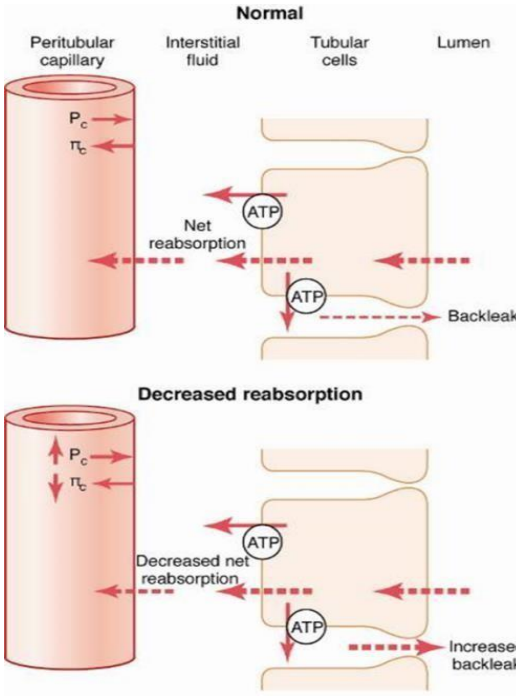
PHYSIOLOGY

- SHEET NO. 7 - edited sheet
- WRITER : 019 Dentistry
- CORRECTOR : Abdelhadi Okasha
- DOCTOR : Ebaa' zayadneh

→ Effect of increased hydrostatic pressure or decreased colloid osmoticpressure in peritubular capillaries to reduce reabsorption.

▪ The first figure shows the case of **NORMAL** hydrostatic and oncotic pressures, where we havea **normal net reabsorption value** (the net forces will be around 10 mmHg).

▪ Referring to the second figure, an **increase in the hydrostatic pressure** of the peritubular capillaries or a re**duction in the peritubular capillaries oncotic pressure** (together or one of them) resultsin a **DECREASE IN THE NET REABSORPTION**, so fluids will accumulate in the interstitial space and will leak through the tight junctions of the tubules



Hormones that affect reabsorption:

1) Aldosterone: stimulated by angiotensin II because of hypovolemia from the renal cortex (Remember renin-angiotensin system)

- **Aldosterone** acts on **late distal**, **cortical**, and **medullary collecting tubules**
- The effect of aldosterone on the principal cells:

a- Increases Na+ reabsorption by sodium transporters and Na/k ATPase

b- Increases K + secretion

- The effect of aldosterone on the intercalated cells:

a- Increases H + secretion

*) How are these effects of aldosterone achieved?

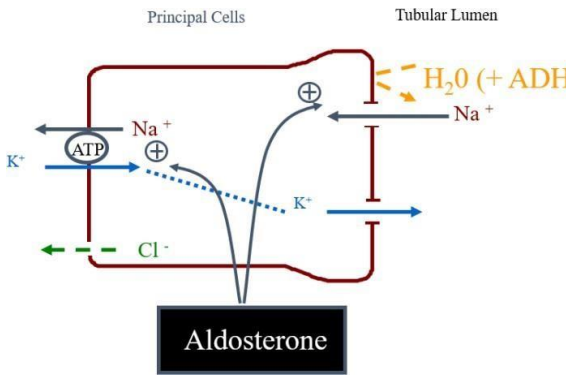
Answer: The figure on the right shows the Aldosterone Function:

▪ We can see the principal cells, tubular lumen, sodium potassium ATPase, & the Na+ channel (ENaC)

▪ Sodium is reabsorbed (enters the principal cells), and at the same time Potassium is secreted → Aldosterone increases the activity of these sodium and the potassium channels.

▪ Aldosterone also increases the activity of the sodium potassium ATPase.

▪ As a net effect, we can say that Aldosterone increases the Na+ reabsorption and K+ secretion.



→ Excess aldosterone (Primary aldosteronism/ Conn's syndrome) is a condition that results in:
1- Excess sodium reabsorption (Na+ retention)
2- Great loss of Potassium, resulting in hypokalemia in the blood.
3- High secretion of Hydrogen ions, resulting in alkalosis.
4- The sodium retention results in water retention, and therefore hypertension

→Aldosterone deficiency (Addison's Disease) is a condition where there is a defect in secreting aldosterone from the adrenal gland, which results in:
1- Na+ wasting (no enough reabsorption), as a result sodium will be excreted in a higher percentage in the urine.
2- Potassium accumulation (not secreted), resulting in Hyperkalemia.
3- Sodium wasting will result in water loss and therefore Hypotension.
4 – Acidosis because of lowering H+ secretion

→ Control of Aldosterone Secretion
▪ Factors that increase aldosterone secretion
1- Angiotensin II (it is the first stimulant) o The control of the aldosterone secretion is mainly by Angiotensin II, Angiotensin II is released or stimulated upon the release of renin, resulting in the release of aldosterone.
2- Increased K+ level in the plasma o Because Aldosterone works on decreasing K+ levels
3- adrenocorticotrophic hormone (ACTH) (permissive role)
▪ Factors that decrease aldosterone secretion
1- Atrial natriuretic factor (ANF / ANP "same thing") o Inhibits the release of aldosterone.
2- Increased Na+ concentration (osmolality)

Effects of Angiotensin II: is an important factor that affect reabsorption function especially for Na^+ by:

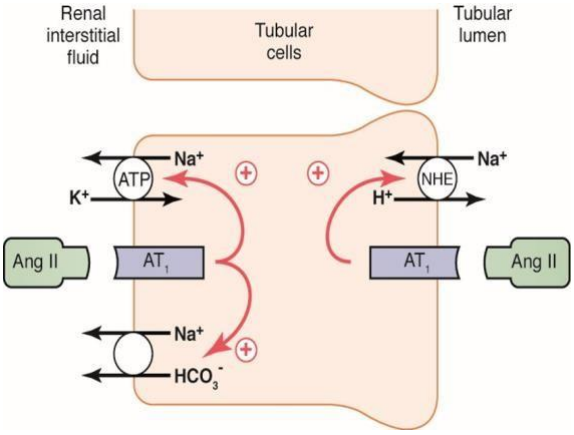
1- stimulating aldosterone secretion (increases reabsorption for Na^+ and secretion of K^+ and H^+ .

2-Directly increasing Na^+ reabsorption (it works directly on the nephron segments on the proximal , loop, distal, collecting tubules)

3- constricting the efferent arterioles more than the afferent arterioles which will causes :

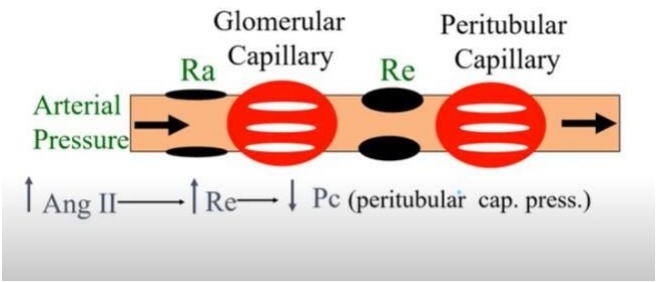
- increasing the resistance in the peritubular capillary will decreases the renal flow and the hydrostatic pressure in the peritubular capillary which will increase the reabsorption .
- Also decreasing the renal plasma flow will increases the filtration fraction, which will increases the peritubular colloid osmotic pressure.

We can see in this figure that Ang II affects directly on the transporters (directly affects reabsorption) by stimulating the function of the Na^+ /K^+ ATPase channel , also it stimulates the transport of HCO_3^- (Na^+ /HCO_3^- co-transporters) , also it increases the function of NHE (Na^+/ K^+ exchanger) , which will all increases the reabsorption of Na^+ .

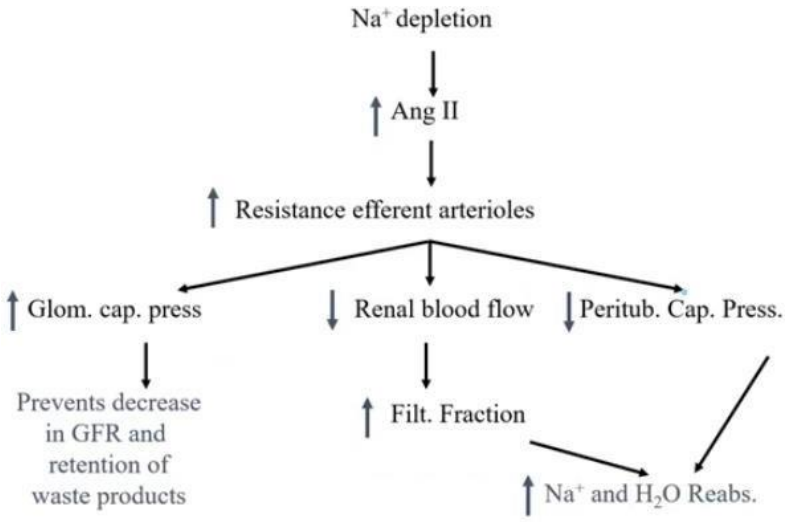


The effect of Ang II on the peritubular capillary dynamics :

we know that Angiotensin II increases the resistance of the efferent peritubular capillary rather than afferent ones which will1- decreases peritubular capillary pressure and this will increases the reabsorption .2- also decreases the renal blood flow which means that the filtration fraction will increase which increases the oncotic pressure hence increasing the reabsorption.



This table is a summary for all the effects of Ang II on the nephrons…



The effect of Ang II blockade on reabsorption :

By Taking hypertensive agents, such as:

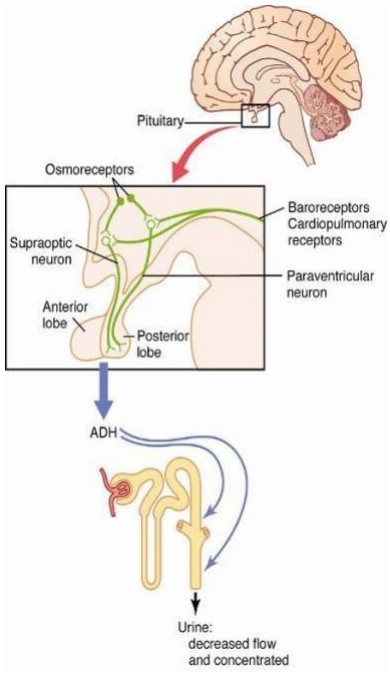
1. ACE inhibitors (captopril, benazepril, ramipril)
2. Ang II antagonists (losartan, candesartan, irbesartan)
3. Renin inhibitors (aliskirin)

that inhibit or reduce Ang II and aldosterone secretion, which directly inhibit Na+ reabsorption in all the segments of the nephrons and decrease the efferent arteriolar resistance .The inhibition of Na reabsorption and the decrease in efferent arteriolar resistance ultimately lead to the increase in peritubular capillary hydrostatic pressure and thus to the decrease in net reabsorption. All these effects result in natriuresis(increased Na + excretion) and diuresis (Increased urine production) thus reduction in blood pressure.

<u>Antidiuretic Hormone (Vasopressin)</u>, is another hormone that affect reabsorption :

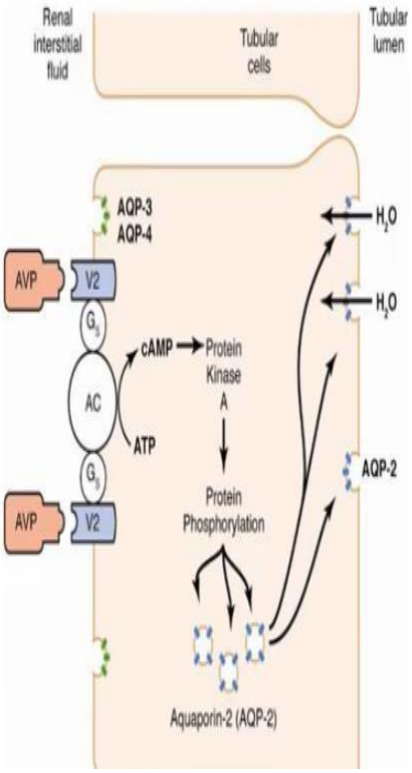
- it is secreted by posterior pituitary
- the main effect is to Increases H2O permeability and reabsorption in distal and collecting tubules
- Allows differential control of H2O and solute excretion

• Important controller of extracellular fluid osmolarity



ADH is synthesized in the magnocellular neurons of the hypothalamus and released by the posterior pituitary. ADH acts on kidneys on the late distal and collecting ducts to increase water reabsorption and decrease the urine volume and increases the concentration of urine.

Mechanism of action of ADH



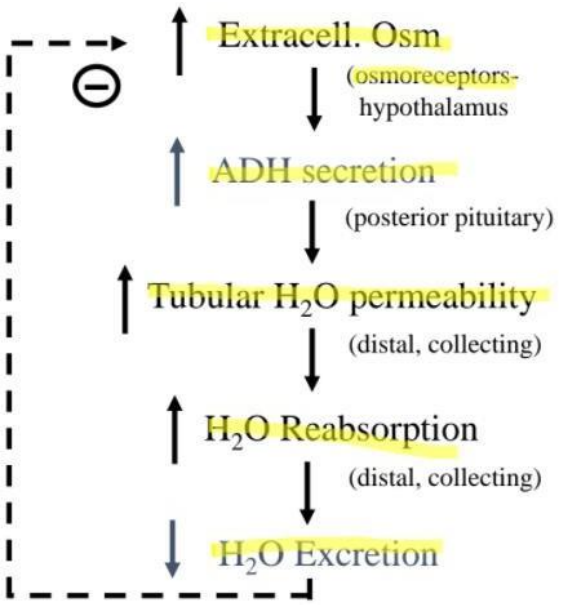
The vasopressin hormone (AVP) will bind to the G-protein coupled receptor, vasopressin receptor 2 (V2).

The activation of the V2 receptors activate the second messengers, cAMP. cAMP stimulates protein kinase A and thus protein phosphorylation of the aquaporin channels (AQP-2).

These channels will then be inserted on the apical or the basal membrane increasing the permeability of the distal tubule and collecting ducts to water; thus facilitating water reabsorption by osmosis. This process prevents urine dilution and result in concentrated urine.

The mechanism for ADH secretion depends on negative feedback mechanism. When the extracellular osmolarity increases, the osmoreceptors found in the hypothalamus become activated and stimulate ADH secretion from the posterior pituitary.

This will result in increase tubular H2O permeability in the distal tubule and collecting duct which will thus increase water reabsorption and decrease water excretion to correct the osmolarity level.



<u>Abnormalities of ADH</u>

1. Inappropriate ADH syndrome (excess ADH)

- Decreased plasma osmolarity due to excessive water reabsorption

- Decreased Na+ concentration in blood due to increased solvent level

(hyponatremia)

2. “Central” Diabetes insipidus (insufficient ADH)

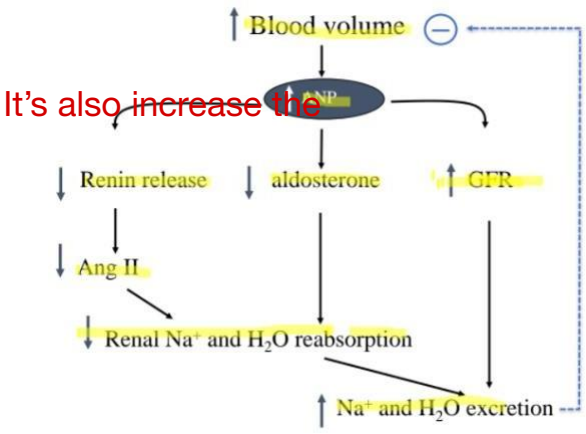
- Increased plasma osmolarity due to more water excretion

- Hypernatremia due to increased Na+ concentration in the blood

- Excessive thirst due to increased osmolarity; because the thirst center is stimulated by the increase in osmolality .

Atrial Natriuretic Peptide (ANP) hormone

- Secreted by cardiac atria in response to increased blood pressure and stretch (increased blood volume)
- Diuretic hormone
- Directly inhibits Na+ reabsorption and thus increase Na+ excretion
- Inhibit renin release and aldosterone formation
- Inhibit ADH release
- Increases GFR because it's a potent vasodilator that dilates the efferent arterioles mainly and thus increases the filtration rate; which reduces absorption and increases excretion
- Helps to minimize blood volume expansion and thus decreases blood pressure



It's also ~~increase~~ the

This graph summarizes the effects of the ANP hormone. As you can see here, increased blood volume and blood pressure induce the release of ANP from the heart. ANP result in the inhibition of renin release and thus inhibition of Ang II synthesis. It will also inhibit aldosterone release and will increase GFR by vasodilating the efferent arterioles.

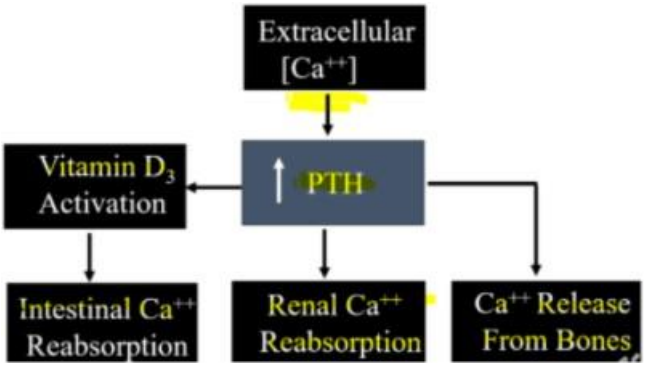
The result of the inhibition of renin and aldosterone is a decrease in renal Na+ and water reabsorption and this will increase Na+ and water excretion.

It also increase the hydrostatic pressure and renal plasma flow which both decrease réabsorption

Parathyroid Hormone

- Released by parathyroids in response to decreased extracellular Ca2+
- Increases Ca2+ reabsorption by the kidneys
- Increases Ca2+ reabsorption by the gut
- Decreases phosphate reabsorption by the kidney
- Helps to increase extracellular Ca2+(the net result) .

Control od Ca^{+2} reabsorption by parathyroid hormone

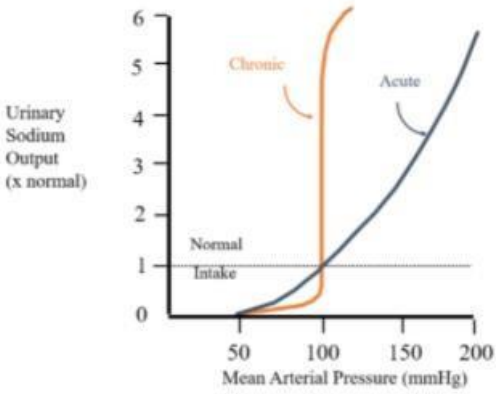


If the parathyroid hormone was stimulated, due to decrease in extracellular Ca2+ concentration, the net effect is the activation of vitamin D3 to increase the intestinal reabsorption of Ca2+. PTH also increases Ca2+ reabsorption from the kidneys and release Ca2+ from the bones.

The effect of the sympathetic nervous system on the reabsorption of Na+

The sympathetic nervous system, by the effect of the catecholamines (Epinephrin and Norepinephrine), stimulate Na+ reabsorption directly by increasing the activity of the Na+ transporters. The sympathetic nervous system also stimulate renin release. Only under high levels of sympathetic stimulation, the GFR level and the renal blood flow decreases.

Effects of renal arterial pressure on urinary Na+ excretion



Here we see the relationship between sodium excretion and mean arterial pressure.

The normal mean arterial pressure is 100 mmHg Acute changes in mean arterial blood pressure as the mean arterial pressure is increased beyond 100 mmHg, the urinary Na+ excretion increases and this is called pressure natriuresis

The dashed line in the figure represent the normal intake of Na+.

When the Na+ intake is normal, the dashed line intersect the normal arterial pressure (100mmHg). At this point, urinary excretion is at equilibrium with Na+ intake and both of these processes are at normal levels. As Na+ intake is increased beyond normal levels, the mean arterial blood pressure increases. As a result, urinary Na+ output increases. The effect of increased mean arterial pressure in response to increased urinary Na+ output is called pressure natriuresis.

Chronic changes in mean arterial pressure result in much faster responses in pressure natriuresis. Any chronic increase in mean arterial pressure, the urinary sodium output increases sharply and in much higher rate than in acute changes in mean arterial pressure.

The decrease in Na+ reabsorption due to increased arterial pressure is the main cause of pressure natriuresis. Furthermore, the increase in mean arterial pressure leads to the inhibition of the renin–angiotensin system and thereby aldosterone inhibition. The release of intrarenal natriuretic factors such as prostaglandins and EDRF (Endothelial derived relaxing factor) also increase with increased arterial pressure. These factors are vasodilators that also increase the GFR and thus decrease Na+ reabsorption and increase Na+ excretion.

Osmotic effects on reabsorption

• Water is reabsorbed only by osmosis through the paracellular route or through aquaporin channels

• Increasing the amount of unreabsorbed solutes in the tubule decreases water reabsorption due to the high osmotic pressure and thus lower osmosis rate

Examples:

- diabetes mellitus: unreabsorbed glucose because of excretion of glucose in tubules and this increase the osmotic pressure in the tubular fluid causes diuresis and water loss

- osmotic diuretics (mannitol): taking mannitol to reduce the pressure through diuresis : mannitol's concentration increases in the tubular fluid which increases the osmotic pressure and induce diuresis.

Ways to assess kidney function

• Plasma concentration of waste products (e.g. BUN, creatinine)

• Urine specific gravity, urine concentrating ability

• Urinalysis test reagent strips (protein, glucose, etc)

• Biopsy

• Albumin excretion (microalbuminuria)

• Isotope renal scans

• Imaging methods (e.g. MRI, PET, arteriograms, iv pyelography, ultrasound etc)

• Clearance methods (e.g. 24-hr creatinine clearance)

"Clearance" describes the rate at which substances are removed (cleared) from the plasma.

Renal clearance of a substance is the volume of plasma completely cleared of a substance per min by the kidneys.

We can get the clearance from this equation .

$$Cs \times Ps = Us \times V$$

$$Cs = \frac{Us \times V}{Ps} = \text{urine excretion rate} / \text{Plasma conc. s}$$

Where : Cs = clearance of substance S
Ps = plasma conc. of substance S
Us = urine conc. of substance S
V = urine flow rate

Substance	Clearance (ml/min)
glucose	0
albumin	0
sodium	0.9
urea	70
inulin	125
creatinine	140
PAH	600

The renal clearance of different substances is different. glucose and albumin have zero clearance because their excretion is zero . The clearance rate of the exogenous substances, such as inulin and PAH and the endogenous like creatinine is very high because these substances are toxic and thus the body works to get rid of them

For a substance that is freely filtered, but not reabsorbed or secreted (inulin, ^{125}I-iothalamate, creatinine), renal clearance is equal to GFR. Thus, the clearance of these substances can give estimation of GFR

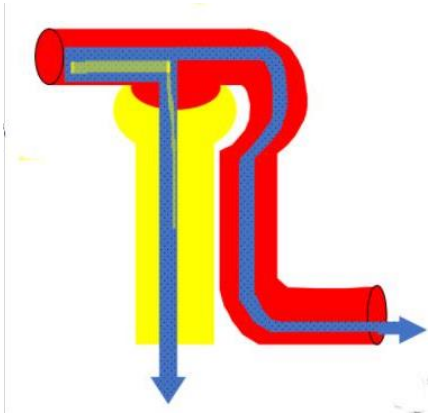
amount filtered = amount excreted

$$GFR \times Pin = Uin \times V$$

$$GFR = \frac{Uin \times V}{Pin}$$

P_{in} → Plasma concentration of inulin

U_{in} → Urine concentration of inulin



Calculate the GFR from the following data:

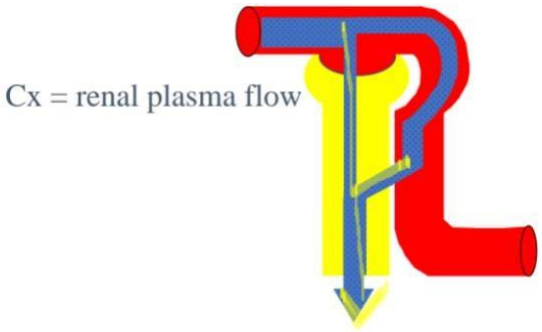
P_{inulin} = 1.0 mg / 100ml
U_{inulin} = 125 mg/100 ml
Urine flow rate = 1.0 ml/min

$$GFR = C_{inulin} = \frac{U_{in} \times V}{P_{in}}$$

$$GFR = \frac{125 \times 1.0}{1.0} = 125 \text{ ml/min}$$

Once we take the plasma concentration for inulin from a blood sample and taking the urine concentration for inulin and the urine flow rate after 24 hours collection of urine from the patient then we apply the equation we will have the clearance of inulin which equals the GFR and equals 125 ml/min.

Theoretically, if a substance is completely cleared from the plasma, its clearance rate would equal renal plasma flow.
These substances give an estimation of renal plasma flow



Cx = renal plasma flow

Paraminohippuric acid (PAH) is freely filtered and secreted and is almost completely cleared from the renal plasma. Since almost 90% of this substance is cleared from the plasma and only 10% remains in the plasma concentration, it can be used to estimate the renal plasma flow.

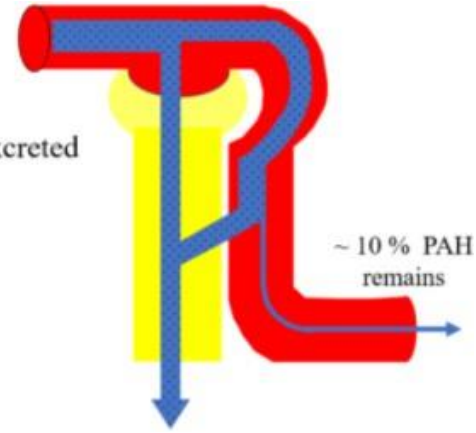
1. amount enter kidney = $RPF \times P_{PAH}$

2. amount entered ≅ amount excreted

3. $ERPF \times P_{pah} = U_{PAH} \times V$

$$ERPF = \frac{U_{PAH} \times V}{P_{PAH}}$$

ERPF = Clearance PAH



Since 10% of PAH remains in the plasma and is not completely cleared, the ERPF value obtained from the clearance rate of PAH must be corrected to get the actual renal plasma flow level.

Important <= it's required

(We are [redacted] required to know the correction calculations)....

$A_{PAH} = 1.0$

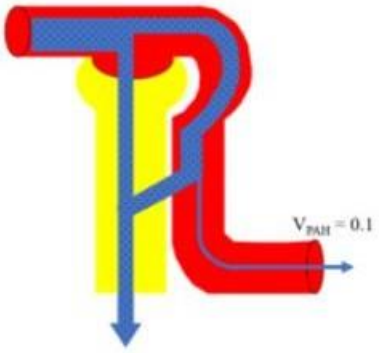
$$E_{PAH} = \frac{A_{PAH} - V_{PAH}}{A_{PAH}}$$

$$= \frac{1.0 - 0.1}{1.0} = 0.9$$

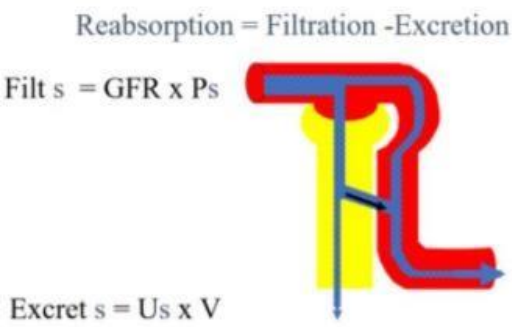
normally, $E_{PAH} = 0.9$

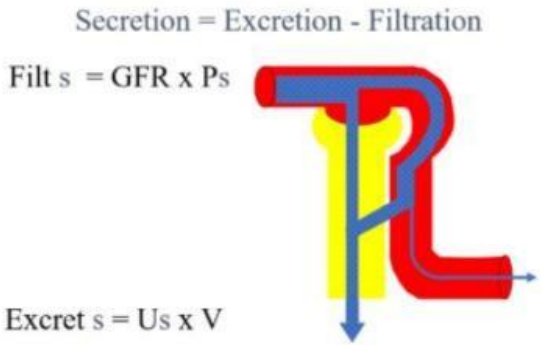
i.e PAH is 90 % extracted

$$RPF = \frac{ERPF}{E_{PAH}}$$



We should know these two important equations





Q: The maximum possible clearance rate of a substance that is completely cleared from the plasma by the kidneys would be equal to

1. glomerular filtration rate
2. the filtered load of the substance
3. urine excretion rate of the substance
4. renal plasma flow
5. none of the above

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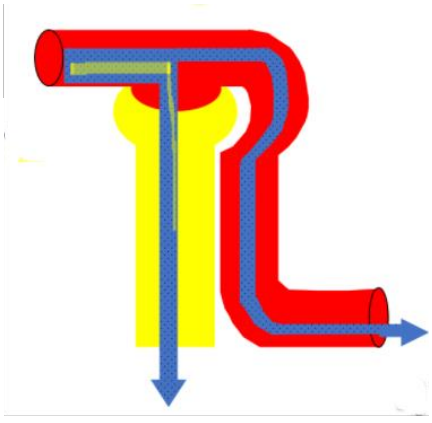

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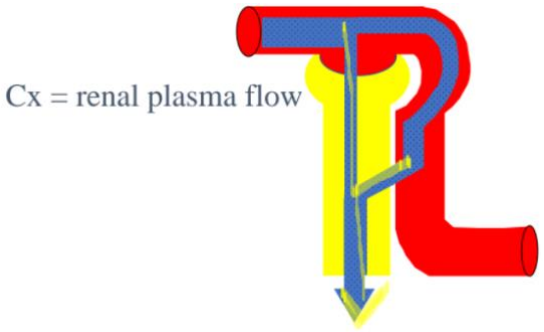

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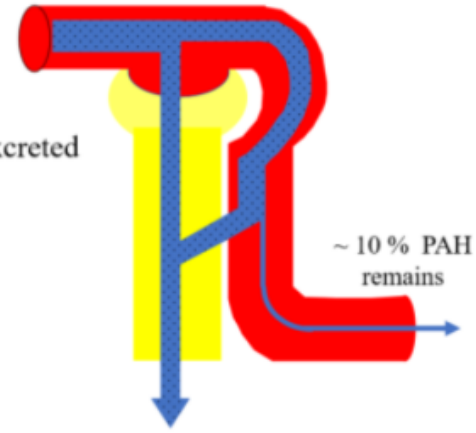

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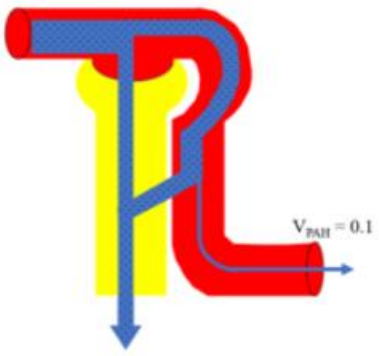
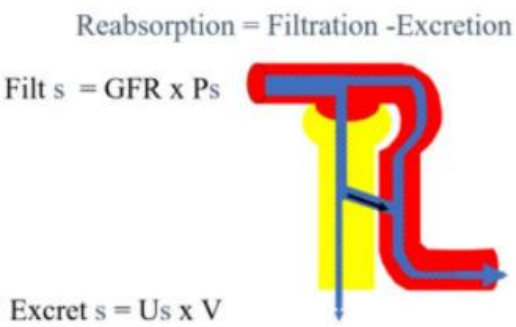
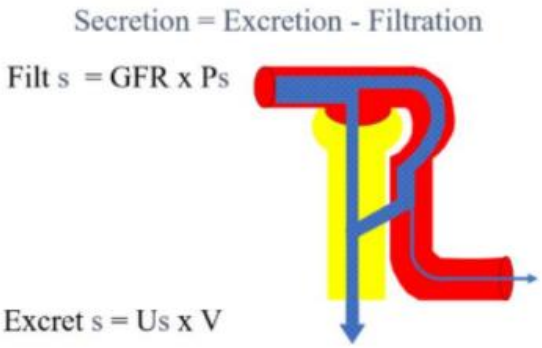


We should know these two important equations





Q: The maximum possible clearance rate of a substance that is completely cleared from the plasma by the kidneys would be equal to

1. glomerular filtration rate
2. the filtered load of the substance
3. urine excretion rate of the substance
4. renal plasma flow
5. none of the above

Substance	Clearance (ml/min
inulin	125
PAH	600
glucose	0
sodium	0.9
urea	70

Clearance of inulin (C_{in}) = GFR

if Cx < Cin : indicates reabsorption of x

if Cx > Cin : indicates secretion of x

Clearance creatinine (C_{creat}) ~ 140 (used to estimate GFR)

Clearance of PAH (C_{pah}) ~ effective renal plasma flow

The clearance of PAH was used to estimated the renal plasma flow while the

clearance of inulin was used to estimate the GFR.

If the clearance rate of a substance was less than the clearance rate for inulin or less then GFR, it means that reabsorption of that substance took place.

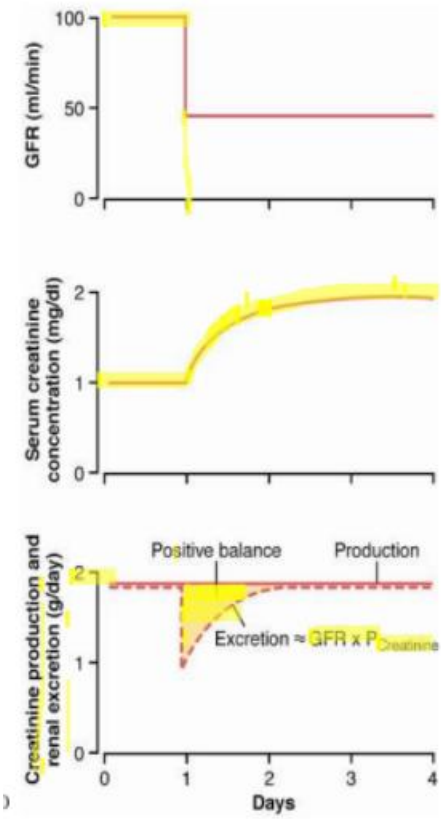
If the clearance rate of substance x is more than the clearance rate of inulin or more than GFR, it means that secretion of that substance to the filtrate took place.

The clearance rate of creatinine is close to the clearance rate of inulin but is slightly

higher (also higher than GFR); due to some level of secretion of creatinin. Although

only a freely filtered substance that doesn't undergo secretion or reabsorption is used to estimate GFR, creatinine is clinically used to estimate GFR because it is easier to track.

Effect of reducing GFR by 50 % on serum creatinine concentration and creatinine excretion rate



Since creatinine clearance rate can be clinically used to estimate GFR, how will serum creatinine concentration be affected if GFR was reduced by 50% ?

1-The first graph depicts the level of GFR. GFR was originally 100 mL/min in day 1 but was reduced to 50 mL/min in day 2

The second graph depicts serum creatinine concentration in mg/dL. Creatinine serum concentration was normal in day 1. However, as the GFR level was dropped by half, creatinine serum concentration was doubled to 2 mg/dL .

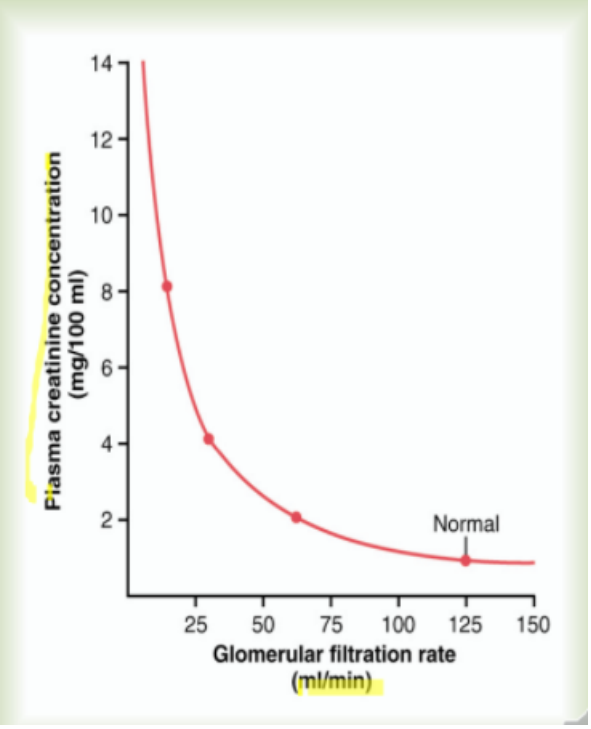
The third figure depicts creatinine production and renal excretion in g/day. Creatinine production is constant at 2 g/day as shown by the solid line on the graph. The renal excretion, as shown by the dashed line, was superimposed to the solid line that represent creatinine production during day 1 when the GFR was normal and serum creatinine concentration was also normal. However, when the GFR was reduced to half and creatinine serum concentration was doubled in response on day 2, creatinine excretion is reduced to half. This is the acute effect of reduced GFR level. However, creatinine excretion start to increase gradually. This is because, according to this equation:

$$\text{Excretion} = \text{GFR} \times P_{creatinine}$$

As GFR level was reduced by half, plasma creatinine concentration was doubled; thus creatinine excretion was able to gradually increase to be equal to creatinine production during the next day. Thus, as plasma creatinine concentration increases even though GFR level decreases, creatinine excretion increases to

bring, creatinine levels in the blood back to normal. This relationship maintains constant levels of serum creatinine concentration and prevent the plasma creatinine concentration to exceed 2 mg/dL.

Plasma creatinine can be used to estimate changes in GFR



This plot shows the relationship between the GFR (mL/min) and plasma creatinine concentration (mg/100mL). Using this plot, the plasma creatinine concentration can be measured by matching it with the corresponding estimated GFR.

This plot differs according to

different body weights, body mass index (BMI), age and gender.

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