Sheets Physiology

Number: 6

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Correction:

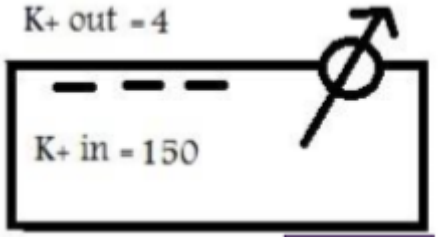
Potassium secretion

In this sheet, we will continue talking about ultrafiltration in kidney but with different substance which is K+.

Here are some informations that you should know about potassium;

- The concentration of potassium **normally** inside the cell = 150 mEq/L, and outside the cell = 4 mEq/L, this concentration should be constant (potassium homeostasis), so if the intake increases, the excretion should increase too but this situation is applicable to a certain concentration, after this concentration the potassium will accumulate in the blood which is very dangerous as we will see later in the lecture.
- Neuronal cell **at rest** has more permeability for K+ than for Sodium, so the equilibrium potential (E_k) for potassium determines the resting membrane potential in this cell;

  E_k = -61 log ([k] inside / [k] outside).



- If the potassium channels open, the potassium will move down its concentration gradient so it will go to outside of the cell but this will generate negative charge inside the cell (because we are removing positive charges from inside the cell so what is left is negative), and this negative charge will prevent further removing of potassium to outside of the cell (keep the rest inside); so we conclude that there are two forces that control movement of potassium across the cell membrane:

  1- chemical gradient (favors outflux)

  2-electrical gradient (favors influx)

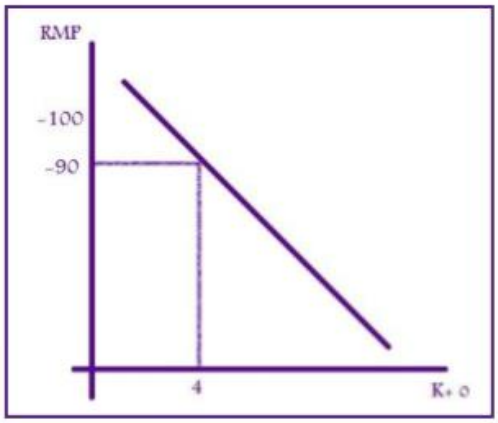
  When these two forces are equal; the potassium reaches its E_k; E_k = -61 log(150/4) = -90 mV and this is the resting membrane potential in cardiac cell (ventricular cell) .*

*side note: in the peripheral neurons the resting membrane potential is less negative than the cardiac cell (around -60mV); but why? Because there is sodium contribution here (Sodium contributes in the resting membrane potential in these cells and when it gets inside it makes the resting membrane potential less negative).

So what happens if the K+ concentration outside the cell becomes more (we will explain how it become more in the next section)?

To answer this question you should know first that the fast Sodium channels are in one of three states; open, closed active or closed inactive.

In the resting membrane potential of -90mV for example, the channels are closed and active, and it will become open when the stimulus reaches the threshold, after that, when the action potential becomes less negative and closer to zero it will become closed and inactive; the fast channels are now canceled and the only working channels are slow channels (during repolarization), when potential is back to resting membrane potential the channels will be in closed and active state again. But what is the relation of this with the potassium?



When potassium concentration outside the cell becomes more **(hyperkalemia)**, the resting membrane potential is less negative and closer to zero (this is the same thing that happens in repolarization); so the fast sodium channels will be canceled (closed and inactive) and slow sodium channels will only remain, so depolarization in cardiac muscle will be slow and this will lead to **arrhythmias** and **cardiac arrest**.*

*Cardiac muscles are in syncytium, Phase zero (Depolarization) of the first cell is so fast and is followed by the depolarization of the next cell by gap junctions (normally work by fast sodium channels), so the depolarization will move from the first cell to the last one in NO TIME.

And also a decrease in [k+] outside the cell **(hypokalemia)** is not good; it will increase the RMP and this will decrease excitability of the cell (more negative, away from threshold) and this will lead to **paralysis.**

So the most important thing that we as doctors are afraid of in renal failure is increase potassium in blood.

* Some people with renal failure have **normal** concentration of sodium; logically sodium will increase with renal failure, but also water excretion decreases and thus maintaining the same sodium concentration in the blood, however, they will have **hypervolemia** instead.

- Normal K+ concentration in blood that should be maintained = 3.5-5.5 mmol/L.

- Potassium concentration is normally 4 mmol/L; if it exceeded 7 mmol/L, cardiac arrest will happen in the same mechanism we talked about.

- 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).

equivalent= number of molls number of charge; in potassium=1 mol*1=1 so when we say 1mmol/L it is the same as we say 1mEq/L.

- Potassium intake should equal Potassium output >>> **Potassium homeostasis**.

- Daily intake of potassium is 100 mmol and the output is absolutely 100mmol but how? 95mmol is excreted by the kidneys and 5 mmol by other routes; so the kidney is the major contributor for potassium excretion (by filtration or by secretion).

- If we have a meal with 50 mEq of potassium; the potassium will distribute in extracellular fluid in general by 50mEq/14L* of extracellular fluid= 3.5mEq/L.

So in the blood, its concentration will be 4mEq (constant in the body) +3.5mEq (that we took from the meal) =7.5 mEq/L >>> arrhythmia and cardiac arrest will happen! But this situation is not compatible with life, it is not logical that death will happen if we eat anything with potassium! (we said that 100meq is the daily intake; how come 50meq cause death?), So our body will secrete insulin after the meal intake that will work on glucose and **potassium** and pushes potassium inside of the cell, instead of being outside the cell which is dangerous as we said, so inside the cell; the concentration will be 150(normally)+3.5(form meal) =153.5 mmol/L which is not a problem because the cell will get rid of this extra potassium toward the blood **slowly** (instead of rising [k+] outside the cell form 4 to 7.5 suddenly; the cell with help of insulin will rise it form 4 to 4.1 or 4.4 mEq/L of blood which is compatible with life and then it will be excreted by the kidney without any problem).

*total body water is 60% of the body weight, so if a person weight = 72 kg then his total body water amount is 42L; 28L intracellularly and 14L extracellularly (plasma and interstitial fluid).

Potassium excretion by the kidney:

Filtration load= GFR*[K+] in plasma

GFR=125ml/min; 125*60min*24hour ml = 180000ml/day >>180L/day.

➔ Filtration load for potassium with 100mEq ingestion of K+ per day=180 L/day * 4mEq/L (our aim is to maintain this concentration in plasma) =720 mEq/day (in bowmen space).

- We said that of this 100 mEq ingested per day; 95 mEq (95%) is excreted by the kidney, and 5 mEq (5%) is excreted by other routes.

But how does this 95 mEq, as in our example, get excreted by the kidney?

first of all to answer this question we should know that 65% of filtration load gets reabsorbed in proximal tubules, and 25% reabsorbed by ascending limb of Henle, zero reabsorption in descending limb of Henle. (90% is the total reabsorption)
>> Reabsorption portion from 720 mEq filtration load is = 90% = 648 mEq/day reabsorbed by these routes.

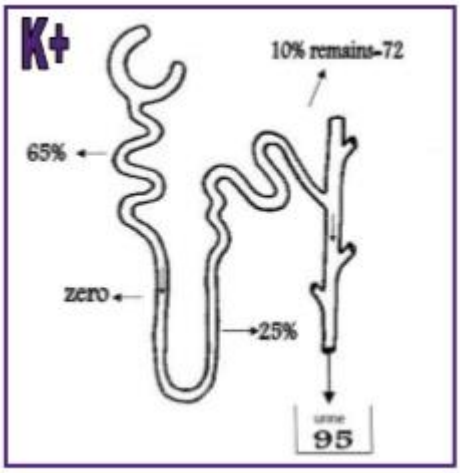
What is remained for excretion is 10% from filtered load = 10%*720=72 mEq/day (for simplicity we usually say 70) >>> 70 mEq of potassium is <u>excreted by filtration</u> per day form kidney.

BUT, we said that we should excrete 95 mEq per day form kidney to urine! So, there is 25 mEq of this 95 mEq of potassium (of 100 mEq potassium intake per day) gets <u>secreted</u> per day in distal tubules by the help of aldosterone*, so the net becomes 95meq in urine as we said and potassium homeostasis achieved.

*Aldosterone works on principle cells of distal tubules to increase the reabsorption of Na+, and secrete K+ toward the lumen.

*<u>note</u>: 70 mEq that we get from filtration does not change (constant), we can only manipulate the secreted part (increase it or decrease it according to our daily activity).

For example: if I eat a meal with 200 mEq potassium; I will get rid of this entire amount by two ways; 95% by kidney, and 5% by other routes.



Of that, 95% =190 mEq is excreted by kidney; 70 mEq (constant) by filtration, and the rest, which is 120 mEq, is excreted by secretion (increased by increasing intake).

- Aldosterone affects principle cells in proximal tubules by

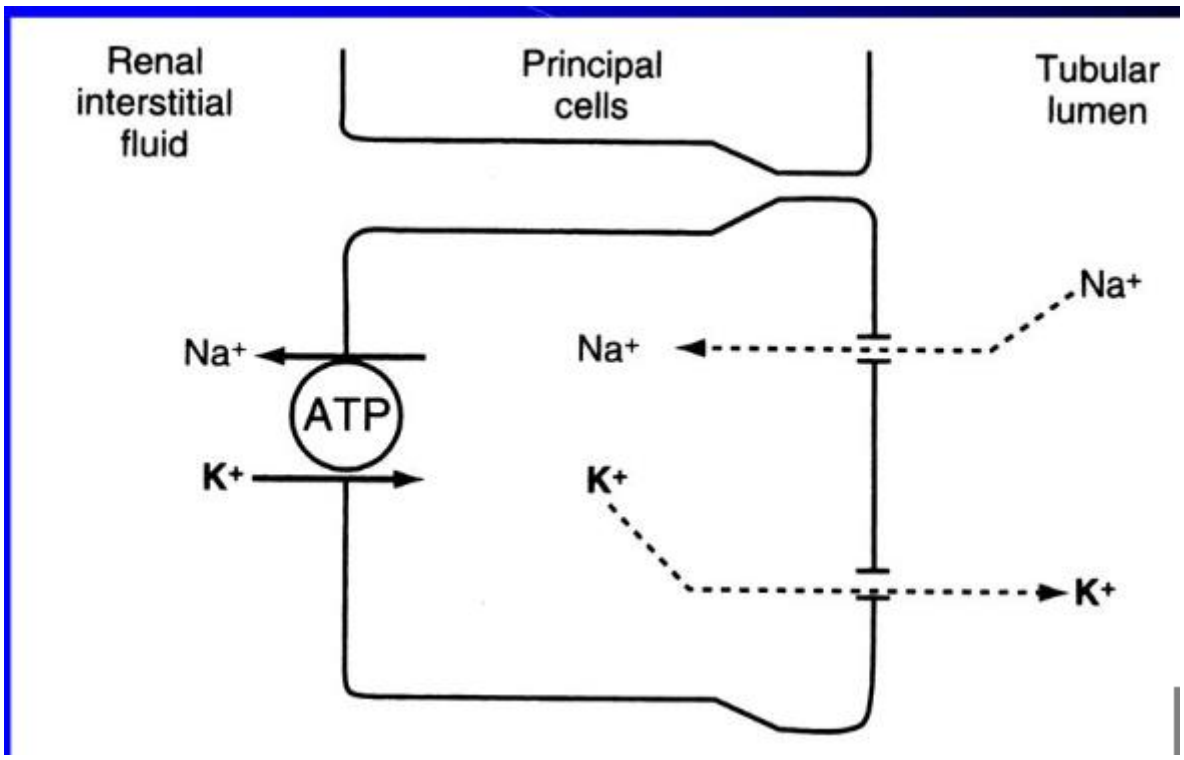
2 ways (we talked about them in sheet 4):
1- affects transcription of enzymes that generates ATP.
2-generates Na+/k+ pump in basolateral surface of principle cell.

3-generates Na+ and k+ channels in luminal surface.

*we all know that the concentration of sodium outside the cell is higher than inside the cell, and the opposite is for potassium.

*so to move potassium from plasma to principle cell we need a pump, and then from the cell to lumen (urine) we need a channel (passive diffusion).

For sodium, to move it from the lumen to the cell (absorption) we need channel (that is why we have k+ and Na+ channels in luminal surface) and then from the principle cell to plasma (or interstitium) we need pump (that is why we have pump on basolateral surface).



So all in all, it will increase Sodium reabsorption and Potassium secretion, if we have a tumor that secretes a lot of Aldosterone (hyperaldosteronism/Conn's disease), this will lead to hypertension, secondary hypertension, and hypokalemia in the body.

*note: hypertension is either primary, 90% of cases, or secondary, 10% of cases; due to pheochromocytoma or Conn's disease or increase renin in blood due to afferent arteriole constriction and decrease of GFR …etc.

How can I increase or decrease potassium secretion in distal tubules?

I can increase it by using diuretics, but how? Using diuretics will wash the potassium that is newly secreted form principle cells; and by that, it keeps the gradient difference across the membrane (between the cell and lumen) so more secretion of potassium will happen.

>>> So diuretics (some of them) are **potassium wasting agents**, specially the first two groups; thiazide and furosemide.

- Aldosterone antagonists (rarely used): **potassium sparing agents**; increase potassium in the body by inhibition of its secretion.

So if a patient takes potassium wasting diuretics, he should take a banana after the drug (to compensate for potassium loss), if this does not work we give him potassium supplements, or I can give him aldosterone antagonists.

-what stimulate aldosterone secretion form zona glomerulosa of adrenal cortex?

1- Increase potassium in blood.
2- Decrease sodium in blood.
3- Angiotensin 2.

Concentrated urine formation

This test is very important to indicate that if the kidney is back to being fully functional and normal after acute renal failure (95% is reversible) or not; because the last thing that returns to normal after acute renal failure is the ability of the kidney to make concentrated urine.

- There are a lot of tests that measure the osmolarity in the urine; we will talk about them in the next lecture.

- This topic includes anything considered a waste product; such as creatinine, urea, electrolytes, but **not** amount of proteins or blood cell or stones in urine; so be careful.

- What determine the ability of kidney to make concentrated urine? And what is the maximum ability for that in humans?

The human kidney is able to make concentrated urine of 1400 mOsm/L because of:

1-presence of juxtaglomerular nephrons in the kidney (long loop of Henle); the more juxtaglomerular nephrons kidneys have, the more concentrated urine it is able to make; for example: fish have cortical nephron **only;** that is why they are not able to make concentrated urine and the amount of urine they excrete per day is very large .

However, desert animals have only juxtaglomerular nephrons and that is why they make a very concentrated urine and in less amount (so that they do not need to drink a lot of water as type of adaptation to their environment) so their ability to make concentrated urine can reach 10,000 mOsm/L of urine and minimal obligatory renal output for them is less (around 50 ml), instead of 0.5 L in human where the kidney's capacity to concentrate urine is less.

Humans are in the middle, the major type of nephrons they have is the cortical but they also have juxtamedullary nephrons.

2-Urea cycle, which makes interstitium around the collecting duct hyperosmolar as we said in last lecture. Example: a vegetarian person does not have much proteins; so no urea exists; so the urea cycle is not there and the osmolarity in interstitium is not 1400 mOsm and thus the urine will be more diluted.

3-high permeability to water in collecting duct; this is achieved by ADH; we talked about it in the last lecture. (Figure 2)

4-blood flow in vasa recta, if it was high; such as when we give the patient dilators, it will wash out the sodium in interstitium thus making it less, and this will make the urine more diluted.

5-diuretics; make less osmolarity in interstitium so more diluted urine.

- A bed-ridden person's body makes 700 mOsm/day.

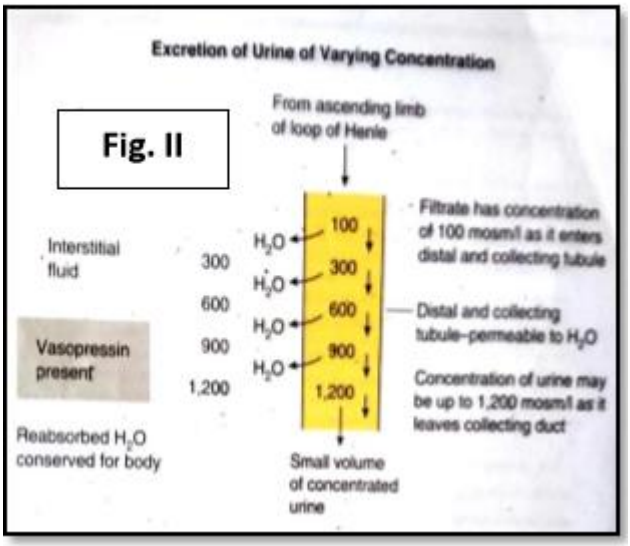
- Under normal diet & physical exercise the body makes 1000 mOsm/day of waste products and it MUST get rid of these 1000 mOsm in urine.

- The urine is **normally** hyperosmolar (twice as much as the plasma).

- so the minimum urine output the human can make= 0.5 litter per day* , which equals 20ml per hour; less than that >>>renal failure will happen (oliguria) so this amount is called **minimal renal obligatory output**- the minimum amount of urine that a normal person can excrete per day, and less than this amount kidney failure will appear.

*1400 mOsm per litter (maximum concentration the kidney can make) → so 700 mOsm (minimum amount the body needs to excrete) per how much litter? 0.5

*if you drink a sea water which has an osmolarity about 2400 mOsm/L then how much excretion will be? 1000 (normally you can make)+ 2400 (from sea water you drink)= 3400 mOsm; so the litters we need here are (3400/1400=2.4 litter!) which is huge amount of water; because of that you get dehydrated after sea water drinking, and start drinking a lot of water to compensate.



Minimal renal obligatory output for children is less; for adults it equals 0.5 L/day =500ml/day, but in children this number is normal and the minimal obligatory output is less.

- There is an equation to determine the minimal renal obligatory output in different ages which is = **300ml/m^2 surface area/ day**

Example: for an adult person with 1.5 m^2 surface area, the minimal renal obligatory output will be 450 ml/day (approximately 500 ml / day as we said).

Good luck