Sheet ○ Slide ○ Handout

Number

6

Subject

Na^+ & K^+ homeostasis

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** This sheet was written acording to section 1 records with a different arangment.*
** Main topics; Reabsorption and secereton along different parts of the Nephron, Na+ hemostasis and K+ homeostasis .*

❀ Reabsorption and secereton along different parts of the Nephron

Fig-1 → The **X-axis** indicate **parts of Nephron** (proximal tubule, loop of Henle, distal tubule, and collecting duct) while the **Y-axis** indicate **tubular fluid/ plasma concentration ratio**;this diagram shows how each segment/ part of Nephron handle different substances, for example:

- **Na^+** concentration in the proximal tubule **remains the same**, then it will **increase** in descending limb of Henle (this portion is permeable to water not to sodium) but in ascending limb of Henle, Na+ **decrease** even beyond the original value.
- **Creatinine** is increasing.
- What is **increasing** more than Creatinine is para amino hippuric acid (**PAH**) because there is **secretion**; the ratio increase to 10, 15 folds, eventually reaching **585** fold.
- **Amino acids and glucose** become **zero** before they leave the proximal tubule (all are totally reabsorbed so their concentration in the Tubular Fluid = 0 & the ratio = 0)
- **Bicarbonate** (HCO_3^-) → we don't tolerate losing bicarbonate in the urine that's why **all the Nephron reabsorbs bicarbonate**
  (Note: according to the figure; HCO_3^- in tubular fluid / HCO3- in the plasma will be 0.1 → its wrong; this is too much).
- Note: in the Y-axis; above **1** → ↑ tubular concentration of the substance → ↑ **secretion**
  Below **1** → ↓ tubular concentration → ↑ plasma concentration → ↑ **reabsorption**
- The kidney is the major organ in regulating Na+ and K+ concentrations

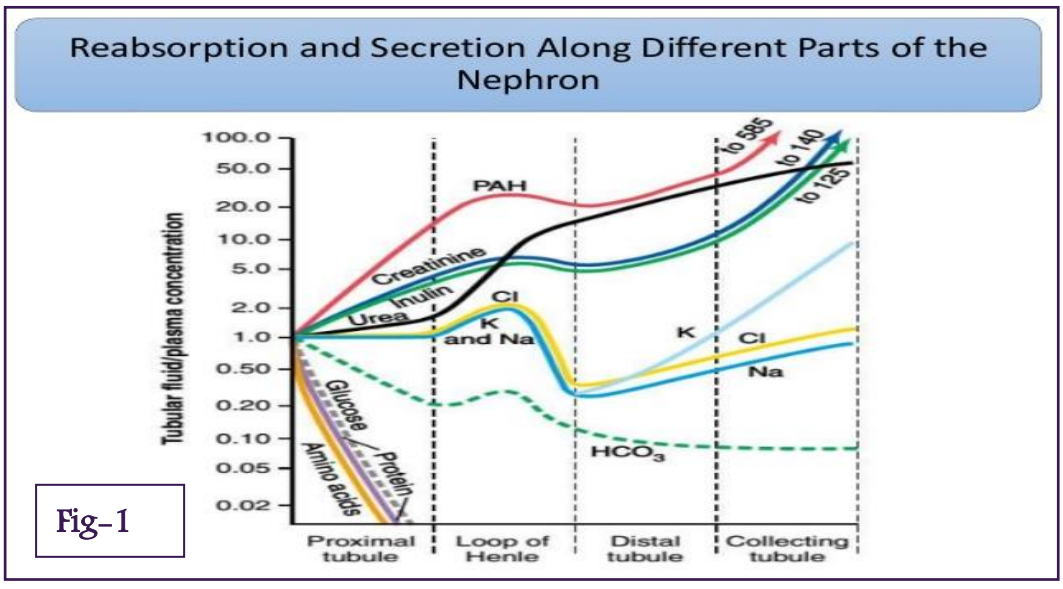
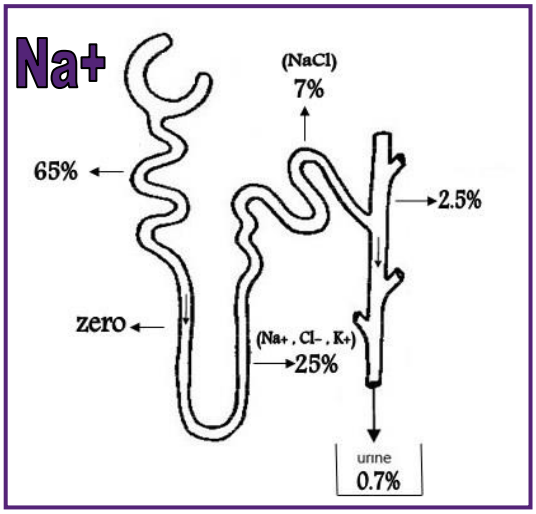


Fig-1

Na⁺ Homeostasis



- Two thirds (65%) of **Na+** is reabsorbed in the proximal tubule
- Zero reabsorption in the descending limb of Henle
- **25% reabsorption in the ascending limb of Henle** (co-transport of Na+, Cl- and K+),
- 7% reabsorption in the distal tubule (as NaCl)
- 2.5% reabsorption in the collecting duct.

GFR = (125ml/day) * (60min/h) * (1L/1000ml) = **180 L/D** (24h/day)*

✓ Normal Na^+ intake per day = **155 mmol/day**,

- **150** are removed through the kidney (150 per 1.5 liter of urine → **100 per 1 liter**)
- **5** are removed through other sources

→ **So the kidney is the major organ regulating Na^+ concentration in our body**

✓ what we **excrete is 0.7% of Na+** , because:

Na+ Filtered load = (P_{Na+} * GFR) = (140 * 180 L/D) = 25,200

What we excrete in the urine = (Na+ removed through the kidneys / Filtered Load) * 100%

→150/25,200 * 100% = **0.7%**

✓ **Na^+** filtered load is extremely high, so the clearance of Na+ equals:

$C_{Na} = (U_{NA}/P_{Na}) * \dot{V} = 100/140*1 \rightarrow$ <1 ml

❖ Na+ homeostasis is regulated by 3 factors:-

1st factor → GFR

- If you ingest too much Na+, it will:
  - Increase your **ECFV** (extracellular fluid volume), this will result in: **decreased colloid osmotic pressure** (decrease in protein concentration) → ↑ **GFR**
  - Increase **blood volume** and decrease **blood flow** → ↑ **GFR**.
  - Increase in **blood pressure** (P)→ ↑ **GFR**

Note: when you increase blood volume and blood pressure, **sympathetic stimulation decreases** (sympathetic cause vasoconstriction for the afferent arteriole → If no vasoconstriction → Afferent arteriole vasodilation→ ↑ blood flow to the kidney, thus higher GFR).

- **Increase in GFR will get rid of this excess Na+ you ingested.**
- ↑ GFR ↑ Na+ excretion

Note: If you have increased **Na+ intake** that result in increase in **ECFV,** eventually this will increase **ANF** (3rd factor).

- 2nd factor → Aldosterone

- Excess **Na^+ intake** will inhibit aldosterone → resulting in decreased Na+ reabsorption.
- Remember: Aldosterone increase Na+ reabsorption and K+ secretion.
- Aldosterone is a **steroid**.
  - Steroids don't see barriers in their eyes (just like O_2, CO_2 and thyroid hormone); they **cross the membrane** (which is lipid bilayer) as it doesn't exist. Therefore; their receptors are inside the cell (not outside the cell/not on the cell membrane)- intracellular receptors, and sometimes intranuclear.
  - All Steroids makes mRNA which makes proteins and that requires time (2 hours): Steroid binds to the receptor → translocate to the nucleus → transcription → mRNA → proteins.
- Aldosterone act on the **distal tubules** (on the **principle cells** there) and does 4 things:

1) It facilitates the formation of proteins, so **it inserts Na+ and K+ channels on the luminal membrane** (these channels are nothing but proteins).
2) It makes **Na+/K+ pump (proteins) on the basolateral membrane;**
   (2 K+ enter -from low to high conc.- ||| 3 Na+ leave -from low to high conc.-)

> *Note:* By activating this pump, we increase K+ concentration inside the cell (it's already high there = 150 mM), so we make a **gradient for K+ secretion** → high intracellularly & low in the lumen of distal tubule.

3) **It makes the enzymes needed to make ATP for the pump.**

4) **It helps in making the proteins which facilitate the diffusion of sodium** (for facilitated transport).

- **3rd factor → ANP**

Note: In the past, the **3rd factor** was unknown -we just knew that there is a 3rd factor- after studies, it was identified as a **peptide** so we called it **ANP** (Atrial natriuretic peptide), then they found out that it is secreted from a place (right atrium) but affect another place (kidney) and due to this fact, they called it a **hormone (ANH).**
So different names across ages (factor, peptide, hormone) and **you can find it with**

- **It's released from the right atrium upon expansion (volume receptors).**
- By ingesting excess Na+ → increased ECFV → **hypervolemia** → **ANP** is released
- **It's the only hormone which promotes the increase in Na^+ excretion**
- **ANP** does 3 things:
  - **Dilates the afferent arteriole,** making more blood available to the glomerulus → higher GFR, thus more Na+ excretion .
  - **Inhibits aldosterone secretion** → inhibits Na+ reabsorption.
  - **Directly inhibits Na+ reabsorption** at the distal parts.

❖ Again, in the thick ascending limb 25% of Na+ reabsorption will occur, therefore **making the interstitium hyper-osmolar**.

➔ That will give the chance of **making concentrated urine,** and by this you'll be able to **retain & conserve body water.**

(Drinking too much water makes diluted urine, diluted urine means you get rid of water)

➔ **This is the most important function of the tubules;** **which is the ability of the tubules to make concentrated urine or diluted urine**

- **Acute renal failure** is somehow common; any patient with vomiting or diarrhea should be sent to the clinic and should be given IV fluid to avoid acute renal failure.

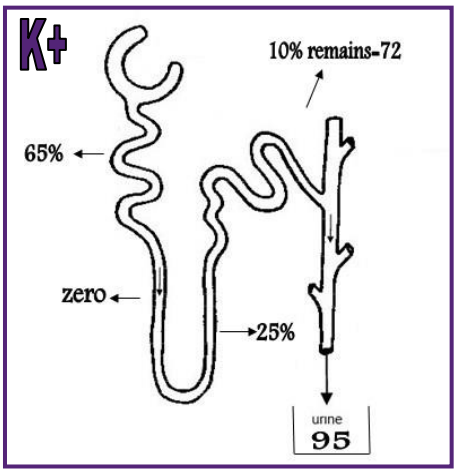
  - ➔ In Acute renal failure **urine output will decrease and urea & Creatinine will increase**. In 85% of cases this is reversible, **but what takes long time to get back to normal is the ability of the kidney to make concentrated urine**.

  - ➔ **If you want to know if the kidney has recovered all of its function;**
    The last test should be is to check if it can make concentrated urine or diluted urine.

    If yes; it means it's **100% normal kidney**.

    Because this is a yubular function, it is the last function to come back to normal.
    (i.e. Urea and Creatinine get back to normal within a weak, but this does NOT mean that the kidney is normal, unless this tubular function is back to normal).

❀ K^+ Homeostasis



❖ K+ intake = 100 mM/day

- The kidney remove **95 mM**
- 5 mM are removed through other routs

→ **So the kidney is the major organ regulating K^+ concentration in our body**

✓ **K+** filtered load = (P_{K+} * GFR) = (4 * 180 L/D) = 720mM/day

➔ 720mM entered bowman's space, **95 mM are removed in urine**.

❖ **K+** balance means → **intake=output**

(positive balance → intake more ||| negative balance → output more).

❖ How does the kidney handle K^+?

- 65% of K+ is reabsorbed in the proximal tubules
- Zero reabsorption in the descending limb of Henle
- **25% reabsorption in the ascending limb of Henle (same as Na+)**
- What is left is **10%**; → 10% of 720 = **72 (70 for simplicity)** but in urine there is **95**! So for sure there is secretion.

So, kidneys handle K+ by Filtration, reabsorption and secretion while they handle Na+ by Filtration and reabsorption

➔ **So K+ in the urine comes from 2 sources:**

- **Filtered not reabsorbed fraction**
- **Secreted**

✓ If you ingest **200** mM of K+ per day, (you ate too much banana or dates or drank Citrus…)

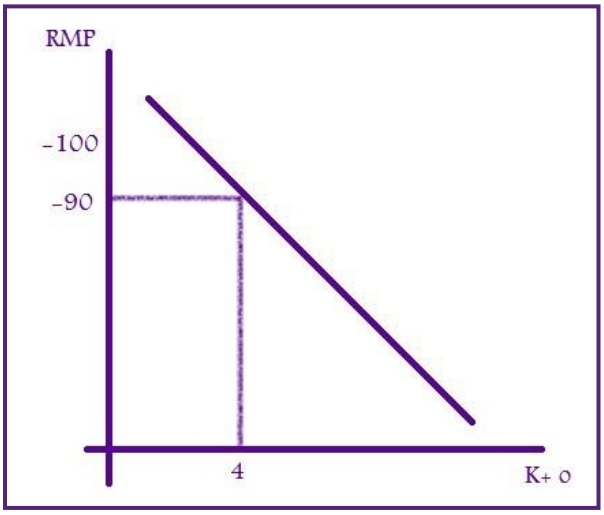
The kidney is still capable of getting rid of this 200, how?

→**70 mM filtered not reabsorbed** & **130 mM secreted**.

Here, the secreted portion is more than the filtered not reabsorbed, which mean that the **filtered load remained the same** (of the 720; 65% are reabsorbed, and 10% remain giving 70 that are filtered not reabsorbed to the urine), but we had **200** mM in the urine, **so 130 mM is secreted.**

So ingestion of **300** mM; **70** filtered not reabsorbed & **230** secreted **OR 400**mM; 70 and 330…

➔ So secreted portion is the most important & filtered portion remains constant.



✓ K+ levels in the blood range from 3.5-5.5 mEq/L.

Below 3.5 → hypokalemia ||| Above 5.5→ hyperkalemia (arrhythmia occurs at both hypokalemia & hyperkalemia), above 7 → cardiac arrest.

✓ If a patient comes with K+ levels above 7 you go for an ECG, If there are any ECG changes → go for dialysis immediately (The purpose of this dialysis is the removal of K+ mainly, NOT urea or Creatinine).

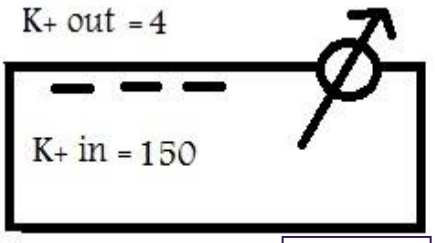


Fig-2

A Flash Back…

ꕥ Nernst equation

E_{K+} = -61 log (K+ in / K+ out)

= -61 log (150/4)

= -61 log 35

= -61 * 1.5 = -90

So, E_{k+} = -90 , what does that mean ?

➔ E_{k+} is the equilibrium potential for K+;

If K+ inside = 150 and outside = 4, according to its gradient it should come out -if its channel is open- ; when it comes out, the cell becomes negative from inside, that will develop electrical force opposing the outward movement of K+.

When the electrical force is equal and opposite to the chemical force → K+ is at equilibrium.

How negative should be the inside? We use Nernst equation.

E_{K+} = -90, E_{Na+} = +61 , E_{Cl-} = +150

➔ Since resting membrane potential of cardiac cells = -90, it equal to E_{K+} that means; Na+ channels and Cl- channels are closed while K+ channels are opened, why ?

→ → **Across the cell membrane, every ion tries continuously (day & night) to bring the membrane potential toward its own equilibrium potential. because every ion tries to live at equilibrium (at rest).**

Which one determines the resting membrane potential? **The one that has its channels open.**

ꕥ According to Nernst equation, if we spot **"K^+ out"** on the X-axis and the **"resting membrane potential"** on the Y-axis we can derive the following curve (Fig-2 up) .

✓ **The more the K^+ out → the less negative the resting membrane potential.**
(4 K^+ out & -90 RMP is normal).

✓ When you increase K^+ out → **(k^+i/k^+o)** will decrease (20 instead of 35 for example) → (-61*log 20) = (-61*1.25) → giving **less negative results** (i.e. the line is moving downwards).

✓ RMP becomes **Less negative** if we **increase K+ out** and it becomes **more negative** if we **decrease K+ out**.

→ **More negative** means **away from threshold** >> **NO excitation** >> **Paralysis**

→ **Less negative** means either the cell become **more excitable** & **closer to the threshold** Or it changes the behavior of the membrane from **fast response action potential to slow response action potential.** (Less negative RMP **cancels fast channels**, so the membrane will work only with the **slow channels** → conduction become sslow & might lead to **cardiac arrest**).

ꕥ Notes:

✓ **Na+** channels are in **3 forms:** (-) Closed active (-) Open (-) **Closed inactive.**

When it becomes closed inactive? **When the membrane potential becomes less negative (close to zero),** so you **cancel the fast channels** (they are inactive now) and work with the **slow channels** instead→ everything have changed, and that's **why arrhythmias occur**.

✓ **Resting membrane potential: the potential across the cell membrane when the cell is resting.**

In the heart, **purkinje cells** are the fastest cells, due to the fact that the slope of **phase zero** is almost = ∞, thus it reaches the maximum level in **no time**, HOW?

→ Cardiac muscles are in **syncytium** (group of cells working together, they work like a domino; if you drop one piece, the other pieces will fall). Phase zero (**Depolarization**) of

the first cell is so fast and is followed by the depolarization of the next cell,so **the depolarization will move from the first cell to the last one in NO TIME**

That's why conduction velocity in the ventricles takes only 0.06 sec.

❀ Back to K+ homeostasis…

✓ Again, K+ intake = K+ output , intake = 100 mM which is excreted by 2 ways; renal and extra renal → the renal is the major rout (95mM)

✓ K+ in the urine comes form: 1- **filtered not reabsorbed**, 2- **secreted**

✓ Remember: K+ outside is normally **4**, and if it exceeded **7** → cardiac arrest!

All extracellular fluid volume (ECFV) = 14 L, after each **meal,** you add **50** mM of **K^+** to this 14L, so **each liter** will take **3.5mM** (=50/14) ; eventually, theoretically speaking, you will end up with **3.5+4 = 7.5 mM/L.** If it's just like this, then you'd die after each meal, but:

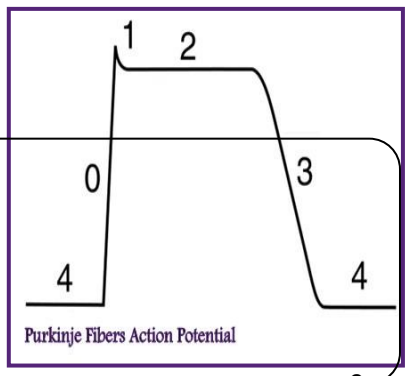
➔ The 50 mM taken after the meal are distributed in the extracellular space making **K+=7.5** and this too much; so **the first objective must be is to push this K+ to inside the cells,** intracellularly, it might become 151,152,…… → that'll be just fine.

➔ Once you eat; **insulin** will be secreted, not to push glucose to the cells but **to push K+.**

- **Clinical note**: If a patient comes with **diabetic ketoacidosis** (high blood glucose = 650), I should give him insulin to push the glucose, but at the same time, insulin will push the K+ **resulting in Hypokalemia** that might result in cardiac arrest! Therefore, that's why I should give the patient **IV K+ supplement along with the insulin**.

✓ At the principle cells, **H^+** should **enter** (inside the cell is a huge reservoir no problem with H+ entering),
if a positive ion entered, another positive ion should **exit to BLOOD**; which it could be **K+** → resulting in **Hyperkalemia**.

- **Clinical note: Acidosis in kidney** → More H^+ exit, trapping K^+ inside the cell & **inhibiting its secretion (to NEPHRON) from the principle cells → Higher chance to go to the BLOOD →**



Hyperkalemia. So most of the time, acute acidosis produces hyperkalemia; If you test the electrolytes → K^+ will be high (5.5-6).

but if **insulin** was given, K levels might drop to 3 for example, resulting in **hypokalemia**.

✓ **So, we conclude that K+ in our body is controlled by 3 hormones:-**

❁ **Aldosterone**

- **The major stimulus for aldosterone secretion is Hyperkalemia** (too much K+ → Aldosterone is immediately secreted).
- It works on the distal tubule to reabsorb Na^+ and secrete K^+.
  - **Clinical note: Conn's disease** → micro tumor making too much aldosterone resulting in **hyperaldosteronism** → excessive Na+ reabsorption → excess water reabsorption → hypervolemia → hypertension.

So this disease is a cause for hypertension and low potassium →hypokalemia.

(Any patient comes with hypertension you should test the electrolytes to know if there is hyperaldosteronism; Conn's is a micro tumor might not be shown in CT scan).

Rem. 90% of hypertension is essential (of unknown origin) & 10% is secondary to different diseases.

❁ **Insulin**

- Push K+ intracellularly, can result in **Hypokalemia**.

❁ **Epinephrine (adrenalin)**

- Also helps in Pushing K+ to inside the cells.
- If somebody is taking **β-blockers** (atenolol, propranolol, concor) → he might have **hyperkalemia** –potentially- ; if he exercise → **adrenalin will activate α-receptors** that increase K+ in the blood, so if he is on **β-blockers** & **exercise severely** he will develop **sever hyperkalemia.**

If Adrenalin works through β receptors → K^+ enter the cell

But if it works through α receptors → K^+ gets out.

✓ **Potassium clearance (C_{k+})** = $(U_k/P_k) * \dot{V} = 60/4*1 = 15$

(U_k = 60 for 1 liter of urine, and 90 or 95 for 1.5 liter of urine per day). Rem.: C_{Na} was <1

That was it,

Best regards ❁