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Renal Physiology 4

We are still finishing the slides from the previous lecture

Determinants of Renal Blood Flow (RBF)

RBF = ΔP / R

ΔP = difference between renal artery pressure and renal vein pressure

- The blood pressure in the renal artery is the same as the arterial blood pressure =100mmHg
- While the renal veins, there is a drop in pressure so it reaches 4 mmHg

R = total renal vascular resistance

= Ra + Re + Rv

Ra = resistance in afferent

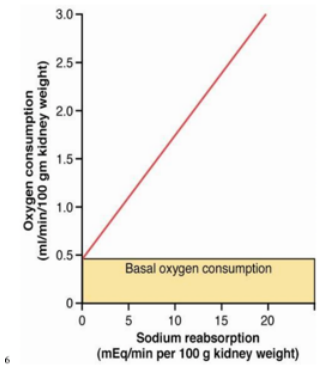
Re = resistance in efferent

Rv = resistance in vein

= sum of all resistances in kidney

Vasculature Renal blood flow

- High blood flow (~22 % of cardiac output)
  - This is higher than what the kidney needs in terms of metabolic needs (a lot higher than what it needs, it has double of what it needs)
- High blood flow needed for high GFR
  - Has a 7x higher blood flow than the brain, this is related to the kidney function
  - For sufficient filtration
- Oxygen and nutrients delivered to kidneys normally greatly exceeds their metabolic needs
- A large fraction of renal oxygen consumption is related to renal tubular sodium reabsorption
  - So they noticed that the oxygen consumption increased every time the sodium reabsorption increased
  - This is because we use a lot of energy when reabsorbing sodium
  - They noticed that (follow along the picture) that when the GFR was constant there was no reabsorption of sodium since there is no filtration of sodium, so they noticed that the oxygen consumption was constant which is the basal oxygen consumption (0.5 ml/min/100gm kidney weight)



The new slides from this lecture

Control of GFR and renal blood flow

- We talked about how important it is to control GFR, we said its very important since its related to homeostasis and clearance of waste and toxins
- Plus the GFR is the filtration process so if the filtration process stopped, there wont be fluid to fill up the tubules so there is going to be a buildup of the salts and solutes that will accumulate causing crystallization resulting in blockage and damage of the nephrons →so its really dangerous if the GFR just stopped (this is in extreme cases)
- 2 main types of regulation of the GFR:
  - Neurohumoral
  - Local (Intrinsic)/ Autoregulation – MOST IMPORTANT ONE
    - The kidney does that by itself even if it wasn't connected to any nervous or endocrine control, it does it by itself

Neurohormonal:

1. Sympathetic Nervous System /catecholamines

↑↑RA + ↑RE → ↓GFR + ↓↓RBF

e.g. severe hemorrhage

- We need to differentiate between low level/ moderate level of stimulation and severe levels
  - Low/moderate levels
    - At low to moderate level of stimulation, there is no significant changes of GFR or renal blood flow since its going to get overcome by other process so it wont have any significancy
  - Severe levels
    - But if there is severe level of stimulation of the sympathetic system, it is going to affect the GFR
      - When we say severe we mean severe hemorrhage, severe hypotension or severe hypovolemic shock or severe ischemia
    - At these circumstances there is going to be severe vasoconstriction in the AFFERENT arterioles mainly and this will reduce the glomerular hydrostatic pressure (since less blood flow anyways) so it will reduce the GFR, plus the renal blood flow would decrease

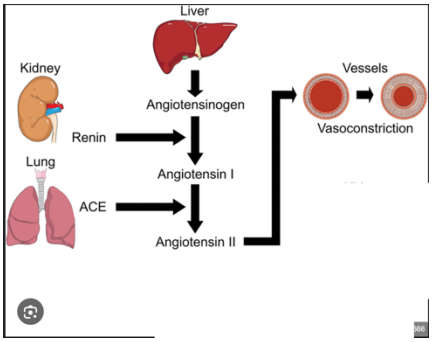
2. Angiotensin II

↑RE → ↔GFR +↓ RBF

(prevents a decrease in GFR)

e.g. low sodium diet, volume depletion

- The angiotensin II is part of the renin-angiotensin-aldosterone system



- It can be considered a part of the humoral endocrine control as well as the local control
- It gets released when there is hypotension (hypovolemia), low salts/sodium and when there is hemorrhage, in these cases there is stimulation of the renin enzyme
- Production of angiotensin II
  - and this renin enzyme when released into the blood it would cut the angiotensinogen which will result in the production of the angiotensin I peptide and this peptide will be cut by ACE in the pulmonary circulation which will convert it into angiotensin II
- Effect of Angiotensin II
  - This angiotensin II peptide is vasoactive, it goes to all vasculature and induces vasoconstriction, so it raises blood pressure directly
  - In the kidney it has a preferential role, in which it induces constriction more in the EFFERENT arteriole more than the afferent
    - there could be multiple reasons like density of receptors, or there are vasodilators that affect the afferent arterioles so the efferent is there to remove the effect of them
  - So the effect of the Angiotensin II is that it would increase the blood pressure increasing the glomeruli hydrostatic pressure, increasing the GFR, BUTTTTTTTTTTTT when I say I increased the GFR I mean I increased it to reach the normal, it wont increase to become higher than the normal, so it prevented a decrease in GFR

3. Prostaglandins (mainly PGE2)

↓↓RA + ↓RE → ↑GFR + ↑↑RBF

Blockade of prostaglandin synthesis ⟶ ↓ GFR

This is usually important only when there are other disturbances that are already tending to lower GFR

e.g. nonsteroidal anti-inflammatory drugs in a volume depleted patient, or a patient with heart failure, cirrhosis, etc

- We know that there are types of prostaglandins, in which the ones in the kidney are vasodilators so they induce vasodilation mainly for the AFFERENT arterioles, and this enhances blood flow so increasing the glomeruli hydrostatic pressure resulting in an increase in GFR and renal blood flow
- Blockade of prostaglandins by taking NSAIDs, especially for ppl who have abnormal kidney function (their GFR is below normal) those would be affected and they're contraindicated to take NSAIDs, cause this will remove the effect of prostaglandins

4. Endothelial-Derived Nitric Oxide (EDRF)

↓↓RA + ↓RE → ↑GFR + ↑↑RBF

Protects against excessive vasoconstriction

Patients with endothelial dysfunction (e.g. atherosclerosis) may have greater risk for excessive decrease in GFR in response to stimuli such as volume depletion

- similar to prostaglandins in which it induces vasodilation in the AFFERENT arteriole mainly thus increasing both RBF and GFR

5. Endothelin

↑↑RA + ↑RE → ↓GFR + ↓↓RBF

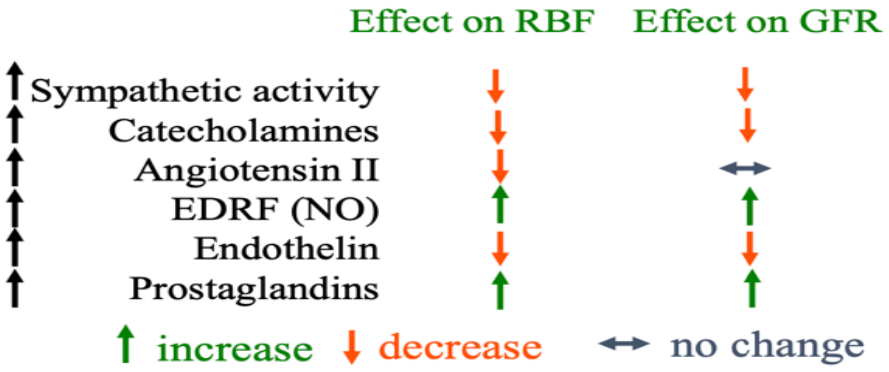
Hepatorenal syndrome – decreased renal function in cirrhosis or liver disease?

Acute renal failure (e.g. contrast media nephropathy)?

Hypertensive patients with chronic renal failure?

Endothelin antagonists may be useful in these conditions

- it's a local hormones that is secreted when there is a cut in vessels, its effect is vasoconstriction to reduce bleeding but it was found to be associated with many diseases like hypertension and pregnant women and in certain types of hypertension, in which endothelin is what causes it
- in the kidneys it causes vasoconstriction in the AFFERENT arterioles mainly reducing the glomeruli hydrostatic pressure reducing GFR and Renal blood flow

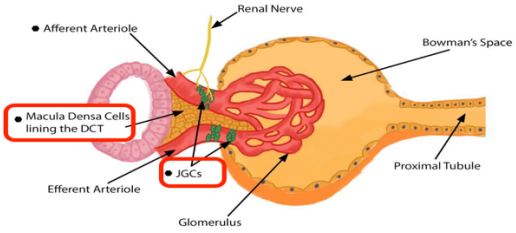


Autoregulation of GFR and Renal Blood Flow

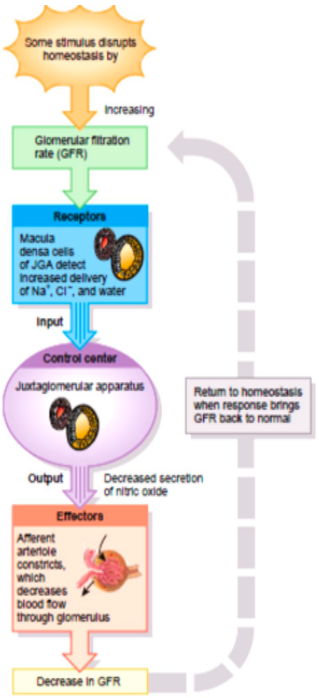
- Myogenic Mechanism
- Macula Densa Feedback (tubuloglomerular feedback) – MOST IMPORTANT ONE
  - It's the juxtaglomerular apparatus/complex
- Angiotensin II (contributes to GFR but not RBF autoregulation)
  - As we said before, its preferential increase in resistance in the efferent arteriole (works on the afferent too but mainly on the efferent) increasing the GFR, preventing it from declining
  - Works in the kidneys since the renin is released from the kidney

Renal Autoregulation of GFR

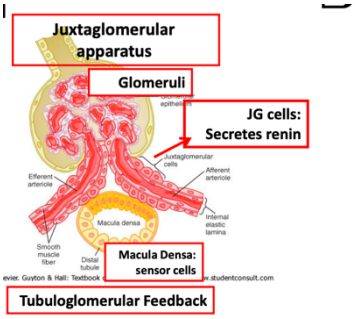
2. Tubuloglomerular feed back mechanism:
    - As we said before the macula densa was part of the distal convoluted tubule, and its very close to the juxtaglomerular cells (which are part of the afferent and the efferent arterioles), in which they come very close together (the juxtaglomerular cells and the macula densa) forming a feedback loop between them



    - So its called tubuloglomerular feedback since the change in NaCl is detected by the macula cells in the distal convoluted tubule and it sends signal to the juxtaglomerular cells
    - This feedback keeps occurring when there is a change of GFR so it corrects it
    - The loop of feedback:
        - The kidneys have a special feedback mechanism that links changes in sodium chloride concentration at the macula densa with the control of renal arteriolar resistance and autoregulation of GFR



        - This feedback helps ensure a relatively constant delivery of sodium chloride to the distal tubule and helps prevent spurious fluctuations in renal excretion that would otherwise occur.
        - If the GFR was high that means we have high NaCl that will be sensed by the macula densa in the distal convoluted tubule, and it will then send signals to the juxtaglomerular cells to reduce the GFR and it does so in many ways:
            - Inhibition of NO synthesis
                - As we said before, NO causes vasodilation of the AFFERENT arteriole, increasing blood flow, increasing the hydrostatic pressure thus increasing the GFR
                - Inhibiting NO, reduced vasodilation of the AFFERENT arteriole, reducing blood flow, reducing hydrostatic pressure, thus reducing the GFR
            - Inhibition of Renin
                - It would get inhibited due to high GFR
        - If the GFR was low, the NaCl would also be low in the distal convoluted tubules so the macula densa there would sense it and send a signal to the AFFERENT arteriole(juxtaglomerular cells) to increase the GFR either by:
            - Synthesizing more NO



- As we mentioned above the NO would cause vasodilation of the AFFERENT arteriole which in turn would decrease its resistance, increasing the blood flow to the glomeruli, increasing the hydrostatic pressure thus increasing the GFR

- Stimulate Renin
  - As we mentioned in one of the previous lectures that the juxtaglomerular cells are the cells that release Renin
  - And this Renin as we mentioned above, results in more Angiotensin II that will increase the systemic blood pressure, increasing the glomeruli hydrostatic pressure thus increasing the GFR
    - Remember Angiotensin II causes vasoconstriction in the EFFERENT arterioles .

- Feedback loop consists of a flow rate (increased NaCl in filtrate) sensing mechanism in macula densa of juxtaglomerular apparatus (JGA)
- Increased GFR (& RBF) inhibits release of the vasodilator ; Nitric Oxide (NO)
- Ang II when blood pressure falls is released increasing systemic BP and increasing glomerular hydrostatic pressure and thus GFR, however, when blood pressure is increased renin and AngII release are inhibited

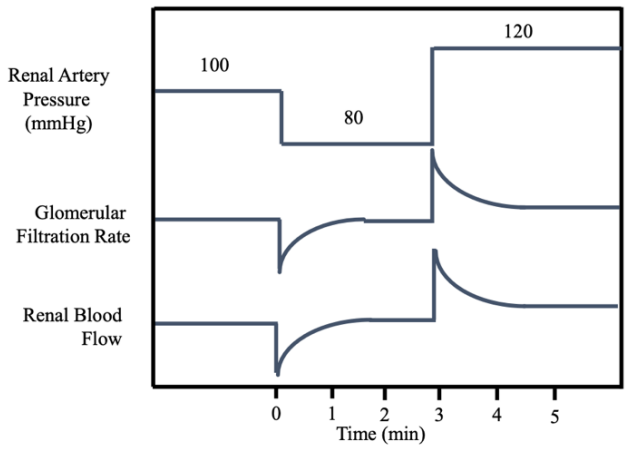
Renin secretion regulation

Stimuli:

1- Perfusion Pressure
   a. low perfusion in afferent arterioles stimulates renin secretion while high perfusion inhibits renin secretion.
2- Sympathetic nerve activity
   a. Activation of the sympathetic nerve fibers in the afferent arterioles increases renin secretion.
3- NaCl delivery to macula densa:
   a. When NaCl is decreased, Renin secretion is stimulated and vice versa. (Tubuloglomerular Feedback)

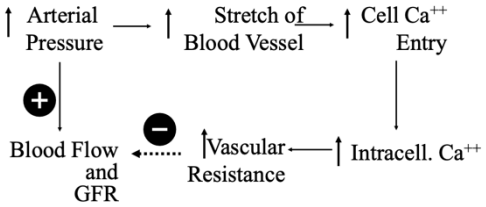
Renal Autoregulation

- Follow along the picture
- Normal Pressure
  - When the pressure in the renal artery is 100, and the glomerular filtration rate is normal here and the renal blood flow is normal
- Low Pressure
  - As soon as there is a drop in pressure in the renal artery (from 100 to 80), we immediately check the GFR
  - GFR
    - you can notice that in the beginning you can see a sudden fast drop in the GFR then there is a gradual increase until it goes back to normal, even though the blood pressure in the renal artery didn't go back to normal, so the GFR corrected itself even if the pressure is still less than normal.
  - Renal Blood Flow
    - Same thing happened to the renal blood flow, there was a sudden drop in renal blood flow in the beginning then there was a gradual increase to reach its normal value again, even though the renal blood pressure was still not corrected and stayed 80
- High Pressure
  - GFR
    - When the renal blood pressure increased, you can notice that the GFR initially increase due to the increase in pressure, but then it started decreasing to go back to its normal value. And same thing here, even though the renal artery blood pressure didn't go back to normal the GFR returned back to normal
  - Renal Blood Flow
    - Same thing happened to the renal blood flow, in which initially it increased due to the increase in renal artery blood pressure, but then it started decreasing to go back to normal, even though the renal artery blood pressure wasn't corrected still
- So initially both the GFR and RBF change initially then there are corrective mechanisms to bring back these values to normal, and this is called renal autoregulation



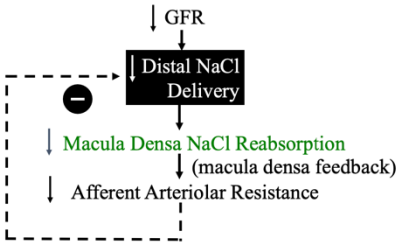
Myogenic Mechanism

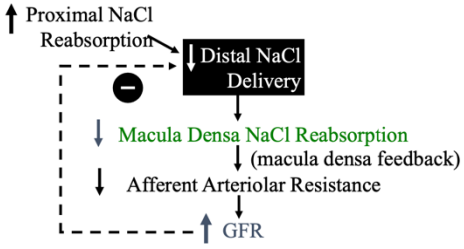
- From its name we can determine that its related to the smooth muscle activity
- When the pressure increased, they noticed there is tension and stretch forces being applied to the vessel wall and this tension causes the blood vessel to constrict by the smooth muscle
- Sequence of events
  - Increase in arterial blood pressure causes stretching of the blood vessels especially the AFFERENT arterioles , this stretching increases the cell Ca2+ entry increasing the Ca2+ concentration intracellular, increasing the vascular resistance due to vasoconstriction (due to the contraction of smooth muscle cells) reducing blood flow and GFR (to correct GFR and RBF)
- This whole mechanisms isn't very well understood

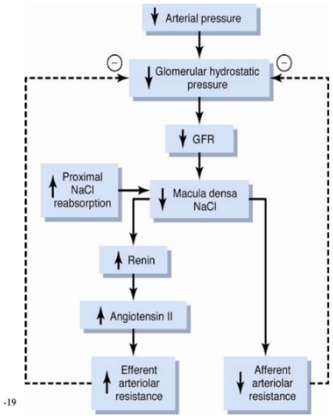


Macula Densa Feedback

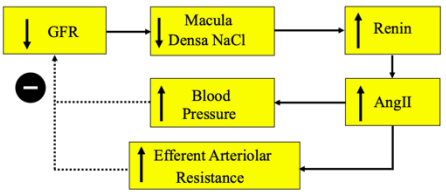
- We mentioned everything above about this whole feedback but there is one point we didn't mention
- The low NaCl doesn't always have to be due to low GFR, it can be due to high reabsorption rate in the proximal tubule (so there is going to be less NaCl reaching the distal convoluted tube so this would be detected by the macula densa cells)
- This high reabsorption rate of NaCl is found in certain conditions like high protein consumption, or high glucose/diabetic hyperglycemia
  - This is because the high protein would mean there is a lot of amino acid and the hyperglycemia means there is a lot of glucose, these would get reabsorbed, but the thing is when they are reabsorbed they are accompanied by NaCl, so this would cause a high reabsorption of sodium chloride (higher than normal), so when we reach the distal convoluted tubule to the macula densa we would have lost a lot of NaCl (since it all got reabsorbed) so the macula densa will just read that there is a low NaCl delivery and so it will send signal to the juxtaglomerular cells to increase the GFR, even if the GFR wasn't high or it was normal. (we explained how it increases the GFR up)
- These pictures summarize the mechanism of the macula densa







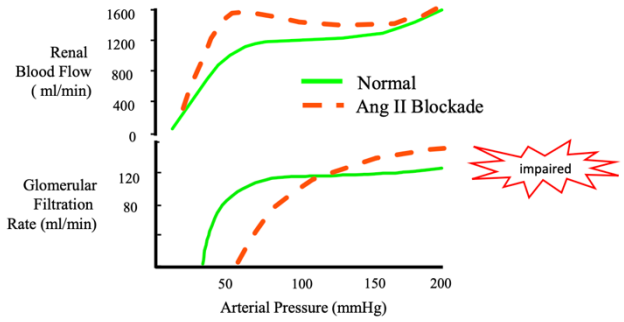
Regulation of GFR by Ang II



- We explained how angiotensin II works above, this picture summarizes it

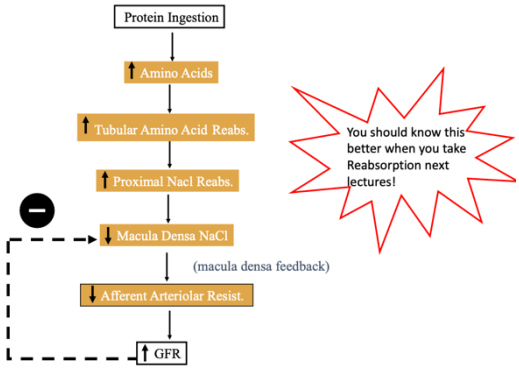
Ang II Blockade Impairs GFR Autoregulation

- Would the autoregulation process of people who take Angiotensin II blockade drug get affected
  - They noticed that with the blockade, the plateau was
  - In which these ppl (the ones who take the angiotensin II inhibitors), in the low pressure values, they weren't protected since GFR was very low
    - They don't have a plateau (nothing is helping them to increase GFR if GFR decreased) this is because they are taking Angiotensin II inhibitors, which we know angiotensin II plays an important role in the renal autoregulation
    - So if these people had low blood pressure, their GFR would have a greater decrease in compared to people who aren't taking the angiotensin II inhibitor drugs
  - But for the renal blood flow, when they take angiotensin II inhibitors they notice that the renal blood flow wasn't impaired, it just increased the RBF because angiotensin II is used to decrease the renal blood flow, so when we blocked it, it increased the renal blood flow



Other Factors That Influence GFR

- Fever, pyrogens: increase GFR
- Glucorticoids: increase GFR
- Aging: decreases GFR 10% / decade after 40 yrs
- Hyperglycemia: increases GFR (diabetes mellitus)
- Dietary protein: high protein increases GFR ,low protein decreases GFR
  - The hyperglycemia and dietary protein was explained above



Importance of Autoregulation

- One of the reasons why controlling GFR is important by autoregulation (follow along with the picture below)
  - Poor autoregulation + no tubular reabsorption
    - If the arterial pressure increased from 100 to 125 , the GFR increased also by 25 (from 125 to 150)
    - So there was a parallel increase in GFR when the blood pressure increased
    - Plus the urine volume would also increase drastically (the normal is 1 L/day) in which the urine volume would be 37.4L/day
      - This would cause dehydration
  - Good autoregulation + no adaptive reabsorption
    - Here even if the blood pressure increased to 120 the GFR just increased to 130 (from 125 to 130) not that big of a difference
    - But if you look at the urine volume there is a 5x increase in which the normal was 1L/day now its 5L/day
  - Good autoregulation + adaptive tubular reabsorption
    - Same thing here even if the blood pressure increased to 120 the GFR just increased to 130 (from 125 to 130) not that big of a difference
    - But here because we have adaptive tubular reabsorption the urine output only slightly increased in which the normal was 1L/day now its 1.2 L/day
  - So this whole table you can see that small changed in the GFR made large changes in the urine output which shows us how important the GFR regulation is