitated diffusion in the ascending thin segment

- Reabsorbed by facilitated diffusion in the collecting ducts deep in the medulla

- *Contributes to the high osmolality in the medulla*

Countercurrent Exchanger: Vasa Recta

- *The vasa recta*
  - Maintain the osmotic gradient
  - Deliver blood to the medullary tissues
  - Protect the medullary osmotic gradient by preventing rapid removal of salt, and by removing reabsorbed H_2O

Formation of Dilute Urine

- *Filtrate is diluted in the ascending loop of Henle*
- *In the absence of ADH, dilute filtrate continues into the renal pelvis as dilute urine*
- *Na^+ and other ions may be selectively removed in the DCT and collecting duct, decreasing osmolality to as low as 50 mOsm*

Formation of Concentrated Urine

- *Depends on the medullary osmotic gradient and ADH*
- *ADH triggers reabsorption of H_2O in the collecting ducts*
- *Facultative water reabsorption occurs in the presence of ADH so that 99% of H_2O in filtrate is reabsorbed*

Diuretics

- *Chemicals that enhance the urinary output*
  - Osmotic diuretics: substances not reabsorbed, (e.g., high glucose in a diabetic patient)
  - ADH inhibitors such as alcohol
  - Substances that inhibit Na^+ reabsorption and obligatory H_2O reabsorption such as caffeine and many drugs

Renal Clearance

- *Volume of plasma cleared of a particular substance in a given time*
- *Renal clearance tests are used to*
  - Determine GFR
  - Detect glomerular damage
  - Follow the progress of renal disease

Renal Clearance

$$RC = UV/P$$

RC = renal clearance rate (ml/min)

U = concentration (mg/ml) of the substance in urine

V = flow rate of urine formation (ml/min)

P = concentration of the same substance in plasma

Renal Clearance

- *For any substance freely filtered and neither reabsorbed nor secreted by the kidneys (e.g., insulin),*

$$RC = GFR = 125 \text{ ml/min}$$

- *If RC < 125 ml/min, the substance is reabsorbed*
- *If RC = 0, the substance is completely reabsorbed*
- *If RC > 125 ml/min, the substance is secreted (most drug metabolites)*

Physical Characteristics of Urine

- *Color and transparency*
  - Clear, pale to deep yellow (due to urochrome)
  - Drugs, vitamin supplements, and diet can alter the color
  - Cloudy urine may indicate a urinary tract infection

Physical Characteristics of Urine

- *Odor*
  - Slightly aromatic when fresh
  - Develops ammonia odor upon standing
  - May be altered by some drugs and vegetables

Physical Characteristics of Urine

- *pH*
  - Slightly acidic (~pH 6, with a range of 4.5 to 8.0)
  - Diet, prolonged vomiting, or urinary tract infections may alter pH
- *Specific gravity*
  - 1.001 to 1.035, dependent on solute concentration

Chemical Composition of Urine

- *95% water and 5% solutes*
- *Nitrogenous wastes: urea, uric acid, and creatinine*
- *Other normal solutes*
  - Na^+, K^+, PO_4^{3-}, and SO_4^{2-},
  - Ca^{2+}, Mg^{2+} and HCO_3^-
- *Abnormally high concentrations of any constituent may indicate pathology*

Acid-Base Balance

- *pH affects all functional proteins and biochemical reactions*
- *Normal pH of body fluids*
  - Arterial blood: pH 7.4
  - Venous blood and IF fluid: pH 7.35
  - ICF: pH 7.0
- *Alkalosis or alkalemia: arterial blood pH >7.45*
- *Acidosis or acidemia: arterial pH < 7.35*

Acid-Base Balance

- *Most H^+ is produced by metabolism*
  - Phosphoric acid from breakdown of phosphorus-containing proteins in ECF
  - Lactic acid from anaerobic respiration of glucose
  - Fatty acids and ketone bodies from fat metabolism
  - H^+ liberated when CO_2 is converted to HCO_3^- in blood

Acid-Base Balance

- *Concentration of hydrogen ions is regulated sequentially by*
  - Chemical buffer systems: rapid; first line of defense
  - Brain stem respiratory centers: act within 1–3 min
  - Renal mechanisms: most potent, but require hours to days to effect pH changes

Renal Mechanisms of Acid-Base Balance

- *Most important renal mechanisms*
  - Conserving (reabsorbing) or generating new HCO_3^-
  - Excreting HCO_3^-
- *Generating or reabsorbing one HCO_3^- is the same as losing one H^+*
- *Excreting one HCO_3^- is the same as gaining one H^+*

Renal Mechanisms of Acid-Base Balance

- *Renal regulation of acid-base balance depends on secretion of H^+*
- *H^+ secretion occurs in the PCT and in collecting duct type A intercalated cells:*
  - The H^+ comes from H_2CO_3 produced in reactions catalyzed by carbonic anhydrase inside the cells

Reabsorption of Bicarbonate (See Figure 26.12)

- *Tubule cell luminal membranes are impermeable to HCO_3^-*
  - CO_2 combines with water in PCT cells, forming H_2CO_3
  - H_2CO_3 dissociates
  - H^+ is secreted, and HCO_3^- is reabsorbed into capillary blood
  - Secreted H^+ unites with HCO_3^- to form H_2CO_3 in filtrate, which generates CO_2 and H_2O
- *HCO_3^- disappears from filtrate at the same rate that it enters the peritubular capillary blood*

Generating New Bicarbonate Ions

- *Two mechanisms in PCT and type A intercalated cells*
  - Generate new HCO_3^- to be added to the alkaline reserve
- *Both involve renal excretion of acid (via secretion and excretion of H^+ or NH_4^+*

Excretion of Buffered H^+ (See Figure 26.13)

- *Dietary H^+ must be balanced by generating new HCO_3^-*
- *Most filtered HCO_3^- is used up before filtrate reaches the collecting duct*

Excretion of Buffered H^+

- *Intercalated cells actively secrete H^+ into urine, which is buffered by phosphates and excreted*
- *Generated "new" HCO_3^- moves into the interstitial space via a cotransport system and then moves passively into peritubular capillary blood*

Ammonium Ion Excretion (See Figure 26.13)

- *Involves metabolism of glutamine in PCT cells*
- *Each glutamine produces 2 NH_4^+ and 2 "new" HCO_3^-*
- *HCO_3^- moves to the blood and NH_4^+ is excreted in urine*

Bicarbonate Ion Secretion (Opposite to reabsorption as in Figure 26.12)

- *When the body is in alkalosis, type B intercalated cells*
  - Secrete HCO_3^-
  - Reclaim H^+ and acidify the blood

Bicarbonate Ion Secretion

- *Mechanism is the opposite of the bicarbonate ion reabsorption process by type A intercalated cells*
- *Even during alkalosis, the nephrons and collecting ducts excrete fewer HCO_3^- than they conserve*

END OF OUTLINE

References

Marieb, E. N. & Hoehn K (2010). Human Anatomy and Physiology. 8th Edition, Pearson, Benjamin Cummings.