Physiology lecture 5,6 + some notes from Pharmacology lectures.

Renal threshold: (1st appearance of the substance in urine)
High threshold: Glucose, amino acid, vitamins. Medium threshold: K+, urea.
Low threshold: Phosphate, uric acid. No threshold: Creatinine, Mannitol, inulin.

Tubular transport maximum: It is the maximal amount of a substance (in mg) which can be transported (reabsorbed or secreted) by tubular cells/min.
Tmax for the kidneys, which is normally about 375 mg/min, is reached when all nephrons have reached their maximal capacity to reabsorb glucose

Transported substances move through three membranes:
– Luminal and basolateral membranes of tubule cells
– Endothelium of peritubular capillaries
Ca2+, Mg2+, K+, and some Na+ can be reabsorbed via paracellular pathways.

Transport through:	-

Proximal convoluted tubules (Isosmotic)

Type of Diuretic work here:
1-Carbonic anhydrase inhibitors, inhibits (CA) enzyme in proximal convoluted tubules thus interferes with NaHCO3 re-absorption and causes diuresis.
2-Mannitol

Reabsorption Coarse adjustment	**Secretion**
● Leaky epithelium permeable to ions & water (67% of filtered water get reabsorbed here) ● ~ 70 % of Na+, Cl-, K+, water absorbed passively (follows Na)	Endogenous: End products of metabolism. Bile salts. Creatinine. Catecholamines (adrenaline noradrenailne) Exogenous:: Penicillin NSAIDs (e.g. ibuprofen) Morphine

In the Early segment:	**In the Mid segment:**	**In the Late segment:**
Sodium is reabsorbed by: 1-co-transport along with Glucose, Amino acid. 2-exchanged with H+,but HCO3- reabsorbed .	About 40-70% of filtered load of urea is reabsorbed	Na+ reabsorbed mainly with Cl-. 1-transcellular: Na+ entry using NHE & 1 or 2 Cl-- anion antiporters 2-Paracellular: Passive diffusion

Loop of henle

Type of Diuretic :
1-loop diuretic , Inhibit Na+ / K+ / 2 Cl- co-transporter, Inhibit Ca & Mg re-absorption.
2-2-Mannitol on Descending limb

Descending	Thin Ascending	Thick Ascending	Special Carrier
-H2O permeable -permeable to water (filtrate hyperosmotic)	-H2O impermeable -Solutes (NaCl) permeable, absorbed passively.	-Impermeable to water (isosmotic) -Important in concentrating urine -25% NaCl, K+ reabsorbed as well as Ca2+, HCO3-occurs in	**1Na,2Cl,1K co-transport** -The filtrate is **hypo-osmotic** due to the absorption of solute without water.

Distal convoluted tubules (ADH dependent)

- About 40-70% of filtered load of urea is reabsorbed
- 7% NaCl, 8–15%water reabsorbed (needs ADH), Some K+, H+ secreted into tubule.
- Type of Diuretic work here: Thiazide diuretic ,acts via inhibition of Na/Cl co-transporter on the luminal membrane of distal convoluted tubules.

Early duct	Late duct	
Reabsorbs Na+,Cl- (impermeable to water)	Principal cells	Intercalated cells
	Reabsorb Na+ Reabsorb water secrete K+ Aldosterone: ↑ Na reabsorption by principle cells, ↑ K+ secretion	Secrete H+ Reabsorb HCO3- Reabsorb K+

Medullary collecting Duct

- About 40-70% of filtered load of urea is reabsorbed
- The permeability of the medullary collecting duct to water is controlled by the level of ADH.
- Reabsorb <10% of sodium & H2O.
- Highly permeable to urea It has a role in acid base balance by secreting H+ against concentration gradient.
- Final site for processing urine so determine final urine output of H2O and solutes.
- Type of Diuretic work here: K-Sparing diuretic, Act in collecting tubules and ducts by inhibiting Na re-absorption and K & H excretion (blocking NA channels + antagonizing aldosterone)

Glucose reabsorption:	1-From tubular lumen to tubular cell: Sodium co-transporter (Carrier-mediated secondary active transport). 2-From tubular cell to peritubular capillary: Facilitated diffusion (Carrier-mediated passive transport)
Urea reabsorption:	-Normal plasma level of urea 2.5-6.5 mM/L (15-39 mg/100ml) -Due to water reabsorption in the first half of PCT, the conc. of urea is increased in the second half and urea is reabsorbed by simple diffusion (downhill) اليوريا يبدأ ٥٠٪ ريابسوربشن بالبروكسمال الباقي ال٥٠٪ يروح للوب اوف هنلي خصوصا اللونق منه و يصير ل٦٠٪ منه سكريشن ٥٠+٦٠=١١٠ و راح يكون الريمينق ١١٠ في الكوللكتق دكت +تبيول و لازم هنا اكتف ريابسوربشن لليوريا بواسطة الانتي ديورتك هرمون ٧٠٪ يصير له ري ابسوربشن ٤٠٪ راح يصير فلترد
Sodium reabsorption:	Primary Active Transport - Na+ enters the tubule cells at the luminal membrane then it's actively transported out of the tubules by a Na+-K+ ATPase pump
Water reabsorption:	-PCT cells permeable to water, Reabsorbs 67% of filtered water. -Transtubular Passive (osmosis), due to osmotic active substances that are absorbed, ↓ tubule osmolality ↑ intracellular space osmolality Solvent drag: K+, Ca2+, carried with water & hence reabsorbed
Bicarbonate reabsorption:	The renal tubules are poorly-permeable to HCO3–. However, it is still reabsorbed but in the form of CO2 (to which the tubules are very highly permeable). This occurs through the following steps: 1. H+ is formed inside the cells then secreted in the tubular fluid. 2. H+ combines with HCO3– in the tubular fluid forming H2CO3. 3. By activity of the Carbonic anhydrase enzyme in the tubular cells, H2CO3 dissociates into CO2 & H2O. 4. CO2 diffuses into the cells where it combines with H2O (by activity of an intracellular C.A.), forming H2CO3 which dissociates into HCO3– & H+. 5. HCO3– passively diffuses into the interstitial fluid (then to the blood) while H+ is secreted into the tubular fluid to help more reabsorption of HCO3–. Factors affecting Bicarbonate reabsorption: Arterial Pco2,Plasma[K+],Plasma Aldosterone,Plasma [cl-]
Protein reabsorption:	reabsorbed in PCT, Undergo Endocytosis into PCT, either intact or after being partially degraded by enzymes, Once protein inside the cell, enzyme digest them into amino acids, which leave the cell to blood. Has a maximum capacity - too much protein filtered = proteinuria

Physiology Lecture 7 regulation of body fluids

ICF vs ECF: 1-Ionic **composition very** different 2-Total ionic **concentration** very similar 3-Total **osmotic concentrations** virtually identical	1-Body water balance must be **maintained.** 2-Kidneys concentrate or dilute urine. 3-To remain hydrated, **water intake must equal water output**. 4-Increases in plasma osmolality trigger thirst and release of (ADH)

Control of circulating volume: All down to Na+ balance.

Volume sensors (Effectively pressure receptors):

a) Vascular:

1-Low pressure sensors: Cardiac atria (ANP), pulmonary vasculature.

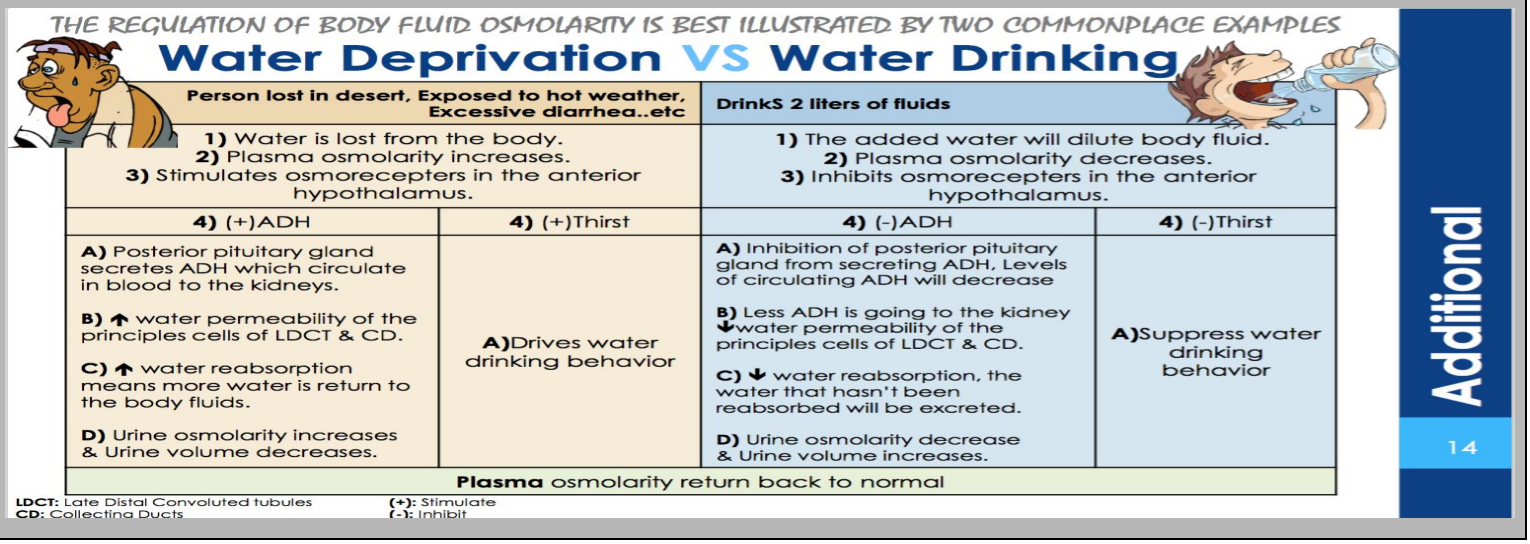
2-High pressure: carotid sinus, aortic arch and juxtaglomerular apparatus of the kidney.

b) Central nervous system.

c) Hepatic.

Volume sensor signals/Mediators:

Neural	Hormonal
If pressure ↓ Renal sympathetics: **1) afferent & Efferent arterioles constrict** i) GRF ↓ ii) less Na+ filtred iii) more Na+ absorbed by PCT **2) renin released** i) ↑ aldosterone ii) ↑ angiotensin II	**1-Renin-angiotensin-aldosterone system (↓ pressure):** **Renin secreted, by**: a) Sympathetic stimulation b) ↓ perfusion pressure c) ↓ Na+ reaching macula densa **Angiotensin II:** i) aldosterone release by adrenal cortex ↑ Na+ reabsorption ii) Vasoconstriction iii) ADH release iv) ↑ Na+ reabsorption in PCT **2-ANP (atrial nitric peptide):** From atrial myocytes Released by stretch of atrium ⇒ ↑ NaCl & water excretion **Antagonist of renin-angiotensin**: i) vasodilation of afferent arteriole, vasoconstriction of efferent ii) ↓ renin release iii) direct ↓ aldosterone release iv) ↓ Na+ reabsorption in CD v) ↓ ADH release



Physiology Lecture 8 (Urine concentration): a very important lecture.

Countercurrent system:
A system in which inflow runs parallel and in close proximity but opposite to the outflow.
The operation of such a system allows the outgoing fluid to heat the incoming fluid.
-Loop of henle primary function is: to determine osmolarity of urine using Countercurrent multiplier system
-While collecting duct is where urine concentration is determined .

Mechanism of urine concentration depends on:
1-HYPERosmotic Renal medullary interstitium fluid (cortico.papillary osmolarity gradient)
Body function best at osmolarity of 290.
2- Antidiuretic hormone.

Concentrated urine (ADH DEPENDENT).	Dilute urine (LOW OR NO ADH)
1-Isosmotic fluid from PCT 2-thin descending limb permeable to water , less for NaCl 3-Thin AL impermeable to water, permeable to NaCl (passive). Volume unchanged , NaCl 4-Thick AL impermeable to water. NaCl reabsorbed (Active) diluting tubule fluid 150 mOsm/kg water. 5-Fluid reaching CD hypoosmotic (due to urea).ADH causes water to diffuse out up to a max of 300 mOsm/kg water 6-Osmolality of medullary tissue high up to 1200 mOsm/kg water .early CD impermeable to urea 7-ADH allows water reabsorption(passive). When ADH levels high urea levels in medullary collecting duct and interstitium equilibrate. Most of water reabsorbed in the cortical collecting duct.	1-Isosmotic fluid from PCT 2-thin descending limb permeable to water , less for NaCl 3-Thin AL impermeable to water, permeable to NaCl (passive). Volume unchanged , NaCl 4-Thick AL impermeable to water. NaCl reabsorbed (Active) diluting tubule fluid 150 mOsm/kg water. 5-Collecting duct reabsorb NaCl. osmolality which reach 50 mOsm/kg water

Diabetes Insipidus	Nephrogenic Diabetes Insipidus	Diabetes Mellitus
Cause		High specific gravity urine (concentrated urine)
Inability to produce or release ADH	Inability of kidney to respond to ADH	
• Urine : low fixed specific gravity (diluted urine) • Polyuria[1] • Polydypsia[2]	Urine : low fixed specific gravity (diluted urine)	

Diuretics (Lectures 4,5 and 6)

Therapeutic Use	Drug	mechanism	Extra
Open Angle Glaucoma	Acetazolamide (Carbonic Anhydrase Inhibitor)	↓ Iop By Reducing Aqueous Humor Formation In Ciliary Body Of Eye.	
Prophylactic Therapy For Acute Mountain Sickness	Acetazolamide (Carbonic Anhydrase Inhibitor)	↓ Csf Of Brain	Given Nightly 5 Days Before The Ascent ↓ Weakness, Breathlessness , Dizziness, Nausea, Cerebral & Pulmonary Oedema.
Epilepsy	Acetazolamide (Carbonic Anhydrase Inhibitor)	Decrease Cerebrospinal Fluid, CSF	
Cystinuria	Acetazolamide (Carbonic Anhydrase Inhibitor)	Urinary Alkalinization To Enhance Renal Excretion Of Acidic Substances (Cysteine)	
Epilepsy	Acetazolamide (Carbonic Anhydrase Inhibitor)	Decrease Cerebrospinal Fluid, CSF	
Hyperphosphatemia	Acetazolamide (Carbonic Anhydrase Inhibitor)		
Metabolic Alkalosis	Acetazolamide (Carbonic Anhydrase Inhibitor)		
Open-Angle Glaucoma	Dorzolamide (Carbonic Anhydrase Inhibitor)		Used Topically
Acute Renal Failure Due To Shock Or Trauma	Mannitol (Osmotic Diuretics)	Maintain Urine Flow- Preserve Kidney Function	
Acute Drug Poisoning	Mannitol (Osmotic Diuretics)	To Eliminate Drugs That Are Reabsorbed From The Renal Tubules E.G. Salicylates, Barbiturates.	
Cerebral Edema	Mannitol (Osmotic Diuretics)	To ¯ Intracranial & Intraocular Pressure Before Ophthalmic Or Brain Procedures	
Emergency Edema Associated with Congestive Heart Failure	Loop Diuretics	-Inhibit Na+/ K+/2Cl- Co-Transporter In The Luminal Membrane Of The Thick Ascending Loop Of Henle.	Given Orally Or I. V.
Emergency Nephrotic Syndrome	Loop Diuretics		Given Orally Or I. V.

Emergency Acute Pulmonary Edema	Loop Diuretics	-Inhibit Ca++ And Mg ++ Re-Absorption.	Given Orally Or I. V.
Emergency Acute Hyperkalaemia	Loop Diuretics		Given Orally Or I. V.
Emergency Acute Hypercalcemia	Loop Diuretics		Given Orally Or I. V.
Hypertension With Renal Failure	Loop Diuretics		
Edema with Impaired Renal Function	Loop Diuretics		
Severe Congestive Heart Failure (Especially When GF Is Lowered)	Loop Diuretics		
Renal Failure (GFR < 40-50 Ml/Min)	Loop Diuretics		Increasing The Dose With As GFR Goes Down.
Life-Threatening Acute Pulmonary Edema	Furosemide (Loop Diuretics)		
Essential Hypertension	Thiazide Diuretics		Used Alone Or In Combination With Betablockers At Low-Dose (Fewer SE)
Mild Heart Failure	Thiazide Diuretics		
Calcium Nephrolithiasis Due to Hypercalciuria	Thiazide Diuretics	To Increase Calcium Re-Absorption And Decrease Renal Calcium Stones	
Nephrogenic Diabetes Insipidus	Thiazide Diuretics	Decrease Blood Volume And Gfr	
Mild Edema with Normal Renal Function	Thiazide Diuretic		
Mild Congestive Heart Failure With Normal Renal Function	Thiazide Diuretic		
Renal Failure (GFR ≥ 40-50 Ml/Min)	Thiazide Diuretic		
Diabetes Inspidus	Thiazide Diuretic		Reduces Urine Volume

Hepatic Cirrhosis	Potassium-Sparing Diuretics		Drug Of Choice
Secondary Hyperaldosteronism (Chf, Hepatic Cirrhosis, Nephrotic Syndrome)	Potassium-Sparing Diuretics		Iv
Hypertension	Potassium-Sparing Diuretics		Combined With Thiazide Or Loop Diuretics To Correct Hypokalemia
Hepatic Cirrhosis with Ascites	Spironolactone (Potassium-Sparing Diuretics)		Drug Of Choice

Pathology of Nephrotic and Nephritic Syndromes (Lectures 4 and 5)

*Big Thank for the 435 Pathology Team

1. **Nephrotic syndrome:**
   - Heavy proteinuria
   - **Minimal change disease:**
     - § Diffuse Epithelial Cell Disease
     - § Young children.
     - § LM Normal under the microscope.
     - § EM Effacement of epithelial foot processes
     - § Good response to corticosteroid therapy
   - **Focal segmental glomerulosclerosis:**
     - § Sclerosis within capillary tufts.
     - § Increased matrix
     - § Obliteration of capillary lumina
     - § Higher incidence of hematuria & hypertension.
     - § Poor response to corticosteroid therapy.
   - **Membranous glomerulonephritis:**
     - § Azotemia
     - § Spike and dome appearance
     - § Deposits of IgG or C3
     - § Thickened capillary walls
     - § Mostly caused by autoantibodies that cross-react with antigens expressed by podocytes.
   - **Diabetic nephropathy:**
     - § Kimmelstiel-Wilson nodules
     - § EM thickness of glomerular basement membrane
   - **Renal amyloidosis:**
     - § Mesangial amyloid deposits
     - § Congo red stain
     - § Crisscross fibrillary pattern
     - § Apple green birefringence under polarized light
   - **Lupus Nephropathy:**
     - § Deposition of DNA and anti DNA complexes within the glomeruli.
     - § Spike and dome pattern by silver methanamine (jones) stain

- Class one: Normal.
- Class two: Mesangial lupus glomerulonephritis. Immune complex deposits in the mesangium
- Class three: Focal proliferative lupus glomerulonephritis. Swelling and proliferation of endothelial and mesangial cells with neutrophilic infiltration or fibrinoid deposits and capillary thrombi.
- Class four: Diffuse proliferative lupus glomerulonephritis. Similar to class 3 but more diffuse. Immune complexes depositions create an overall thickening of the capillary walls, which resembles rigid “wire loops” on LM.
- Class five: Membranous lupus glomerulonephritis. The patients have severe nephrotic syndrome and there is thickening of the capillary walls due to deposition of basement membrane like material as well as immune complexes.

2. Nephritic syndrome:

- Increase cellularity.
- Proliferation of cells.
- Pigmented granular casts.
- **Poststreptococcal glomerulonephritis (acute proliferative glomerulonephritis):**
  - § Infection
  - § Nephritogenic strains of group A B-hemolytic streptococci.
  - § Urinary red cells and red cell casts
  - § Decreased serum C3
  - § Increased titers of anticationic proteinase (ASO)
  - § EM Humps.
  - § Immunofluorescence Lumpy bumpy.

3. RPGN:

- Progresses rapidly to renal failure
- Crescentic
- Severe glomerular injury.
- EM ruptures in GBM
- Immunofluorescence IgG and C3
- **Type I, anti-GBM disease: (Good pasture syndrome)**
  - § Nerve deaflines and ocular disorders
  - § Hereditary nephritis
  - § Clinically manifested as the nephritic syndrome
  - § Hemorrhagic pneumonitis
  - § Caused by mutation in the gene for the 5-chain type IV collagen
- **Type II, Immune Complex-Mediated Crescentic Glomerulonephritis:**
  - § Granular ("lumpy bumpy") pattern of staining
  - § Severe injury in the form of segmental necrosis
  - § Immunofluorescence **Granular pattern** of immune complex disease
  - § EM demonstrates discrete deposits.
- **Type III, pauci immune (ANCA-associated)**
  - § RPGN is without immune complex deposition or antiglomerular basement membrane antibodies.
  - § Associated with ANCAs.
  - § Segmental necrosis
  - § Oliguria and azotemia are more pronounced
  - § **Wegener's granulomatosis/ microscopic polyangiitis:**
    - Transmural necrosis.
- **Membranoproliferative glomerulonephritis**
  - o Endocapillary proliferation and glomerular basement membrane splitting (double contour) "tram-track" appearance.
  - o Lobular appearance.
  - o GBM thickened.
  - o **Type I:**
    - § **Caused by circulating immune complexes**.

        - § Association with **hepatitis B and C antigenemia**.
    - o **DDD:**
        - § **Excessive complement activation.**
        - § Mutations in the gene encoding the complement regulatory protein **factor H.**
        - § Membranoproliferative pattern
        - § DDD carries worse prognosis than type I..
- **Asymptomatic hematuria/proteinuria:**
    - o Microscopic hematuria with red cell casts
    - o **Alport syndrome:**
        - § Alternating areas of extreme thinning of the glomerular basement membrane
        - § Thick, irregular areas with basket weaving are shown.
    - o **IgA nephropathy (Berger disease):**
        - § Benign recurrent hematuria (gross or microscopic) – stays for several days then subsides only to recur once again.
        - § Deposition of IgA in the mesangium
        - § Abnormality in IgA1 production
        - § Increased frequency in individuals with celiac disease.
        - § Can be a component of the Henoch- Schonlein vasculitis disease.
        - § Children + Young adults.
        - § Focal glomerulonephritis may be the presenting feature

4. Chronic kidney disease:

- o Results from any type of kidney disease
- o It's the result of **progressive scarring**
- o **It leads to end-stage kidney disease.**

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