Physiology Team 434

Last Minute!

REVISION

RENAL PHYSIOLOGY

DONE BY:

Hadeel Alsulami
Moath Aleisa
Moneerah Aldraihem
Nouf Alharbi
Nouf Almasoud
Reem Labani
Sarah Aljasser

Lecture 1: Renal Functions and Glomerular Filtration

★ **What are the functions of the kidney?**

- **Regulation:** Water, electrolytes, body fluid osmolarity, ABP and acid-base.
- **Excretion :** Waste products (urea & Creatinine) and drugs.
- **Synthetic :** Activation of vit.D, Ertheryopoietin and Renin.

Primary function of the kidney is to CLEAR unneeded substances from blood to be excreted in urine

★ **What is the functional and structural unit of the kidney? THE NEPHRON.**

★ **Types of a nephrons:**

Cortical (85%)	Jusxtramedullary (15%)
Glomeruli in outer cortex	Extend to medulla
Short loop of Henle	Long loop of Henle

★ **Renal blood vessels: A**fferent > **G**lomeruli (capillaries) > **E**fferent > **P**eritubular (capillaries)

★ **How much from cardiac output goes to the kidneys? 20%** (1200 ml/min)

★ **Features of renal circulation: 1) High blood flow 2) Two capillary beds**

★ **What are the steps of urine formation?**

- Glomerular Filtration
- Tubular Reabsorption
- Tubular Secretion
- Excretion

- **Step 1: Glomerular Filtration:** Filtration of fluid from glomerular capillaries into renal tubules. Which need to go through a barrier: **Glomerular Membrane, consists of three layers:**
  - **Capillary Endothelium.**
  - **Basement Membrane** (-ve charge).
  - **Bowman's Epithelium** (podocytes).

★ **Glomerular Filtration Rate (GFR):** The rate of production of filtrate at the glomeruli from plasma per minute.

★ **What are the factors determining GFR?**

- **Net Filtration Pressure (NFP)**
- **Filtration coefficient (Kf)**
  - ★ Thus GFR can be measured as : **GFR = NFP x Kf**

★ **Factors Affecting GFR:**

↑Increase GFR	↓Decrease GFR
Afferent dilation, Efferent constriction, Angiotensin II, fever, hyperglycemia and High protein diet,	Afferent constriction, Efferent dilation, sympathetic stimulation (norepinephrine) and aging.

Lecture 2: Regulation of Glomerular Filtration

Definition of GFR	The volume of filtrate produced by **both kidneys** per **min (125 ml/min)**
Changes according to	According to the ABP -NFP (net force pressure)
Importance of regulation	• To prevent loss of substances if it is high • To prevent accumlation of substances (Azotemia develops)
How it is regulated?	• Autoregulation (**within systolic pressure of 75-160 mmHg**) • Hormonal regulation • Sympathetic

✧ Autoregulation

Myogenic Regulation

-High BP (GFR) pressure is going to the kidneys.

-blood will cause stretching of the arteriolar wall.

-Baroreceptors are stimulated causing.

-vasoconstriction of the Afferent arteriole

-GFR back to normal.

Low BP decreases the myogenic mechanism . (dilation)

Tubuloglomerular Feedback

-When the ABP is low :

macula densa cells will sense a drop of NaCl concentration and activation of paracrine secretions and renin release from juxtaglomerular cells

Afferent arteriolar dilation (so more blood coming in) effect of paracrine

Efferent arteriolar constriction. By renin

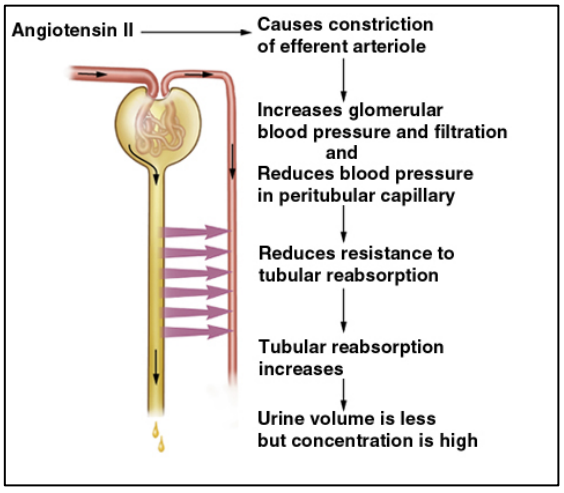
- When ABP is high :

Macula densa will sense the high concentration of NaCl .

Paracrine secretions cause **Afferent** arteriolar constriction

✧ Sympathetic Regulation:

When it is stimulated epinephrine cause vasoconstriction of the afferent arteriole sympathetic also stimulates Angiotensin which acuse vasoconstriction of the efferent



Lecture 3: Renal Clearance

<table>
<tr><td>Renal Clearance</td><td colspan="2">Clearance is the volume of plasma that is completely cleared of a substance each minute</td></tr>
<tr><td>Clearance Equation</td><td colspan="2">Cx = (Ux X V)/ Px
Cx = renal clearance of a substance
(Ux X V) = Excretion rate
Ux = urinary concentration of a substance
V = urine volume</td></tr>
<tr><td rowspan="4">Importance</td><td>1-Measure GFR</td><td>2-Measure RPF</td></tr>
<tr><td>•Creatinine (endogenous)
•Inulin (exogenous)
These substances are freely filtered and NOT reabsorbed neither secreted.</td><td>•Paraminohippuric acid (PAH)
Is rapidly and completely secreted by the renal tubular cells.</td></tr>
<tr><td>3-Determine renal handling of a substance</td><td>Notes:</td></tr>
<tr><td>• = inulin clearance;
Only filtered not reabsorbed or secreted
• < inulin clearance;
Reabsorbed by nephron tubules
• > inulin clearance;
Secreted by nephron tubules</td><td>•Filtration fraction : It is the ratio of GFR to renal plasma flow
•If excretion rate of a substance is greater than the filtered load, then the rate at which it appears in the urine represents the sum of the rate of glomerular filtration + tubular secretion</td></tr>
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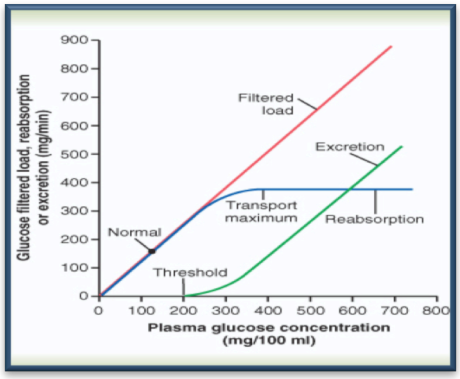


- **TUBULAR TRANSPORT MAXIMUM : molecules such as glucose and amino acids are reabsorbed via transporters which makes them susceptible to saturation (TM)**
- **Exceeding the threshold means some of the nephrons do not completely reasoned (little glucose in the urine)**
- **Exceeding the tubular transport maximum means All the nephrons do not complete glucose abortion (glucose urea)**

Lecture 4: Physiology of Micturation

✧ **Definition:**

A complete autonomic spinal reflex to get urine out side the body, that is facilitated or inhibited by higher brain centers

URINE NEEDS TO GO THROUGH:

- Pelvis: Collect urine from collecting ducts.
- Ureter: Peristaltic contraction.*
- Bladder: Holds urine.
- Urethra: Get urine to the outside.

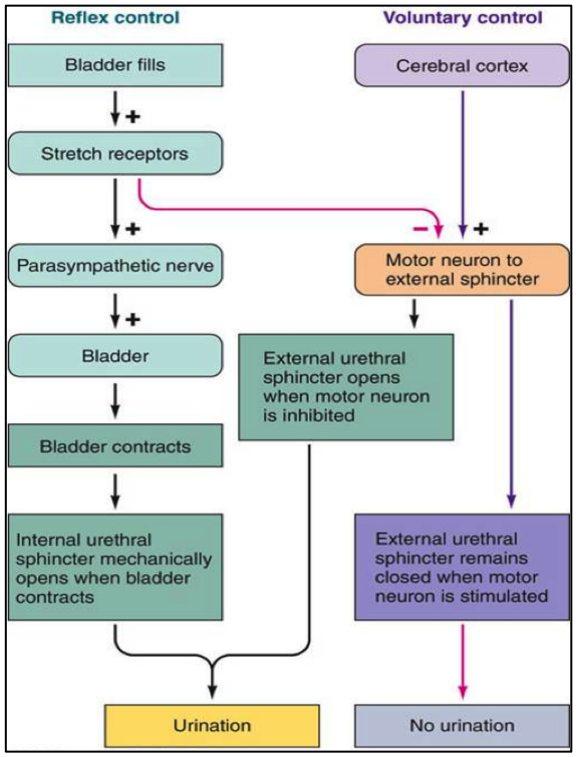
*Peristaltic waves: are initiated by pacemakers in renal pelvis.

✧ Interruption of the flow of urine by obstruction (eg: stones) > ↑Pressure (Back up) > to Pelvis >↑Hydrostatatic pressure of Bowmans' > Hydronephrosis

✧ The autonomic pain fibers in ureter accounts for pain in kidney stones.

✧ **How micturation take place?**

- ↑ intravesical pressure up to 300 ml > ↑ Bladder tone (stretch receptors in trigone very sensitive) > Signals get to pelvis nerves > Central S2, S3 & S4 > Parasympathetic:
  - ✓ Relax the sphincters
  - ✓ Contract the bladder
- Higher Control:
  - Facilitatory area: Pontine.
  - Inhibitory area: Midbrain



✧ **Abnormality of micturition:**

- **Effect of spinal cord transection:**
  - ✓ 1st Stage: Spinal shock: Unresponsive bladder.
  - ✓ 2nd Stage: No voluntary control.

Lecture 5&6: Tubular Reabsorption & Secretion

✧ Introduction:

Excreted urine =GF[1]-TR[2]+TS[3]-Water conservation

Transport within tubules occur through:

- **Active transport: Movement of substances against gradient.**
  - 1ary active transport: **need ATP** e.g Na^{2+}-K^{+} ATPase &H-K^{+} ATPase
  - 2ary active

- Co-transpor: uses the ATP of 1ary active transport. down gradient of one substance mostly Na^{2+} both substances on same direction into the cell> يعني يتمصلح مع الصوديوم عشان يدخل للخلية

E.g SGLT1/2 & Na^{2}-K^{+}-2Cl.

- Counter-transport: same as co-transport but both substances on different direction

E.g Na^{2} - H^{+}.

- **Passive transport: Novement of substances with gradient.**
  - **Simple diffusion :** Cl^{-} & HCO^{3}, urea simple diffusion
  - **Facilitated diffusion:** glucose at basal border by GLUTs
  - **Osmosis:** either through ion channels or pinocytosis/exocytosis water mostly coupled with Na^{2+}. or paracellular

✧ Transport through tubules:

- **PCT[4]: "coarse adjustment"**

***Reabsorption:**

- 65-70% of water and Na^{2+}
- 90% of HCO^{3} ,Ca^{2+} ,K^{+} through passive diffusion
- 100% of glucose and amino acids through Na^{2+}-glucose co-transport /Na^{2+}-amino acids co-transport.

***Secretion:** Organic acids & bases (bile salts,oxalate,urate,catecholamines,some drugs)

- **Why most of transport is in PCT?**
  - ✓ Many proteins = transport channels
  - ✓ Rich in mitochondria→ more receptors /ATP
  - ✓ Brush border → wider surface area

- **Loop of Henle:**
  - **Descending limb**: water permeable Na-Cl impermeable 25% of water reabsorbed
  - **Ascending limb:** water impermeable Na-Cl permeable(passive absorption)
  - **Thick ascending limb:** impermeable to water Na^{2+}-K^{+}-2Cl^{-} cotransport

Results in hypo-osmolar filtrates

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[1] Glomerular filtration
[2] Tubular reabsorption
[3] Tubular secretion
[4] Proximal convoluted tubules

- **Distal convoluted tubules: "fine adjustment"** It has 2 portions:

- **Early:** same as thick ascending but have macula densa cells→ sense change in NaCl.
- **Late:** here fine adjustment depending on what body needs " hormonal control":
  - ✓ **Aldosterone:** control reabsorption of NaCl and secret K (in late portion of DCT[5] by)
  - ✓ **ADH(vasopressin):**: absorb H_2O (in the late portion).
  - ✓ **Parathyroid hormone:** absorb Ca^{2+}

Note: impermeable to urea

- **Medullary collecting ducts:** same as the late DCT but **highly permeable to urea**.

✧ RECAP!! Solutes handling:

Solute	PCT	Loop of Henle	DCT	Collecting ducts
K^+	Passive absorption	Thin descending: non Thin ascending: passive Thick ascending :Na-K-2Cl	Aldosterone present secretion by principal cells	Same as DCT
HCO_3	Only absorbed in PCT: $HCO_3+H^+= H_2CO_3+CA^6 =H_2O+ \{CO_2\}$→Into the cell CO_2+H_2O +CA=H_2CO_3→ HCO_3+H^+ into interstitium → vasa recta			
Na^+	Coupled with other solutes co-transport	Thin descending: non Thin ascending: passive Thick ascending :Na^2-K^+-2Cl	Aldosterone present active transport	Same as DCT
Glucose	Only absorbed in PCT : from tubular lumen to cell through **Na-Glucose co-transport.** from cell to interstitium **GLUTs.** 100% if not >375 mg/min			
H_2O	65% reabsorption passive with Na	**25%** thin descending: passive thin ascending: non thick ascending : non	Reabsorption Under ADH[7] control	Same as DCT

✧ Rgulation of tubular reabsorption and secretion :

- **Hormonal**:
  - ✓ Aldosterone: Na+ reabsorption and K+ , H+ excretion
  - ✓ PTH[8]: ↑ Ca^{2+} reabsorption and ↓PO_4 reabsorption
  - ✓ ADH: ↑water reabsorption in DCT and collecting tubules
  - ✓ ANP[9]: ↑ Na^+ secretion and ↑ diuresis
- **Nervous:**
  - ✓ Sympathetic: ↑Na+ reabsorption
- **Other:**
  - ✓ Atrial pressure (hyprostatic): ↑ in it ↓reabsorption
  - ✓ Atrial oncotic pressure: ↑ in it ↑ reabsorption.

[5] Distal convoluted tubules
[6] Carbonic anhydrase
[7] Antidiuretic hormone
[8] Parathyroid hormone
[9] Atrial natriuretic peptide

Lecture 7: Renal Regulation of Body Fluids

- **Fluid Compartment:**
  - Fluid compartment is approximately 60% of the body weight.
  - ICF = ⅔ of TBW
  - ECF = ⅓ of TBW
  - Plasma = ¼ of ECF
  - Interstitial fluid = ¾ of ECF
- **ECF :**
  - Osmolality of ECF is determined by the amount of extracellular NaCl and water, which depends upon balance between intake and excretion of these substances.
  - Normal plasma Na+ = 140-145 mEq/L
  - Osmolarity = 300 mOsm/L
  - To stay in a state of fluid balance: Fluid intake = Fluid output
- **Control of ECF osmolarity and sodium concentration :**
  - Is controlled by:
    - osmoreceptor-ADH feedback system
    - Thirst center
  - Factors increase the thirst:
    - High osmolarity
    - Low ECF volume
    - Low blood pressure
    - Angiotensin | |
  - Gastric distention decrease the sensation of thirst
- **Osmoreceptor mechanism:**

High ECF osmolarity → Shrinkage of osmoreceptors (in anterior hypothalamus) → firing and send signal through supraoptic nuclei to posterior pituitary gland → release of ADH → enters the bloodstream → increase water reabsorption

- ADH synthesis is happening in supraoptic and paraventricular nuclei of the hypothalamus.
- ADH is released from posterior pituitary gland.

  - Non-osmotic stimuli; effect on ADH :
  - ✓ Low arterial blood volume → increase ADH
  - ✓ Drinking cooler fluid → decrease ADH
  - ✓ Hypoxia and hypercapnia → increase ADH

- Ang II & aldosterone don't have a major role in controlling the osmolarity of ECF.

Lecture 8: Urine Concentration & Dilution

- **Diluting and concentrating mechanisms of the kidney**
  - Urine osmolality varies widely in response to changes in water intake.
  - Human urine osmolarity may reach up to **1200 mOsm/L as concentrated urine** and may decrease to **50 mOsm/L as a diluted urine**.

- **Production of dilute urine:**
  - Produced when circulating ADH is low { e.g: water intake, central diabetes insipidus) or when ADH is ineffective {nephrogenic diabetes insipidus}
  - Mechanism **(NO ADH)**:
    - PCT → Solutes & H2O absorbed in equal proportion (isosmotic with the plasma)
    - Thick ascending loop of henle and early distal tubule → tubular fluid diluted due to 1Na-1K-2Cl and impermeable to water even in the presence of ADH, tubular fluid osmolarity = 100 mOsm/L .
    - Late Distal tubule & collecting tubule → tubular fluid becomes further diluted due to absence of ADH, tubular fluid osmolarity = 50 mOsm/ L.

- **Production of concentrated urine:**
  - Two requirements is needed to form a concentrated urine :
    - ✓ High levels of ADH {water deprivation}
    - ✓ High osmolarity of the renal medullary interstitial fluid
  - The High osmolarity of the renal medullary interstitial fluid:
    - ✓ Is **established** by countercurrent multiplication and urea recycling.
    - ✓ is **maintained** by countercurrent exchange in the vasa recta.
  - The major factors creating hyperosmolar medulla:
    - ✓ Passive reabsorption of **NaCl** by the thin ascending limb of Henle.
    - ✓ Reabsorption of **Na+,2Cl-,K+** by the thick ascending loop of henle.
    - ✓ Facilitated diffusion of large amounts of **urea** from the inner medullary collecting ducts.
  - Maintenance of hyperosmolar medulla:
    - The medullary blood flow is very small {removal of solutes is minimized}
    - Countercurrent exchange (vasa recta mechanism)

- **Any conditions increase medullary blood flow {osmotic diurisis} → decrease urine concentrating ability.**
- **Any conditions decrease medullary blood flow {volume depletion} → increase urine concentrating ability.**

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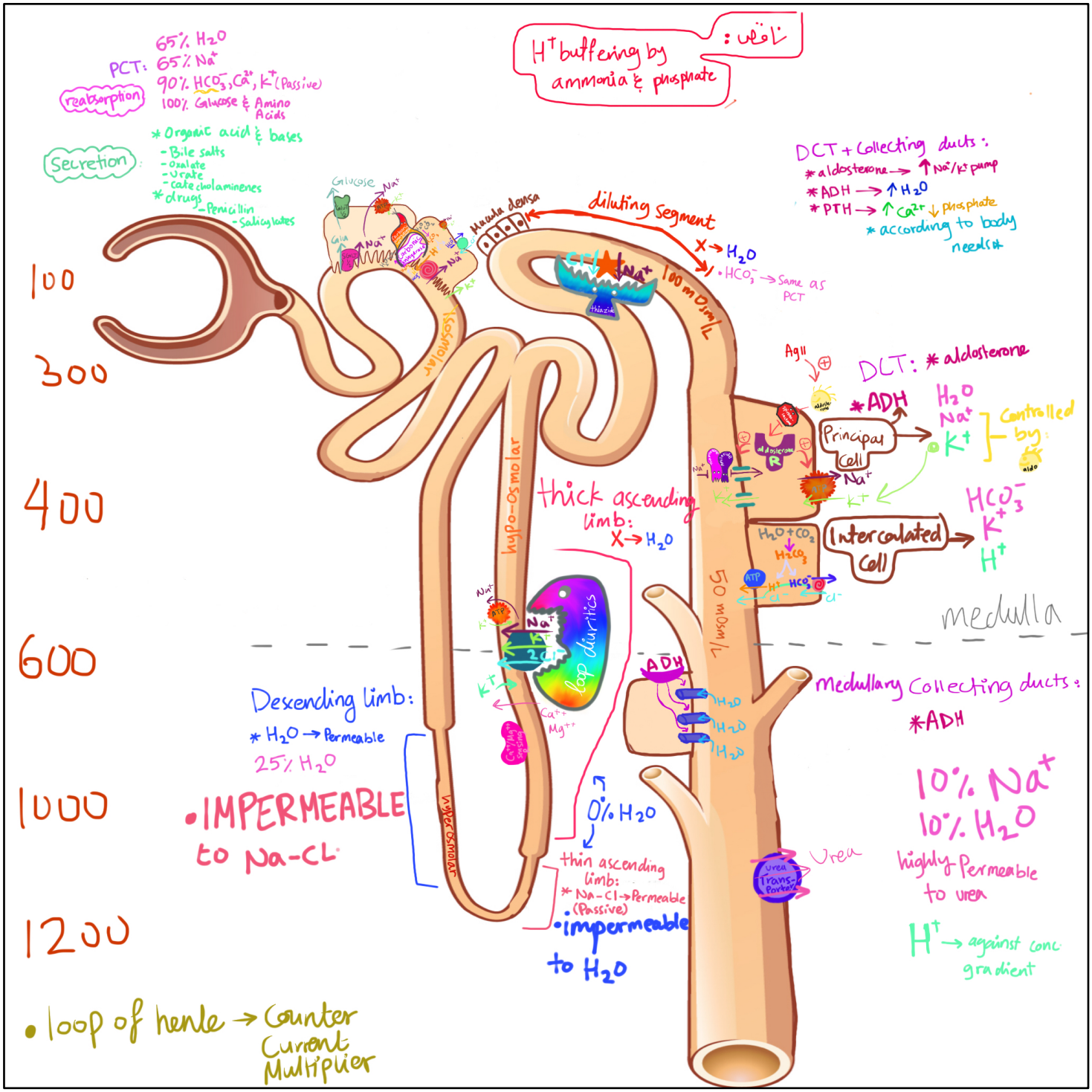


Lecture 9&10: Basics of Acid Base & Buffer Systems

pH↑ = ↓H+ = **Alkalosis** pH↓ = H↑ = **Acidosis**

- **pH=7.35 - 7.45**
  - 6.8 - 8 more or less death occurs
  - **Why important?** 1- Enzymes function 2- Effect electrolytes
    3- Effect hormones 4- Maintain normal synapse

- **Sources of acids?** Food, Metabolism of protein and lipid and cellular metabolism.
- **Body defense:**
  - **1st line = Chemical buffer system**
    - ✓ **Bicarbonate:**

      Components: Sodium bicarbonate (NaHco3) and weak acid (carbonic acid)

      Acts: in both extracellular(most important) and intracellular.

      Concentration in blood =22-27 mEq/L
    - ✓ **Phosphate:** Major intracellular
    - **Why important in renal tubules?**

      1- Concentrated (low permibility cannot be reabsorbed easily)

      2- Pka=6.8 (close to PH in tubular fluid)
    - ✓ **Protein:** most abundant (Hb,plasma protein,intracellular protein)

  - **2nd line = Physiological buffers**
    - ✓ **Respiratory Mechanism**
      - Only volatile Gas ,not Fixed gases like Lactic acid
      - Sense the changes by chemoreceptors
      - Central chemoreceptor sense Co2 ,Prepheral sense H2,Co2
      - Buffers by hyperventilation > wash Co2 (in acidosis)
      - Hypoventilation > accumulates Co2 (in alkalosis)
    - ✓ **Renal mechanism** *most effective buffer*
      - **Action by 3 main process:**

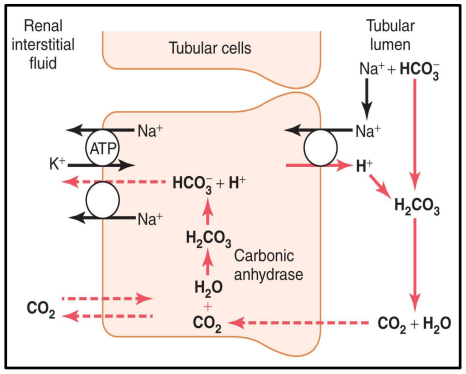
        1-Reabsorb HCO3

        2-Generate new HCO3

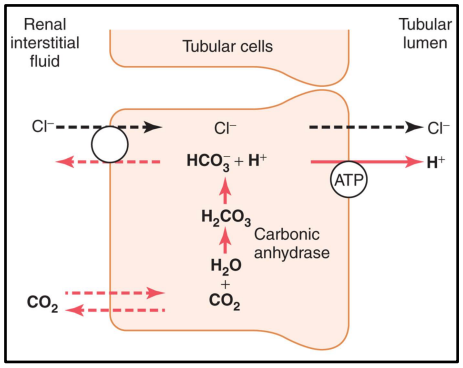
        3-Excrete H+
      - **To excrete H+ it has to be buffered:**
        - **Ammonia forming ammonium NH3>NH4**
        - **Phosphate forming di-hydrogen phosphate**
      - In PCT H+ secreted & New one molecule of HCO3 is formed (doesn't affect PH)
      - In DCT & Collecting tubules gets rid of 80 mEq of H+ per day ,most of H+ combine with buffers but still it affect urine acidity (and also for each H+ there is New HCO3 formed).

Lecture 9&10: Basics of Acid Base & Buffer Systems cont.

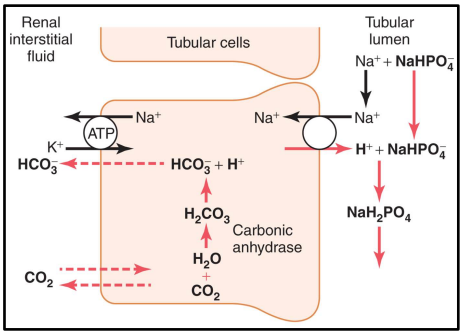
Reabsorption of HCO3 & secretion of H+ In PCT



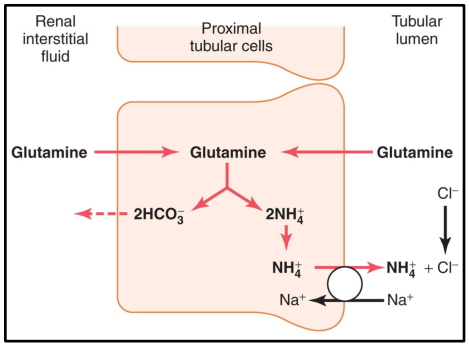
Generation of new HCO3 & secretion of H+ In DCT & Collecting tubules

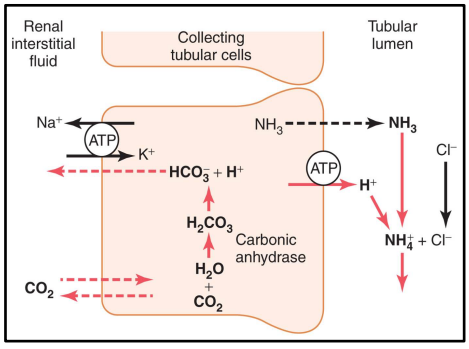


Secretion of H+ & Phosphate Buffer



Secretion of H+ & Ammonium formation and Bufffer





Lecture 11: Disorders of Acid Base

- **What is Respiratory Acidosis?**

↑ in PCO2 (above 45 mmHg)

- **What are the possible causes ?**

- Depression of respiratory centres
- Paralysis of respiratory or chest muscles.
- Emphysema/COPD.
- Pulmonary edema.

- **How will the body compensate?**

1- Renal: reabsorption & forming new HCO3 (↑ plasma HCO3)
2-Buffers

- **What is Respiratory Alkalosis?**

An ↓ in PCO2 (below 45 mmHg)

- **What are the possible causes?**

- Oxygen deficiency at high altitudes.
- »timulate respiratory centres lead to decrease in plasma PCO2(caused by hyperventilation)

- **Compensation:**

By renal increased renal excretion of HCO3

- **What is Metabolic Acidosis?**

↓ in HCO3 (below 22 mEq/L)

- **Causes:**

- Loss of bicarbonate e.g. severe diarrhea.
- Hypoaldosteronism.
- Accumulation of acids e.g. Diabetic ketosis

- **Compensation:**

1- Respiratory: By Increased ventilation rate
2-Renal : By adding new HCO3 to the ECF

- **Metabolic Alkalosis**

↑ in HCO3 (above 27 mEq/L)

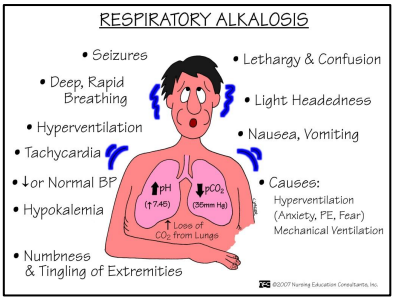
- **Causes:**

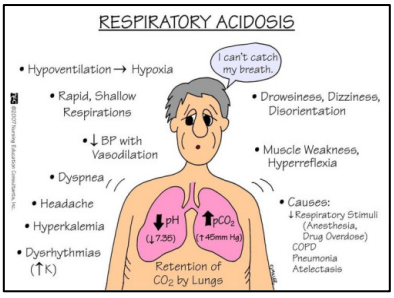
- Excess vomiting = loss of stomach acid.
- Excessive use of alkaline drugs.
- Certain diuretics.
- Endocrine disorders: Hyperaldosteronism.
- Severe dehydration

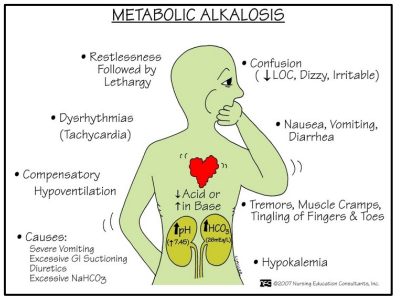
- **Compensation:**

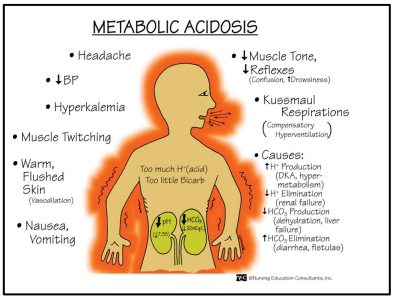
1- Respiratory: By Decreased ventilation rate, which raises PCO2.
2-Renal: By increasing HCO3 renal excretion

Lecture 11: Disorders of Acid Base cont.

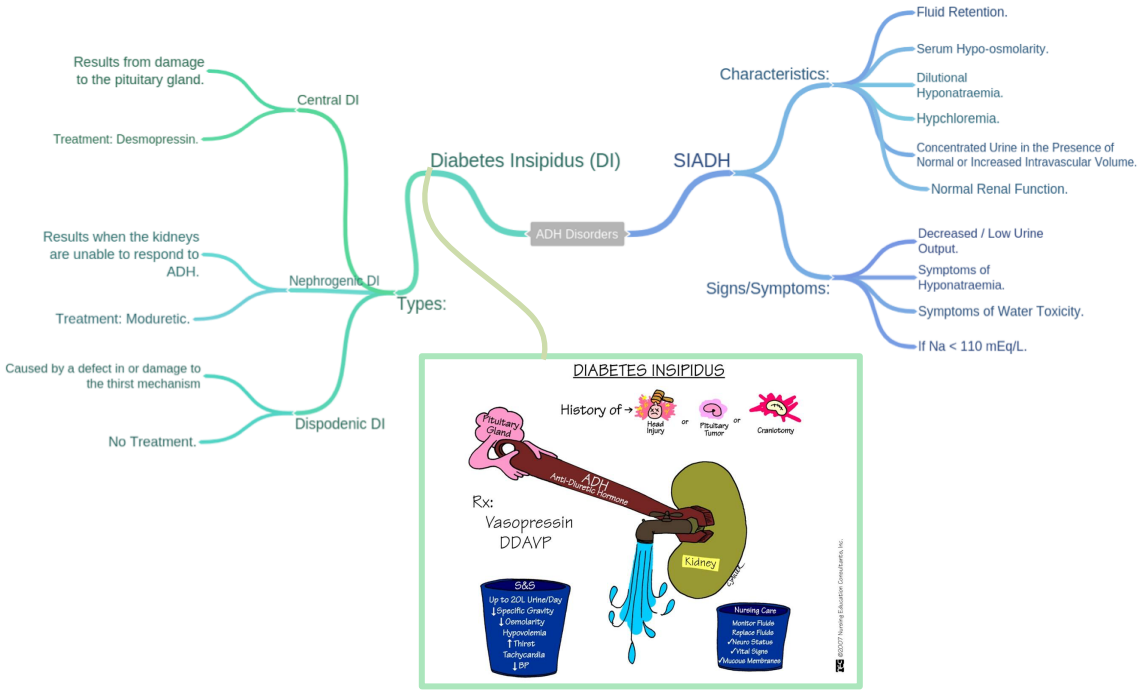








✧ Disorders of ADH secretion:



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