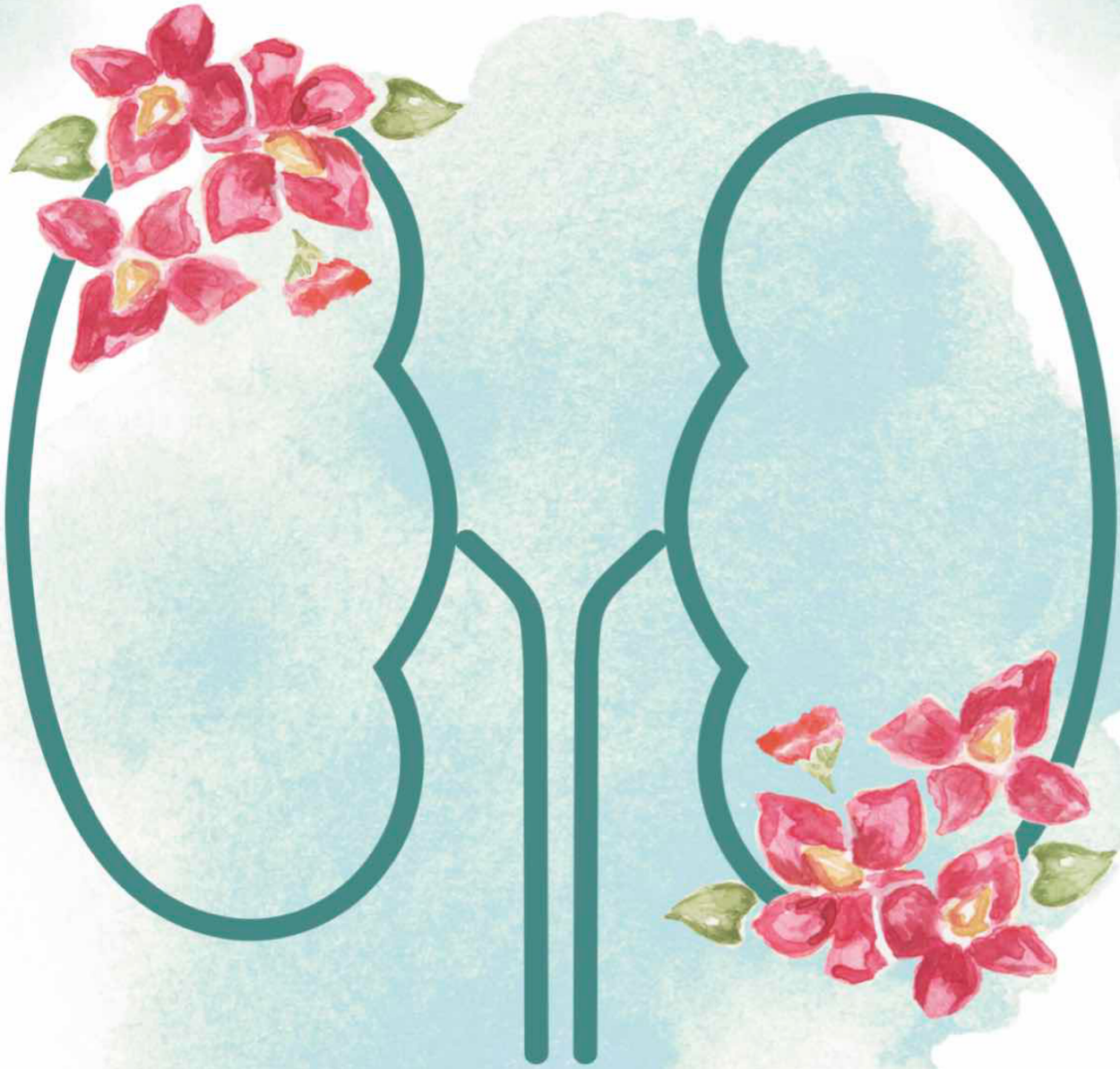


PHYSIOLOGY

- SHEET NO. 3
- WRITER : Dentistry
  0 1 9
- CORRECTOR : Sawsan alqeam
- DOCTOR : Type
  your text

note that renal oxygen consumption (y axis)
is related directly to sodium reabsorption (x axis)
(the more sodium absorbed the more oxygen is consumed ,
because this process needs energy as well as oxygen)

Control of GFR and renal blood flow

- **Any thing contributes to maintain Homeostasis , must be regulated**

GFR is a very important part of the function of kidneys , due to this , it must have regulatory mechanisms

Also RBF is very important to control and maintain and get normal GFR

- **So we have 2 types of regulatory mechanisms** :
  A. Neurohumoral (extrinsic)
  B. Local (Intrinsic)

A. Neurohumoral

✓ When we are talking about Neurohumoral , this means that we are talking about **nervous** system and **endocrine** system

1. Sympathetic nervous system / catecholamines

- Kidney is completely supplied with sympathetic system (no parasympathetic)
- Sympathetic nervous system produces catecholamines (epinephrine & norepinephrine)

What is the effect of sympathetic nervous system on GFR ?

- sympathetic nervous system produces catecholamines (neurotransmitters : epinephrine & norepinephrine) which are **vasoconstrictors**
- the response of these vasoconstrictors depends on the distribution of their receptors (adrenergic receptors) → the response of cells (here we are talking about smooth muscle cells) doesn't depend only on the neurotransmitter (ligand) , but also depend on the receptors and their density الوفرة
- adrenergic receptors are much more available in the afferent arteriole than efferent arteriole , so when there is a sympathetic stimulations , the vasoconstriction in the afferent is way more than in the efferent (vasoconstriction happens in both , but more intense in the afferent)
- so when afferent is vasoconstricted , GFR is decreased, RBF is decreased

- this mechanism isn't caused by mild sympathetic stimulation (when you are nervous because of an exam) , but caused by strong sympathetic stimulation (**sever hemorrhage** for example)
- this response happens due to sympathetic stimulation In case of danger , so body reduce the blood flow to the less important organs and directs blood to vital organs (brain and heart)
- kidney is important but less than brain and heart

2. Angiotensin II

- Angiotensin II is a prat from endocrine hormone system (renin-angiotensin-aldosterone system)
- Angiotensin is produced when there is a Hypotension (happens due to low fluids amount , hemorrhage ...)
- Hypotension → renin is produced from juxtaglomerular cells →goes to the blood circulation and converts angiotensinogen to angiotensin I → angiotensin l is converted to angiotensin II by ACE enzyme . (we will talk about this mechanism in details later)
- Angiotensin II is the **vasoactive** peptide which is the most important in this system (in addition to aldosterone which is stimulated by angiotensin II)

How angiotensin II works ?

- the response of angiotensin II is dependent on the distribution and availability of the receptors (AT receptors , AT1 is the dominant in smooth muscles cells of blood vessels)
- AT receptors is more available (higher density) in efferent than in afferent .
- This result in an increased GFR (vasoconstriction → resistance ↑, hydrostatic pressure ↑ , GFR↑)
- Angiotensin II is produced due to hypotension , so there is a previous tendency of GFR to be reduced , so Angiotensin II acts to get the GFR back to its normal level
- The function of Angiotensin II is to prevent the decrease in GFR

✓ قيمة ال GFR بتكون أصلا قليلة بسبب انخفاض ضغط الدم ، فبسبب انخفاض الضغط ، يتم افراز ال angiotensin II بعدة خطوات ، فوجوده بسبب رجوع ال GFR لقيمتها الطبيعية لأنها كانت منخفضة وهو اجا رفعها (يعني هو تأثيره صح يرفعها بس لمستواها الطبيعي)

- Angiotensin II is produced to prevent the decrease in blood pressure , not to cause Hypertension , but when there is problem with the level of Angiotensin II then this will lead to hypertension (pathologically)
- When Angiotensin II is produced ? low sodium diet, volume depletion (hypotension)

✓ To conclude : physiologically , Angiotensin II is produced to prevent both blood pressure and GFR to decrease below normal , and if it's defect there will be hypertension .

3. Prostaglandins

- Local mediator
- Work as Vasodilators in the kidneys
- Their receptors are more available in afferent more than in efferent
- So what happens when there is a vasodilation in the afferent much more than in efferent ?

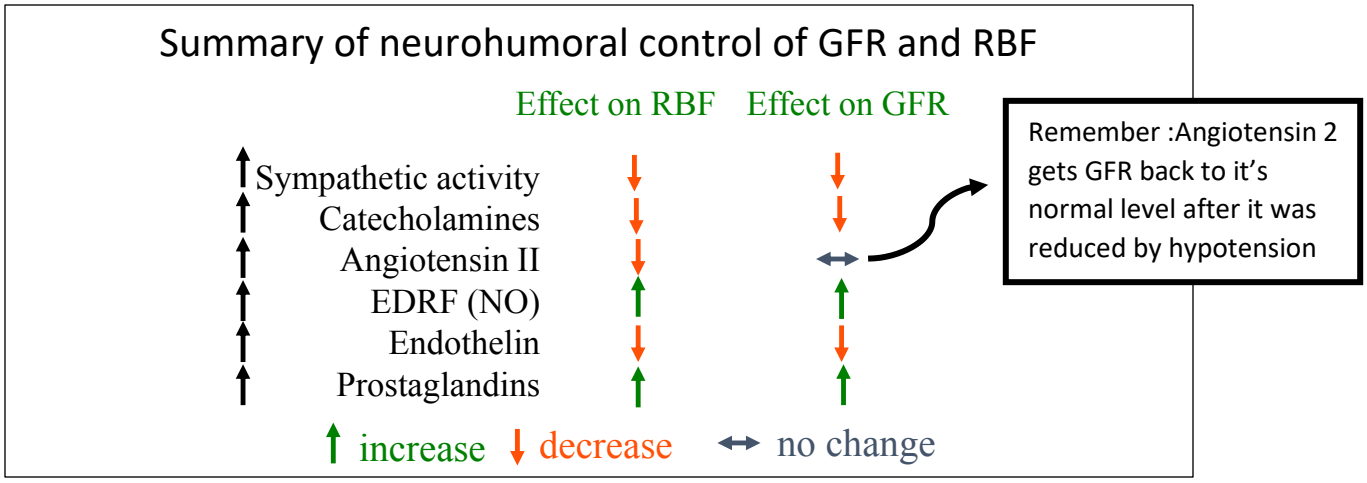
→A build up in the hydrostatic pressure will result , so GFR will increase (blood flow increase to the glomerulus and accumulation of blood)

- ✓ Prostaglandins are helpful in case of kidney diseases because it improves GFR and RBF and function of the kidney
- ✓ Dentist must be very careful when they give a patient nonsteroidal anti-inflammatory drugs (pain-killers) because they prevent the synthesis of Prostaglandins , why ? because patients that have renal disease with low GFR , pain-killers prevent the synthesis of prostaglandins and this will make things worse than before (GFR was low and now it's lower ☺) , **contraindicated** !
- ✓ volume depleted patient, or a patient with heart failure, cirrhosis, etc.. also should not be given prostaglandins blockers for the same reason (they have low GFR and if we give them prostaglandins blockers, then GFR will get lower)

4. Endothelial – derived nitric oxide (EDRF) → NO

- Local factor (can be considered as a hormone)
- Vasodilators produced by juxtaglomerular cells and endothelial cells (Protects against excessive vasoconstriction)
- Their receptors are more available in afferent than in efferent
- Increase in GFR and RBF (so it's helpful for the function of the kidneys)
- Patients with endothelial dysfunction (e.g. atherosclerosis) may have greater risk for excessive decrease in GFR in response to stimuli such as volume depletion → because endothelial cells is unable to produce nitric oxide , so when there is a problem (low GFR) they can't adapt to increase it because nitric oxide is absent

5. Endothelin
    - Local mediator/ factor
    - Vasoconstrictor (harmful)
    - Increases the vasoconstriction in the afferent more than in efferent
    - Decrease in both GFR and RBF
    - Hepatorenal syndrome – decreased renal function in cirrhosis or liver disease? (NOT required)
    - Acute renal failure (e.g. contrast media nephropathy)?
    - Hypertensive patients with chronic renal failure?
    - Endothelin antagonists may be useful in these conditions (if the endothelin is the cause of the problem)



B. Local Control (INTINSIC)

6. Autoregulation of GFR and Renal Blood Flow

✓ Intrinsic means something that is automatic in kidney or a private kidney system that doesn't need any control of nervous or endocrine system to regulate it

✓ It's much more important than extrinsic because it's internal and comes from the renal system itself

1. Myogenic Mechanism (related to the smooth muscles of arterioles)
2. Macula Densa Feedback (tubuloglomerular feedback) In juxtaglomerular apparatus there is a kind of feedback or crosstalk between macula Densa and juxtaglomerular cells
3. Angiotensin II (contributes to GFR but not RBF autoregulation) produced due to the production of renin (from JGC)

Tubuloglomerular feedback mechanism:

- Feedback mechanism → crosstalk between macula Densa and juxtaglomerular cells
- Stimulus of mechanism : disruption of homeostasis

Here in our example (look at the pic) GFR is more than normal

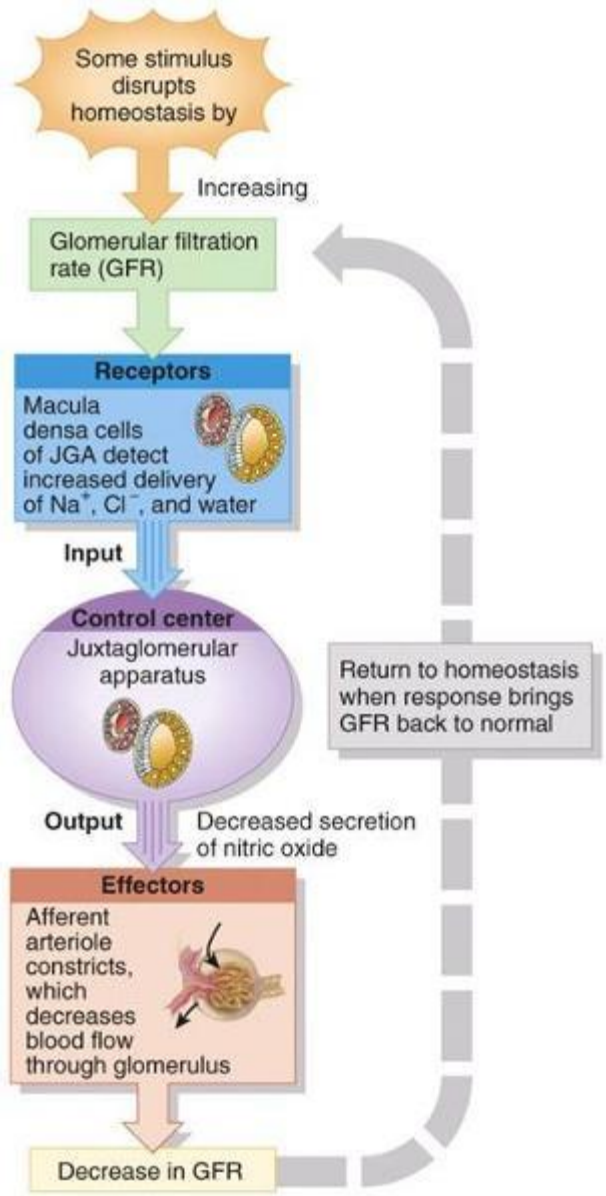
juxtaglomerular apparatus : when the afferent arterioles (juxtaglomerular cells) are very close to the macula Densa which is a part of thick ascending of Henle or distal convoluted tubule

macula Densa → dark in light microscope

- When GFR is increased , the delivery of NaCl will increase in the filtrated fluid that reaches distal convoluted tubules

More NaCl filtration → distal convoluted tubules will receive more NaCl → macula Densa receives more NaCl

- Input: Macula Densa sends feedback to the juxtaglomerular cells (that there is high NaCl in the filtrated fluid)
- juxtaglomerular cells will detect the high level of GFR
- output : GFR must be reduced



how can GFR be reduced by affecting juxtaglomerular cells (modified smooth muscle cells) ?

by vasoconstriction of afferent arterioles → reduction of RBF → reduction of GFR (back to normal)

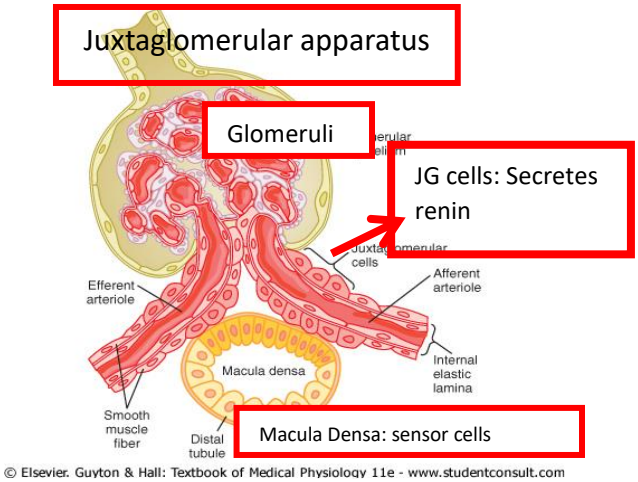
vasoconstricted by : reduction in nitric oxide (enzyme that is responsible to produce NO in the endothelial cells of afferent arterioles is inhibited)

- ✓ feedback continues to take place until homeostasis is maintain again (NORMAL GFR)
- ✓ **Autoregulation**: note that we didn't need any nervous control or adrenal gland or any other gland (internal)
- ✓ ((Deleted note from doctor not required)) About normal ranges of angiotensin II and it's effect, it doesn't give any help in this regulation (decrease in GFR), it may give help in case of presence of very high level of angiotensin II.

Angiotensin II plays an important role in autoregulation. when the GFR drops , it increases GFR after Renin release from JG cells.

juxtaglomerular cells

- JG cells are present In juxtaglomerular apparatus
- Look at their location in the afferent arterioles , very close to the macula Densa (which is a part of distal convoluting tubule or the last part of thick ascending loop of Henle)
- When there is a delivery of NaCl (or any other abnormal sign in perfusion) , feedback or crosstalk between these 2 kind of cells takes place
- Renin is produced by JG cells



Tubuloglomerular Feedback

What are the stimulations of renin production from JG cells ?

1. Perfusion Pressure :low perfusion in afferent arterioles stimulates renin secretion while high perfusion inhibits renin secretion

→if the blood flow is reduced (hypotension) in the afferent arterioles this will stimulate JG cells to secrete renin , if the perfusion is high (hypertension) JG cells will be inhibited so won't secrete renin

2. Sympathetic nerve activity : Activation of the sympathetic nerve fibers in the afferent arterioles increases renin secretion → production of angiotensin II

3. NaCl delivery to macula Densa : When NaCl is decreased, Renin secretion is stimulated and vice versa.

    - ➔ When NaCl is low in the macula Densa , this means that GFR is low because the pressure in the whole body is low , so when juxtaglomerular cells feel this low NaCl by the crosstalk with macula Densa → renin will be secreted → Angiotensin II production → more vasoconstriction in efferent than in afferent (within physiological levels not pathological levels) → increased glomerular hydrostatic pressure → increased GFR
    - ➔ We started with low GFR level and ended with normal level
    - ➔ Note that the function of Angiotensin is to get the level of GFR back to normal not to cause high pressure (but in case there is a problem with angiotensin it causes high pressure)

Go back to (48:10) from lecture for more understanding

GOOD LUCK :P

Renal Auto-regulation

- Its Feedback mechanisms intrinsic to the kidneys normally
  Keep the renal blood flow and GFR relatively constant, despite marked changes in arterial blood pressure.

- The function of blood flow autoregulation :

  1- In general, to maintain the delivery of oxygen and nutrients at a normal level and to remove the waste products of metabolism, despite changes in the arterial pressure.

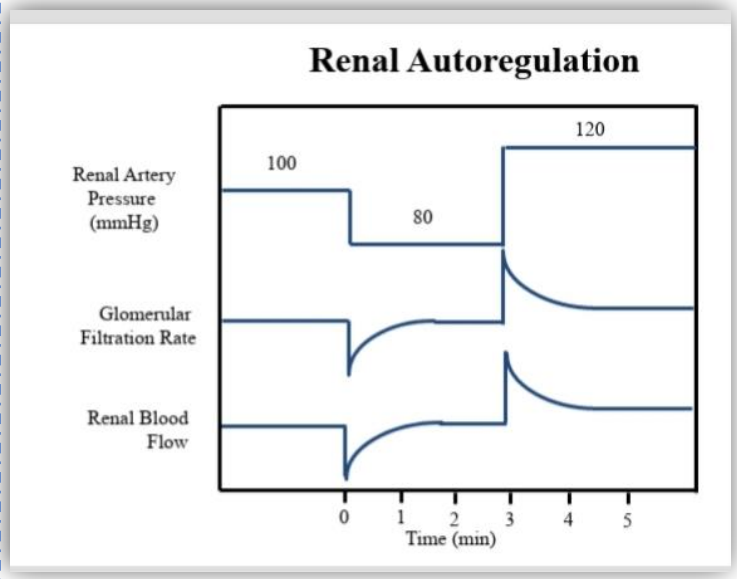
  2- Specifically in kidney, to maintain a relatively constant GFR and to allow precise control of renal excretion of water and solutes.

Look at this picture, you will notice that:

- **Firstly,** we have **normal RAP** , so the GFR and RBF are in their normal level .
- **Then,** the value of **RAP is decreased** due to many reasons, so what will happen to the values of GFR and RBF ?
  - We expect an decrease in these value but what is really happening is sudden and just temporary decrease then they will retain back to normal level (almost normal)
  - Same thing if we have **increase in RBP.**

⇨ **Temporary increase** in **GFR** and **RBF** then will retain back to normal level

We have resistance of changes in GFR and RBF even if the pressure is changed.



This is just to try to understand what we're going to talk about in this lecture

The autoregulation has two mechanisms

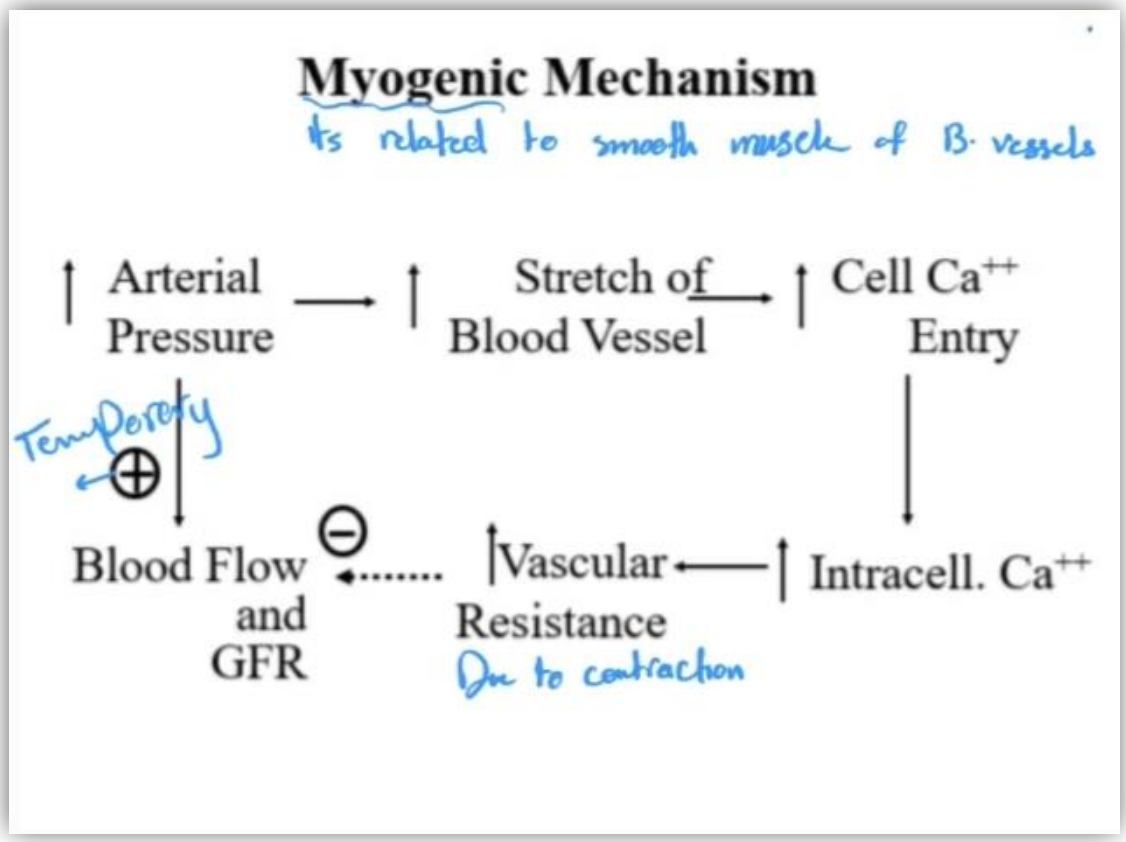
1- Myogenic autoregulation of renal blood flow
2- Macula dense feedback (tubuloglomerular feedback)
   - **Let's start to explain them:**

❖ Myogenic autoregulation of renal blood flow:

- Is the ability of individual blood vessels (especially small arterioles) **to resist stretching** during increased arterial pressure .

- **Stretch** of the vascular wall **allows increased movement of calcium ions** from the extracellular fluid **into the cells**, causing the **smooth muscle cells to contract** so the **diameter will decrease.**

- This contraction **prevents excessive stretch** of the vessel and at the same time, by **raising vascular resistance**, helps prevent **excessive increases in renal blood flow** and **GFR when arterial pressure increases**.



❖Macula densa feedback (tubuloglomerular feedback) :

Decreased macula dense [NACL] causes vasodilation of afferent arterioles and increase Renin release

Before we start we should know:

- The kidneys have a special feedback (tubuloglomerular feedback) that links changes in NACL conc.
- In macula densa with the control of renal arteriolar resistance and autoregulation of GFR , this Feedback helps to ensure a relatively constant delivery on of NACL to the distal tubule and helps prevent spurious fluctuations in renal excretion that would otherwise occur .

The Tubuloglomerular feedback mechanism has two components that act together to control GFR:

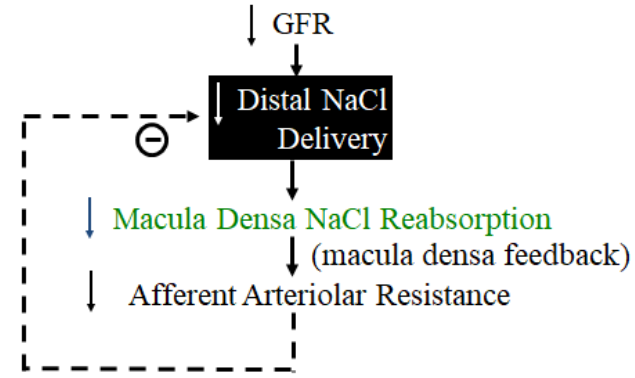
(1) An Afferent arteriolar feedback mechanism .

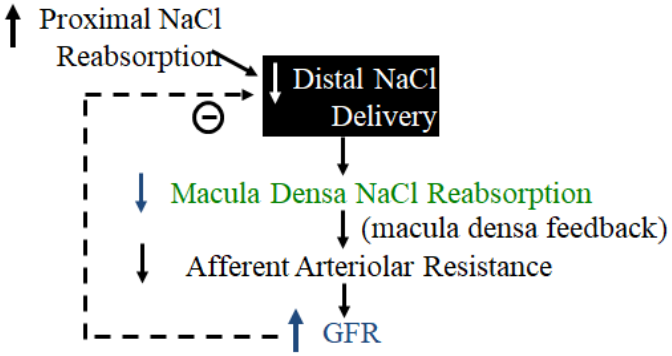
(2) An Efferent arteriolar feedback mechanism.

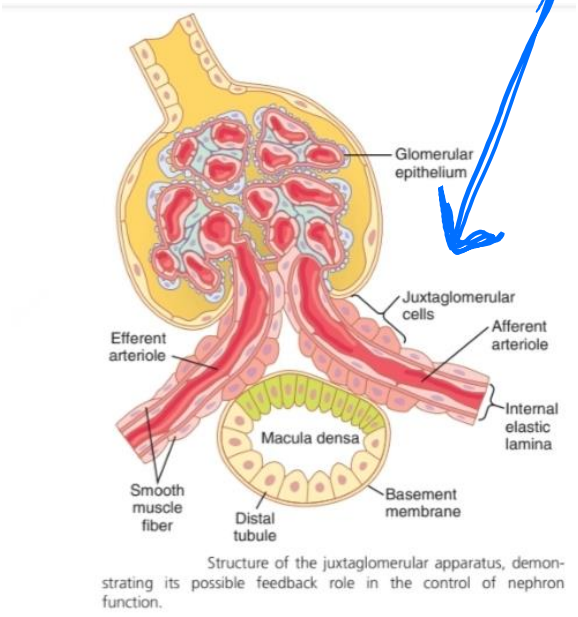
Remember

The juxtaglomerular complex consists of macula densa cells in the initial portion of the distal tubule and juxtaglomerular cells in the walls of the afferent and efferent arterioles

Macula Densa Feedback







Structure of the juxtaglomerular apparatus, demonstrating its possible feedback role in the control of nephron function.

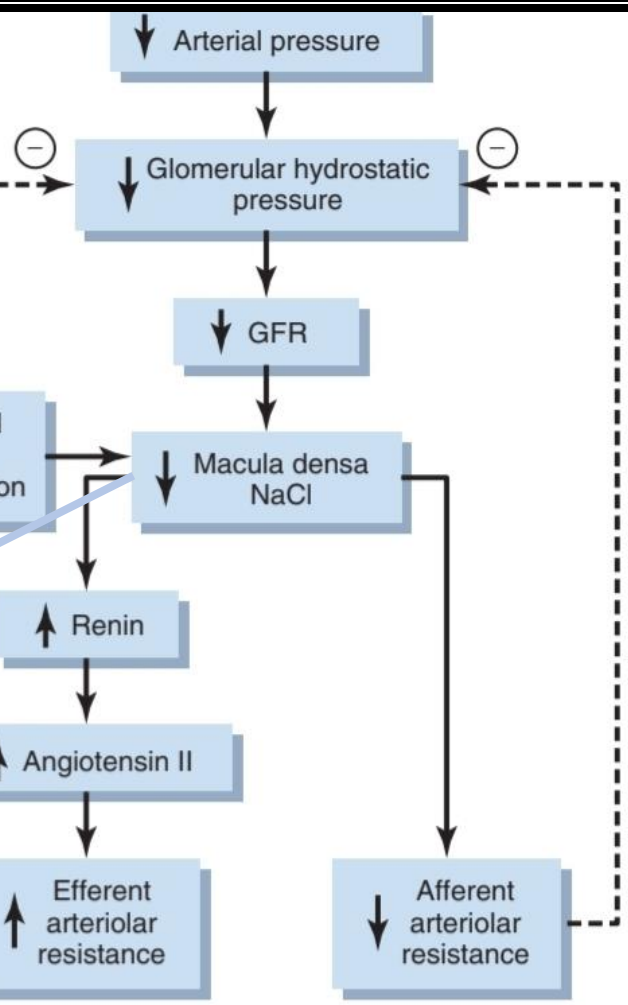
Macula dense feedback mechanism

SO protein ingestion leads to ↑ GFR .

Protein ingestion

↑ Amino acids

↑ Tubular Amino acid reabsorption.



This decrease of sodium chloride concentration initiates a signal from the macula dense that has effects on Efferent and Afferent arterioles

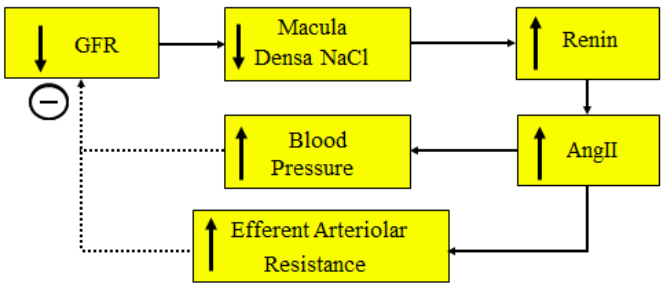
❖ The question now, how the signals that from macula dense effect on afferent and efferent arterioles :

1. **Afferent arterioles**

It stimulates **nitric oxide** synthesis in endothelial cells, then the nitric oxide is considered **vasodilator** for the afferent arterioles so its **resistance to blood flow decrease**, which **raises glomerular hydrostatic pressure** and helps return **GFR toward normal**

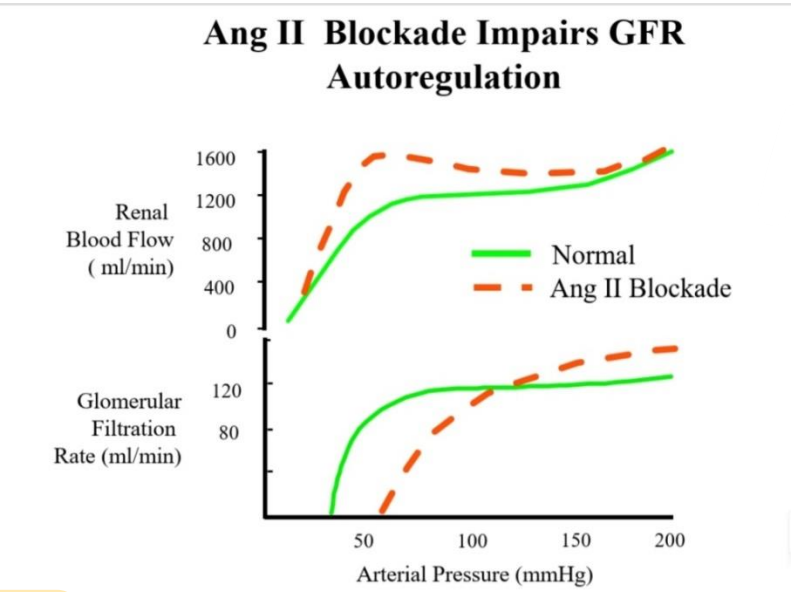
2. **Efferent arterioles**

It **increases Renin** release from the **juxtaglomerular cells** of the afferent and efferent arterioles, **which are the major storage sites for renin**. Renin released from these cells **to blood** then functions as an enzyme to **increase the formation of angiotensin I**, which is **converted to angiotensin II**. Finally, the **angiotensin II constricts** the efferent arterioles, so the **resistance increases** and then **increasing glomerular hydrostatic pressure** and helping to return **GFR toward normal.**



❖ Angiotensin II blockade impairs GFR autoregulation

- You know that some of the drugs hypertensive patients take **inhibit angiotensin II synthesis (such as ACE inhibitors)** , or the **prevention of binding between angiotensin II and their receptors.**
- When we create a blockade for angiotensin II, there will be impairment to the **plateau** that is created naturally (Observed in the normal curves of the graph) . Instead, these patients will have **severe changes** in GFR only .This will cause impairment of autoregulation .
- **angiotensin II prevent GFR drop .**



❖ Other factors that influence GFR

1- **Fever, pyrogens:** increases GFR
2- **High dietary proteins**: increases GFR
3- **Low dietary protein**: Decreases GFR
4- **Glucocorticoids**: increases GFR and reabsorption
5- **Aging**: Decreases GFR (every decade after 40 years results in a 10% decrease in GFR function)
6- **Hyperglycemia**: increases GFR (diabetes mellitus) (Osmotic effect of glucose)

❖ Importance of GFR auto-regulation in preventing extreme changes in renal excretion

In reality, changes in arterial pressure usually exert much less of an effect on urine volume for two reasons:

(1) Renal autoregulation prevents large changes in GFR that would otherwise occur (what we had discussed in this lecture)

(2) There are additional adaptive mechanisms in the renal tubules that cause them to increase their reabsorption rate when GFR rises (what we will discuss in next lectures)

You can understand the quantitative importance of autoregulation by considering the relative magnitudes of glomerular filtration, tubular reabsorption, and renal excretion and the changes in renal excretion that would occur without auto regulatory mechanisms.

Arterial Pressure	GFR	Reabsorption	Urine Volume
Poor Autoregulation + no change in tubular reabsorption			
100	125	124	1.0 → normal
120	150	124	26.0 = 37.4 L/day!
Good Autoregulation + no change in tubular reabsorption			
120	130	124	5.0
Good Autoregulation+adaptive increase in tubular reabsorption			
120	130	128.8	1.2

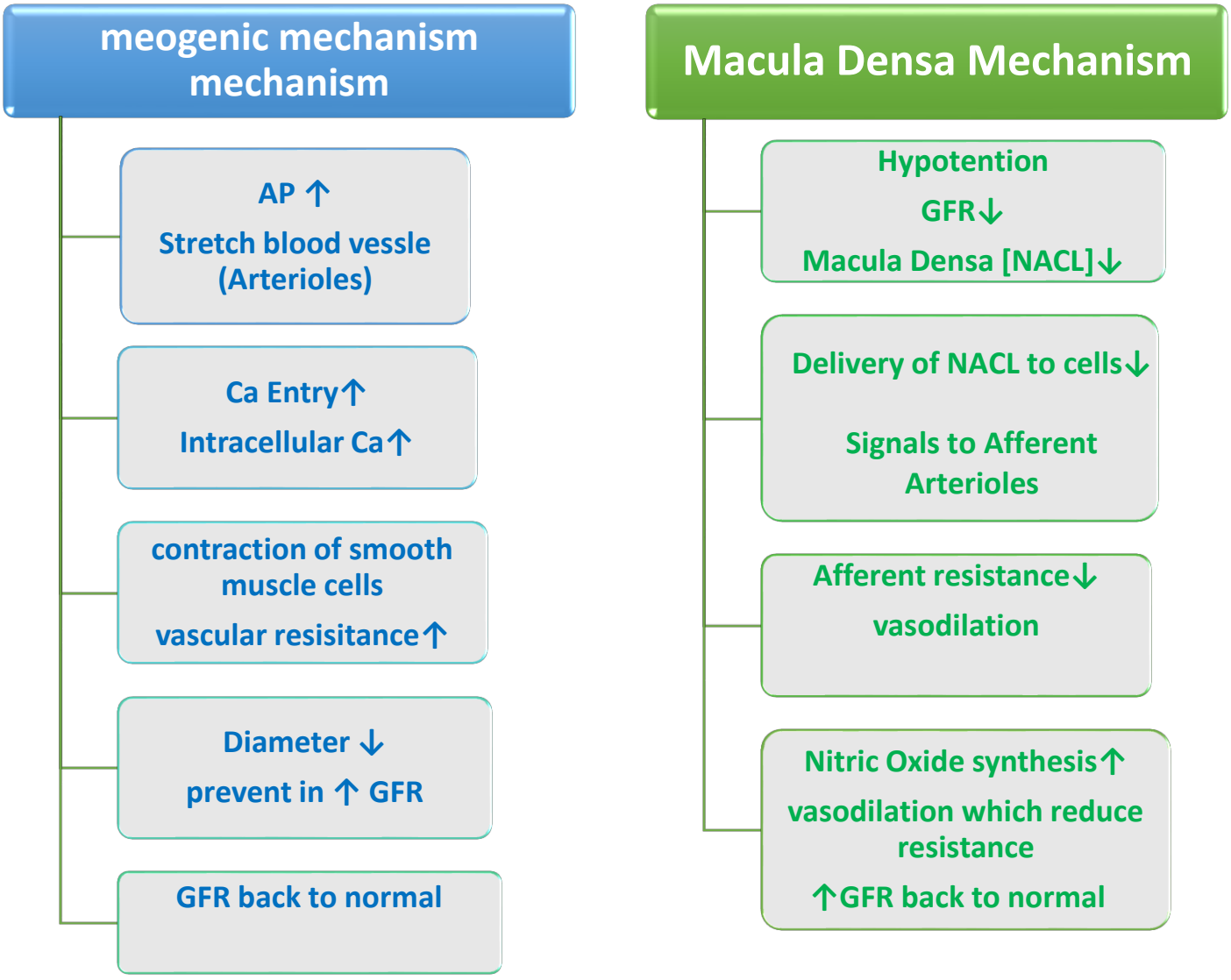
- **If arterial pressure is normal**, the GFR is supposed to be at a value of around 125 , the normal reabsorption rate is 124ml/min , which give us a urine volume of 1ml/min **(filtration – reabsorption)**

- **In the case of increased arterial pressure, poor autoregulation and constant tubular reabsorption**, GFR will be 150 , while reabsorption rate will remain 124ml/ min and the urine output will be **26ml/min!!!**

- **In the case of increased arterial pressure, good autoregulation and constant tubular reabsorption**, GFR will be 130, while reabsorption rate will remain 124ml/ min and the urine output will be 5ml/min.

- **In the case of increased arterial pressure, good autoregulation and adaptive tubular reabsorption**, GFR will be 130, while reabsorption rate will change to 128.8ml/ min and the urine output will be 1.2ml/min.

Soooo ..



Observe and learn, these years are here to teach you.

Good luck