DIURETICS

By: ZAKIRULLAH YOUSUFZAI

THIAZIDE DIURETICS
Chlorothiazide DIURIL
Chlorthalidone GENERIC ONLY
Hydrochlorothiazide (HCTZ) MICROZIDE
Indapamide GENERIC ONLY
Metolazone ZAROXOLYN
LOOP DIURETICS
Bumetanide BUMEX
Ethacrynic acid EDECRIN
Furosemide LASIX
Torsemide DEMADEX
POTASSIUM-SPARING DIURETICS
Amiloride MIDAMOR
Eplerenone INSPRA
Spironolactone ALDACTONE
Triamterene DYRENIUM
CARBONIC ANHYDRASE INHIBITORS
Acetazolamide DIAMOX
OSMOTIC DIURETICS
Mannitol OSMITROL

Summary of diuretic drugs.

Natriuretic: any thing which are introduce into body will increase Na^+ output in urine.

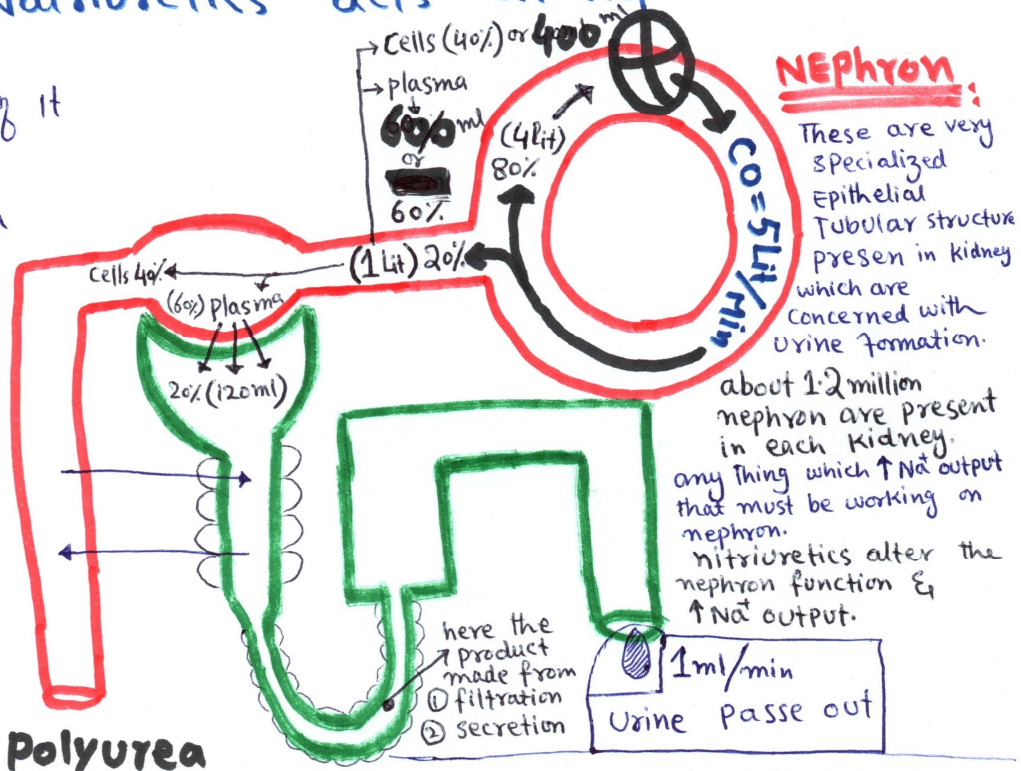
Diuretics: Any thing which increase urine volume.

Natriuretic when cause loss of Na^+, loss of H_2O also occur with Na^+, so Natriuretis are as well diuretics.

Diuretics + Natriuretics acts on nephron.

- out of 5Lit CO, 20% of it enters to kidney.
- out of 600ml of plasma only 20% of it filtered
  e.g: 120ml of fluid is filtered/minutes

G.F.R = 120/min



NEPHRON:

These are very specialized Epithelial Tubular structure presen in kidney which are concerned with urine formation.

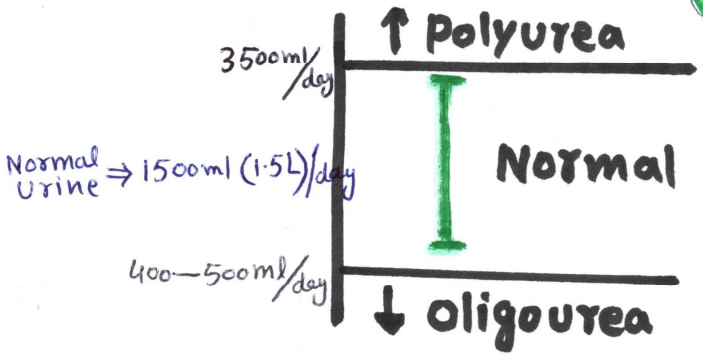
about 1.2 million nephron are present in each kidney.

any thing which ↑ Na^+ output that must be working on nephron.

Natriuretics alter the nephron function & ↑ Na^+ output.

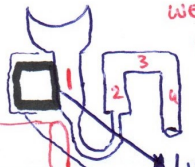
whatever fluid is filtered about 99% are reabsorbed & only 1% pass in urine & waste product pass in this 1ml.

Urine is formed in 3 processes
① filtration
② secretion
③ Reabsorption



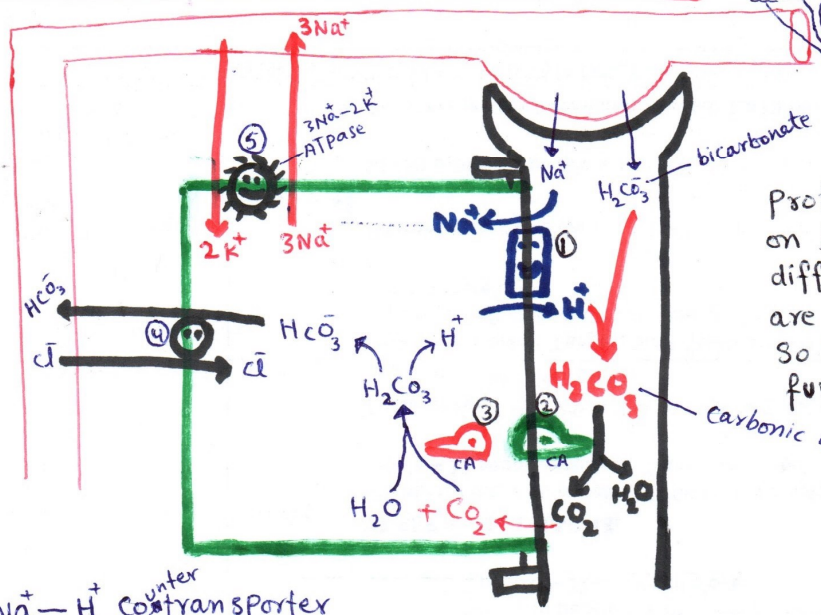
Na^+ reabsorption occur at different Parts of the nephron, so different drugs influence Na^+ reabsorption at different points & increase release of Na^+ in urine & decrease reabsorption of Na^+

How Na^+ Handling occur in nephron?



we will discus the Na^+ reabsorption in these 4-parts of nephron.

Luminal surface the remaining 3 surfaces are called basolateral



Proteins which are present on luminal surface are different than proteins which are present on basolateral side, So both sides have different function.

① $Na^+ - H^+$ counter transporter

this transporter absorb Na^+ & bring H^+ to lumen.

* all Nephronal cells are poor in Na^+, b/c Na^+-K^+ ATPase absorb 3 Na^+ & brin 2 K^+ to cell, So the cell must have to suck Na^+.

② Carbonic anhydrase → Luminal Carbonic anhydrase
- CA which are present on luminal side called luminal carbonic Anhydrase
- the CA which are present in the cell so called cytoplasmic carbonic anhydrase.

The luminal carbonic anhydrase breakdown the

$H_2CO_3^-$ —(Luminal Carbonic anhydrase)→ H_2O + CO_2 (lipid soluble so absorb easily)

③ cytoplasmic Carbonic anhydrase

the cytoplasmic CA make

$H_2O + CO_2 \rightarrow HCO_3^- + H^+$ → used for recycle of $Na^+ - H^+$ Transporter

④ so from here HCO_3^- absorb to blood & Cl^- come cell.

⑤ $Na^+ - K^+$ ATPase absorb 3 K^+ & bring 2 K^+ to cell.

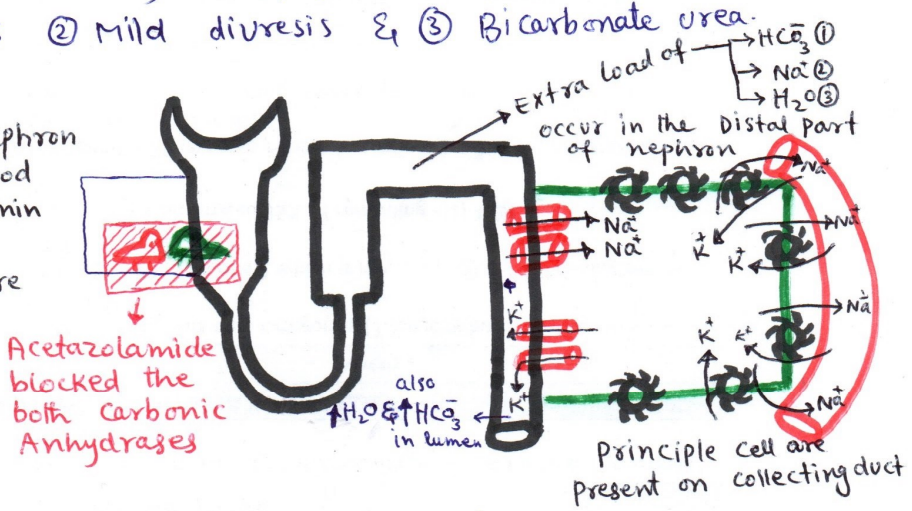
If we give a drug which block the Carbonic anhydrase enzymes, so than reabsorption of Na^+ does not occur, & Na^+ appears in urine **(Natriuresis)**, also HCO_3^- reabsorption does not occur this lead to **(Bicarbonate urea)** plus some of H_2O also move with it so **(Diuresis)** occur.
This type of drug produce Alkaline urine so body become acidic.
Na^+ which is not reabsorbed in PCT, some of them are reabsorbed in distal convoluted tubule, so Mild Natriuresis & Mild diuresis will occur.

ACETAZOLAMIDE

works in PCT on the luminal & cytoplasmic carbonic anhydrase, so develop:
① Mild Natriuresis ② Mild diuresis & ③ Bicarbonate urea.

In principle cell of Nephron Na^+ is reabsorbed to blood & K^+ is secreted to lumin

NOTE Na^+ reabsorption is more than K^+ secretion, so luminal side become more electronegative in principle cells area.

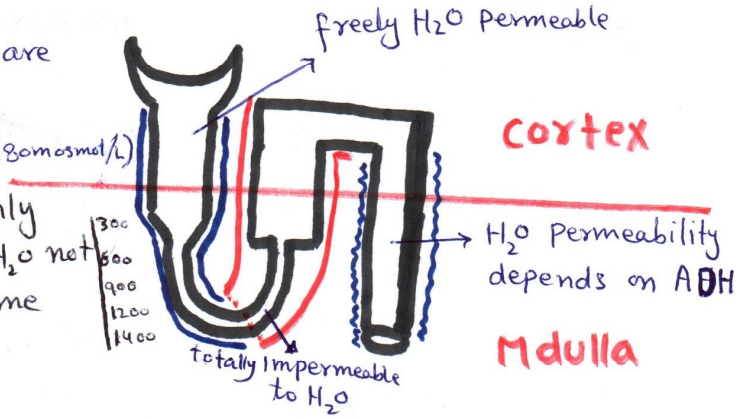


any drug which act on Proximal Convoluted tubule ~~to~~ upto collecting duct, increase the Na^+, HCO_3^-, H_2O, which are loaded in collecting tubule, this increase of load lead to K^+ loss & ↑ Na^+ absorption

① e.g: This excess Na^+ is reabsorbed from cell by Na^+-K^+ ATPas to blood, so K^+ move into cell & than to lumen, on this way K^+ wasting occur so Kaliuresis occur.
② ↑ed HCO_3^- in last part make this part electronegative, so this negativity pull the K^+ out of the cell into lumen, this also lead to K^+ loss in urine (Kaliuresis).
③ ↑ed H_2O in last part ↑ed washout of K^+ from this part ↑ gradiant for K^+ to move from cell to lumen, so further Kaliuresis occur.

All Diuretics which acts on proximal to collecting tubule are K^+ waster.

* In PCT, the solutes & H_2O are Isotonically reabsorbed, so osmolarity remain same (300osmosmol/L)
* in H_2O impermeable part only Solute are reabsorbed & H_2O not absorbed, so lumen become diluted, this part is Called diluting segment.



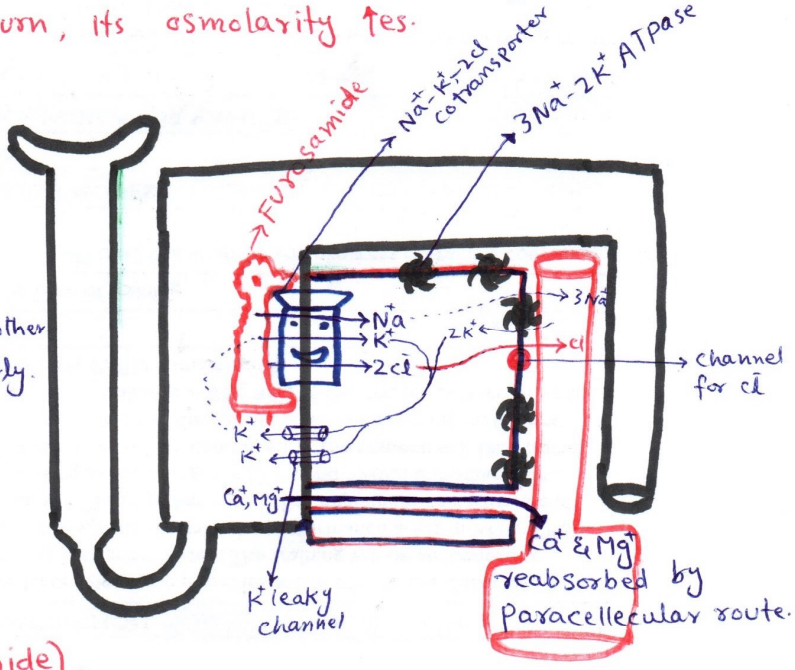
*As we move from Cortex to Medulla osmolarity ↑es in interstitium.

As fluid move from proximal part of loop of henle H_2O is reabsorbed by hyperosmolar interstitium so by the time fluid reaches as Hair Pin turn, its osmolarity ↑es.

As K^+ move into lumen, make the lumen electropositive,

So, Divalent catines (Ca^+, Mg^+) are also +ve charge, so repell oneanother & Ca^+, Mg^+ reabsorb paracellecularly.

& K^+ is recycled by Na^+-K^+-2Cl co-transporter.



Loop Diuretics (Furosamide):

This drug block $Na^+-K^+-2Cl^-$ co-transporter, so no Na^+, Cl^-, & K^+ are reabsorbed. large amount of Na^+ & Cl^- move to DCT & here the interstitium become hypo-osmotic.

As more Na^+ move to distal Part, some of them are reabsorbed & some of its are excreted in urine, leading to: **Natriuresis** & **Diuresis**.

But as some Na^+ is reabsorbed in principle cell & K^+ is secreted to lumen, such person also develop **Kaliuresis**

As $\uparrow Cl^-$ also move into this part, it further make lumen -ve & $\uparrow$es gradiant for K^+ so further **Kaliuresis** occur

As this transporter is not able to transport K^+, so K^+ passage through leaky channel decreases, so this part (thick-ascending loop of henle) become Less electropositive & thus it does not allow Divalent Catines (Ca^+, Mg^+) to be reabsorbed paracellecularly, so:

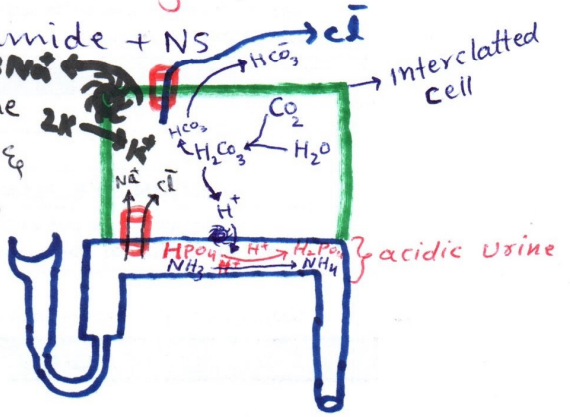
No Ca^+ & Mg^+ is absorb here, so more Ca^+, Mg^+ move to distal part, some of Ca^+ is reabsorbed in DCT but other are not, such patients develop **Calciurea**.

As this Ca^+ comeout it activate Parathyroid hormone to increase Ca^+ reabsorption from bone so such patients develope osteoporosis

Side effect of such a drug is that, it cause dehydration, To prevent this effect we give Normal saline along with these drugs, when administering parentral Furosamide

ie: Managment of hypercalcemia = Furosamide + NS

As Furosamide added more H^+ come into lumen, interact with HPO_4 & NH_3 & makes H_2PO_4 & NH_4 (which are acidic) so urine become acidic



As Furosamide reach to distal part not only Na^+ move in principle cell (-ve develop) and K^+ comes out but H^+ also come out of interclatted cells

This patient which take Diuretic for long term they develop Dehydration & hypovolumia.

This activate Renin-Ang-Aldosteron system, so distal part of nephron is sensitive to aldosterone.

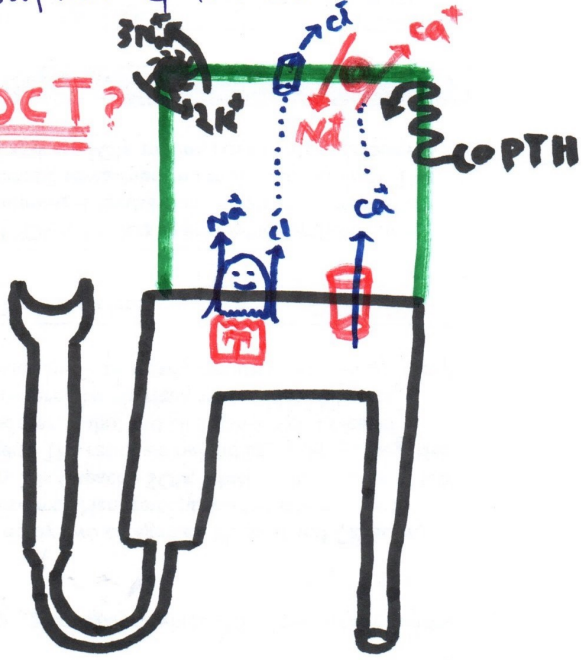
Aldosteron cause $Na^+ + H_2O$ Reabsorption & K^+ + Catines Secretion.

How Thiazide work on DCT?

Thiazide block Na^+-Cl^- Co-transporter,

* As furosamide acts on that part where mor reabsorption of solutes occur, so it lead to heavy natriuresis & Diuresis

* Thiazide acts on that part where only 8% of Na^+ is reabsorbed, so it cause moderate degree of Natriuresis & Diuresis.



when parathyroid hormone (PTH) stimulate its receptor, it give signal intracellecularly, so alot of Ca^+ channel appear on luminal surface & alot of Na^+—Ca^+ Exchanger appears on basolateral surface.

%age of Na^+ reabsorption at different parts of Nephrone.

1. PCT = 60—65%
2. Descending Loop of Henle = 5—10%
3. Ascending " " = 25-30%
4. DCT = 8%
5. Collecting duct (principle cells) = 2-3%

NOTE: * in Ascending loop of henle the Ca^+, Mg^+ not absorb by the influence of PTH but by the electropositivity of K^+ in lumen
* in Distal convoluted tubule the Ca^+ absorb by the influence of PTH.

* with thiazide more Na^+ & Cl^- (exchange with K^+ (Principle cell) ↑ gradiant for K^+; make the lumen -ve so ↑ gradiant for K^+) move distally & both of them increase loss of K^+
* Extra H_2O in this also wash the K^+

* Thiazide is also **K^+ wasting diuretic.**

* Thiazide are **Ca^+ Retaning drug.**

b/c $Na^+ - Cl^-$ co-transporter

because as this cell become poor in Na^+ (block by thiazide + cell become poor of Na^+) so the Na^+ come from blood side by $Na^+ - Ca^+$ exchanger, & the Na^+ is back absorb by $3Na^+ - 2K^+$ ATPases on this way more Ca^+ is absorbed.

• So the person may have **Idopathic hypercalciurea** may be due to defect in Ca^+ reabsorption, so in these patients Ca^+ stones are more common in urinary tract.

One of the treatment in such these patients is to give thiazide for long time but low dose.

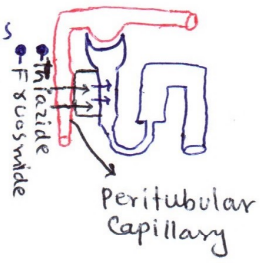
Frusamide is **Ca^+ wasting** diuretic b/c in its presence No absorption of Ca^+-Mg^+ occur by Paracellecular route

* **Thiazide is for thigh,**
Its means thiazide retain Ca^+, so more Ca^+ is absorbed in the femur neck & hip bone, so ↓ osteoporosis

Frusosemide	Thiazide
① work mainly on thick Ascending loop of henle	① work mainly on DCT.
② work on luminal side	② works on luminal side
③ Cause reabsorption + secretion	③ Cause reabsorption + secretion
④ It is Prostaglandine mediated	④ also PG mediated
⑤ both of them are Kaliuretic	* If PG is ↓ both of them not working.
⑥ ↓ Ca^+ reabsorption	⑤ ↑ Ca^+ reabsorption
⑦ Strong diuretic	⑥ Mild diuretic

As both of them enters by peritubular capillary into PCT, & & than to the lumen, so if there is any defect in this part decreases the concentration of these drugs.

if this pathway is used too much by this diuretic as this pathway is used by many organic acid e.g: uric acid, so these also lead to hyperuricemia



In PCT there are many ways to reabsorb Na^+ e.g:

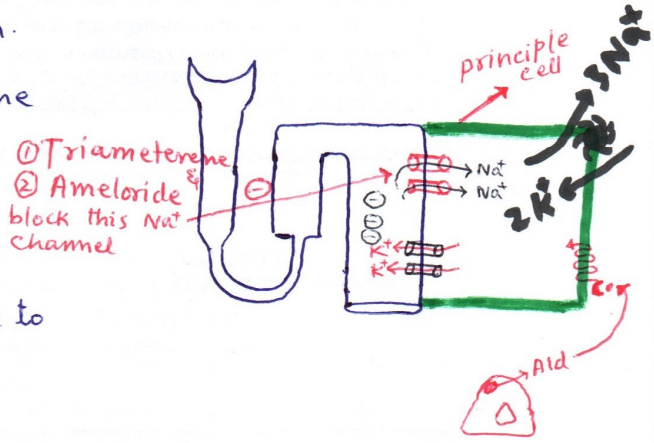
1. Na^+ — H^+ antiport
2. Na^+ – glucose co-transporter
3. Na^+ – Amino acid co-transporter.
4. Na^+ – Cl^- co-transporter.
5. Na^+ – PO_4^- co-transporter

about 65% of Na^+ reabsorbed in PCT, most of Na^+ is reabsorbed along with Cl^- in PCT, so any drug which interfer with this will be Most powerfull diuretic.

The principle cell luminal surface is different from nephron cells because:

1. it has Na^+ channels to cell
2. It has K^+ channels to lumin.

as Na^+ move in, the lumen become electronegative, this electronegativity suck the K^+ to lumen, & H^+ also

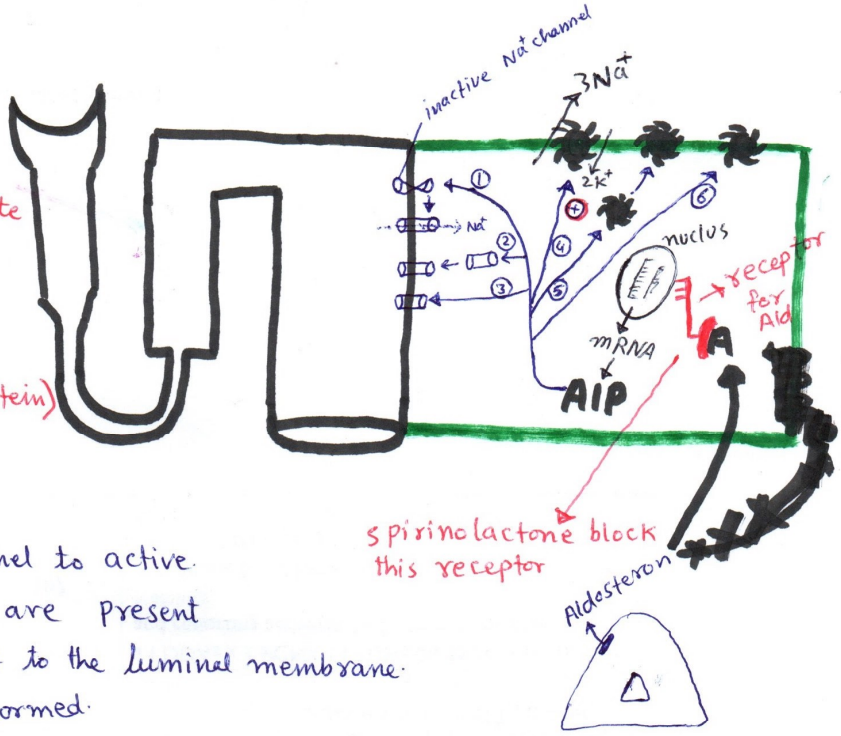


Aldosterone stimulation occur due to

1. low K^+
2. high Angiotensin II

The ↓K^+ & ↑Ang II influence the Aldosteron Production

* The aldosteron bind to its receptor, which activate multiple Genes within the nucleus, & mRNA are formed. the messenger RNA form AIP (Aldosteron Induce protein)



Function of AIP

① Convert inactive Na^+ channel to active.
② The Na^+ channel which are present in the cytoplasm, bring it to the luminal membrane.
③ New Na^+ channels are formed.
④ activate $3Na^+-2K^+$ ATPase on basolateral surface
⑤ The $3Na^+-2K^+$ ATPase, which are present in the cytoplasm, bring it to the basolateral membrane
⑥ formation of New $3Na^+-2K^+$ ATPases

Under aldosteron influence more Na^+ enter to cell & reabsorbed, & K^+ come into cell & expell to lumen, due to more & more Na^+ absorption the lumen become electronegative, so attract H^+, & K^+ to lumen.

* Aldosteron retain [Salt + H_2O] & loss [H^+ & K^+]

* Amiloride + Triemterene are K^+-sparing drug or Antikaliuretic.

Mechanism

① As these drugs block Na^+ channel in principle cell so No Na^+ absorb & No K^+ efflux
② As no more Na^+ in, so no electronegativity in lumen produce, so decrease gradiant for K^+ efflux from cell.

* Spirinolactone: It block the aldosteron receptor, but have no intrinsic activity, so aldosteron mediated actions (above 6 steps) are not occur.

Osmotic Diuretic (Mannitol)

a number of simple, hydrophilic chemical substance that are filtered through the glomerulus such as mannitol result in diuresis.

Filter substances that undergo little or no reabsorption result in a higher osmolarity of the tubular fluid. this prevent further water reabsorption at the PCT & descending loop of henle, resulting in osmotic diuresis with little additional Na^+ excretion. therefor these agents are not useful for treating conditions in which Na^+ retention occur.

* They are used to maintain urine flow following acute toxic ingestion of substances capable of producing acute Renal failure
* osmotic diuretics are a mainstay of treating of patient with increased intracranial pressure.

Manitol is not absorb when given oraly, & should be given IV.

Adverse effects

① dehydration
② Extracellecular water expantion from the osmotic effects in the systemic circulation.

The expantion of extracellecular water occurs b/c the prescence of mannitol in the extracellecular fluid extracts water from the cell & cause hyponatremia until diuresis occur.

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End of Diuretics
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