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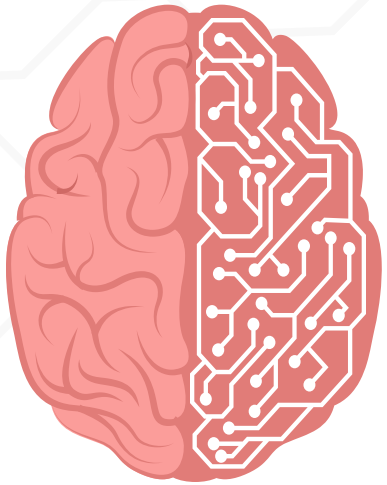

Physiology - GUS

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Renal Physiology Lect-3

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Control of GFR and renal blood flow

Normal GFR is important to keep an efficient kidney function
(to maintain homeostasis, we need a normal GFR)

How does our body regulate the GFR (glomerular filtration rate) & RBF (renal blood flow)?
2 mechanisms:

- Neurohumoral

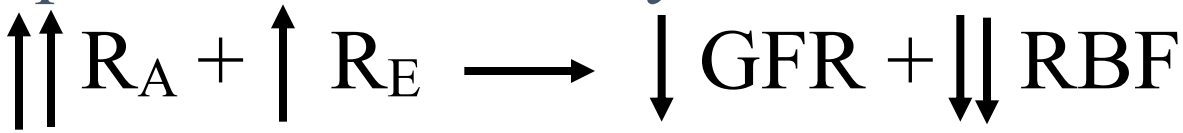
- Local (Intrinsic)

Most important regulatory mechanism for GFR

Neurohumoral Control of GFR and renal blood flow

By neurotransmitters:

1. Sympathetic Nervous System /catecholamines



e.g. severe hemorrhage

Sympathetic stimulation results in increases in the resistance of both afferent and efferent arterioles (because catecholamines (symptomatic system) cause constriction), but the increase is much more in afferent arterioles than efferent arterioles, specially in severe/strong symptomatic stimulation

- ✓ the result: this will reduce the GFR and the RBF

Severe hemorrhage → strong symptomatic stimulation and less blood reaching the kidneys → and this is dangerous because it could injure the nephrons → stopping the filtration → crystallization in the tubular system → necrosis and loss of nephrons (this is irreversible)
So there should be rapid replacement for the lost blood

Neurohumoral Control of GFR and renal blood flow

2. Angiotensin II

$\uparrow R_E \longrightarrow \longleftrightarrow GFR + \downarrow RBF$

(prevents a decrease in GFR)

e.g. low sodium diet, volume depletion

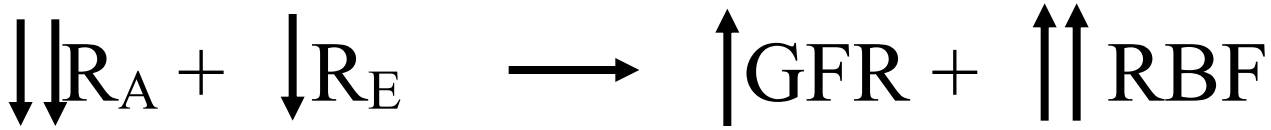
Angiotensin 2 is formed when the blood pressure is low
It has a direct effect (vasoconstriction) and other effects on the kidney functions (will be discussed later)

The receptors of angiotensin 2 are more on the efferent arterioles, so angiotensin 2 causes more vasoconstriction in the efferent arterioles than afferent arterioles, this results in reduction RBF, but the GFR doesn't change
angiotensin 2 is formed in low blood pressure, and low blood pressure tend to decrease the GFR, but the high angiotensin 2 will bend to its receptors on the efferent arterioles → increasing the resistance in these efferent arterioles → increasing the glomerular hydrostatic pressure → preventing the reduction GFR **due to hypotension** → so normal GFR

Neurohumoral Control of GFR and renal blood flow

3. Prostaglandins

Prostaglandins are vasodilators and they're inflammation and pain mediators



Blockade of prostaglandin synthesis → ↓ GFR

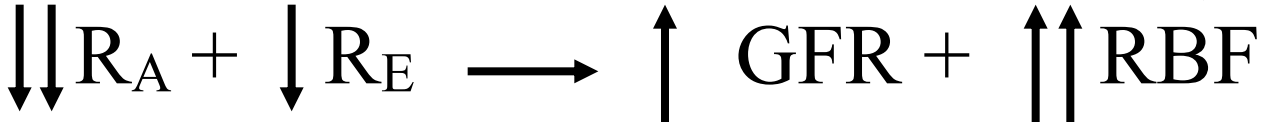
Kidney can synthesize and produce prostaglandins

Prostaglandins cause vasodilation → reduce the resistance in afferent and efferent arterioles, but more in the afferent arterioles → increasing the GFR and RBF
So prostaglandins are good for the kidneys, especially in patients with kidney diseases, that's why it's contraindicated to give anything that inhibits the prostaglandins synthesis (e.g., COX inhibitors, nonsteroidal anti-inflammatory drugs like ibuprofen and diclogesic) to patients who have reduced kidney functions (because blocking prostaglandins synthesis will make their condition worse)

- This is usually important only when there are other disturbances that are already tending to lower GFR
- e.g. nonsteroidal antiinflammatory drugs in a volume depleted patient, or a patient with heart failure, cirrhosis, etc

Neurohumoral Control of GFR and renal blood flow

4. Endothelial-Derived Nitric Oxide (EDRF)

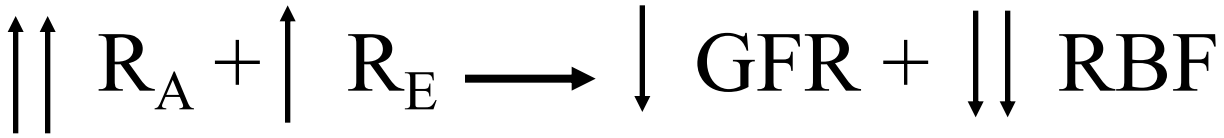


Nitric oxide is produced by the endothelial cells and it's a vasodilator → causes reduction in the resistance in the arterioles, more in the afferent arterioles → increasing the RBF and GFR

- Protects against excessive vasoconstriction
- Patients with endothelial dysfunction (e.g. atherosclerosis) may have greater risk for excessive decrease in GFR (because the don't have good production for nitric oxide) in response to stimuli such as volume depletion

Neurohumoral Control of GFR and renal blood flow

5. Endothelin



Endothelin causes vasoconstriction → it increases the resistance in the afferent arterioles more than in the efferent arterioles → resulting in reduction in GFR and RBF

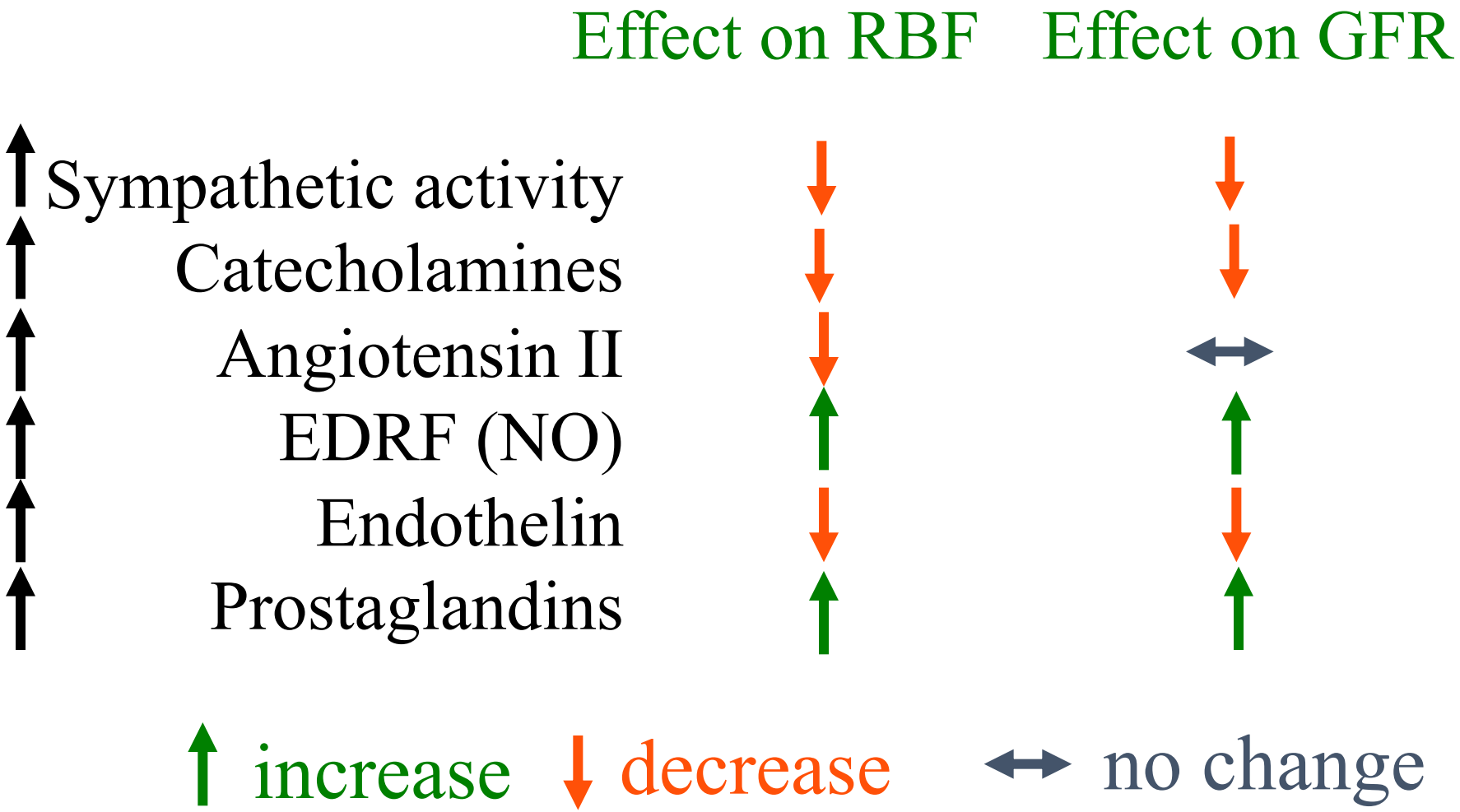
Endothelin's implicated in many conditions like hypertension, acute renal failure and other renal disfunction syndromes

- 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

Endothelin's effect is bad for kidney functions

Summary of neurohumoral control of GFR and renal blood flow

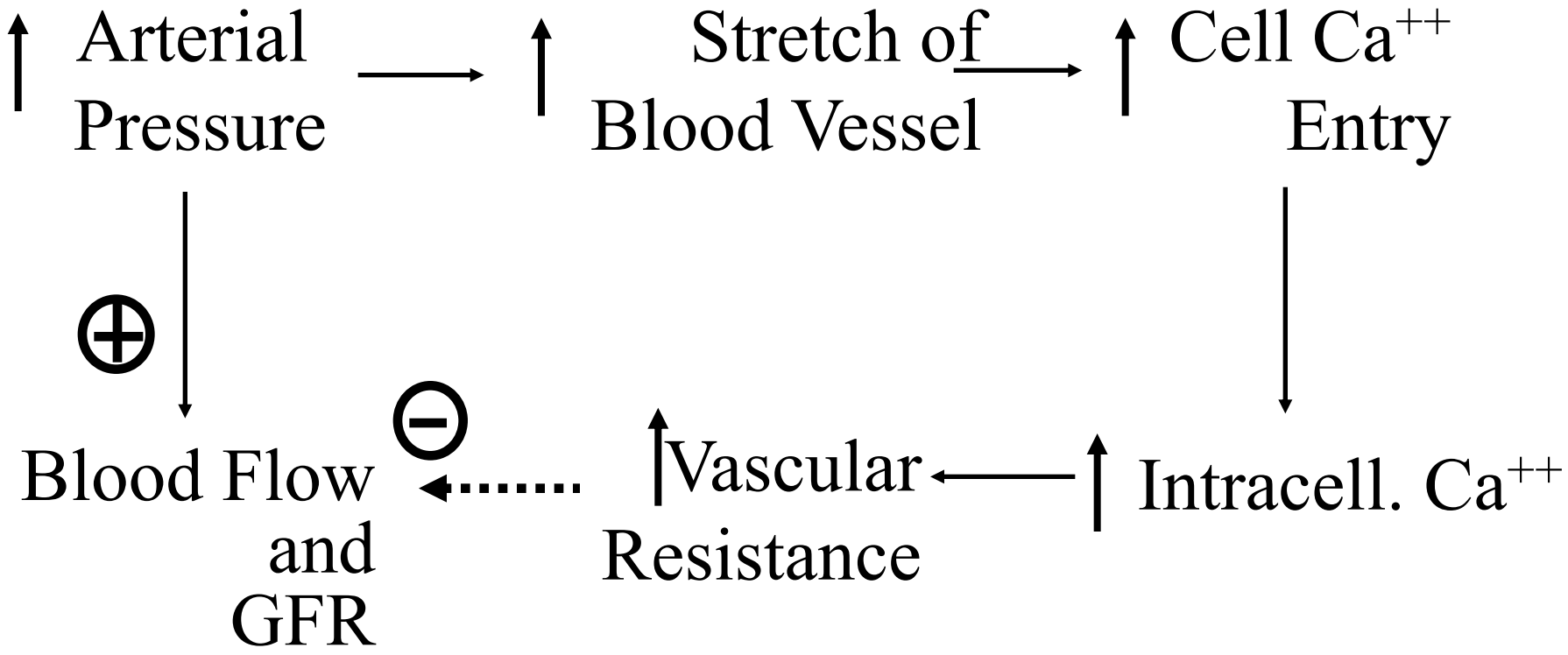


Local (Intrinsic) Control of GFR and renal blood flow

7. Autoregulation of GFR and Renal Blood Flow

- Myogenic Mechanism
- Macula Densa Feedback (tubuloglomerular feedback)
- Angiotensin II (contributes to GFR but not RBF autoregulation)

Myogenic Mechanism



If the arterial pressure increases, you'd suspect increase in the RBF and GFR, but the myogenic autoregulation mechanism (myogenic reflex) will prevent this increase (HOW?)

When the arterial pressure increases → the stretch of the blood vessels increases → signals in the smooth muscle cells of the vessels → increasing calcium entry → higher intracellular calcium → contraction of the smooth muscle cells of the arterioles → increasing the vascular resistance → reducing the RBF and GFR (helps prevent excessive increases in RBF and GFR when arterial pressure increases)

Renal Autoregulation of GFR

Tubuloglomerular feed back mechanism:

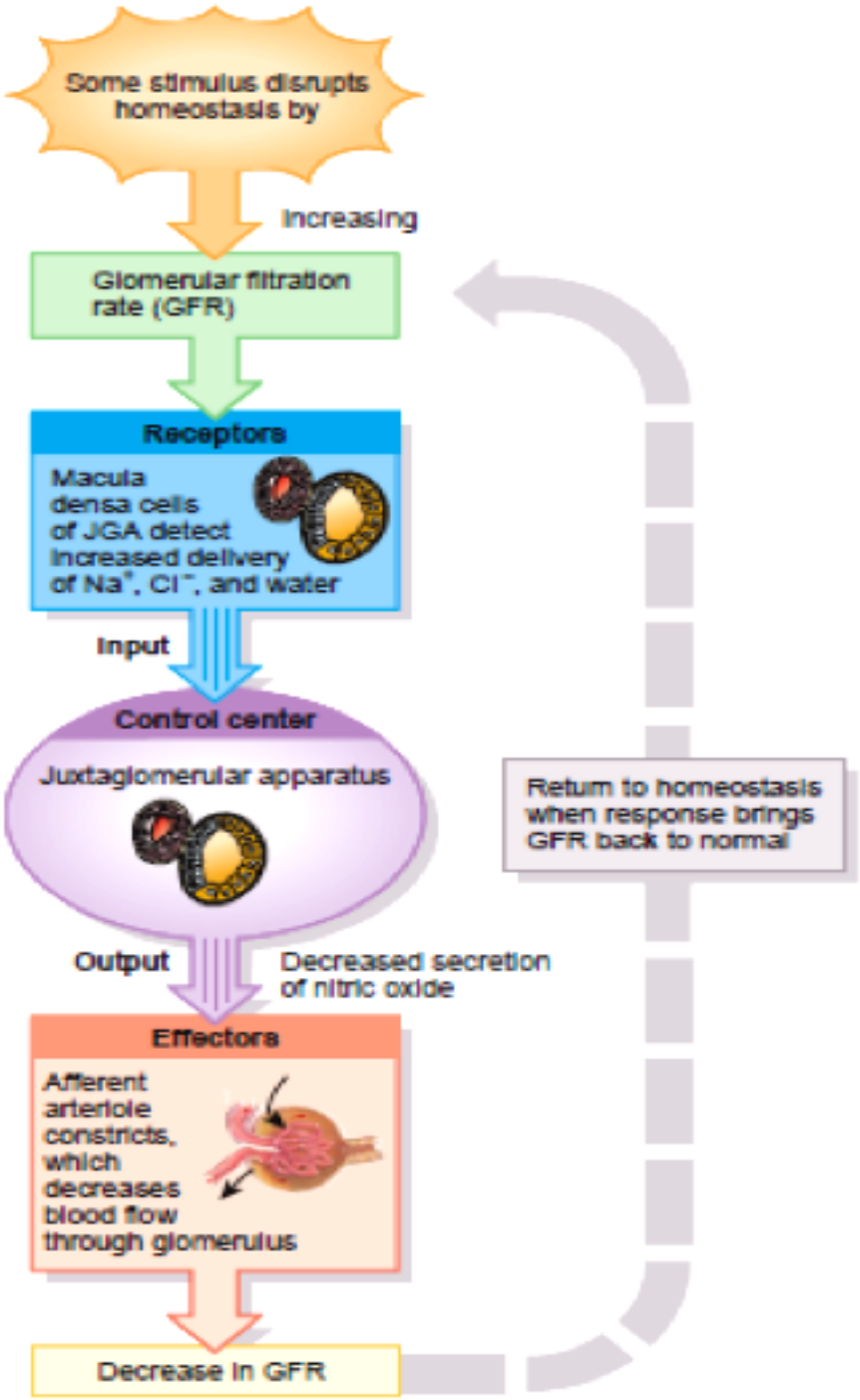
- Feedback loop consists of a flow rate (increased NaCl in filtrate) sensing mechanism in macula densa of juxtaglomerular apparatus (JGA)
- Increased GFR (& RBF) inhibits release of the vasodilator ; Nitric Oxide (NO)

Any increase in the GFR is dedicated by the macula densa cells, which are part of the walls of either [1] the end of the thick ascending loop or [2] the distal convoluted tubule.

- Macula densa cells are very close to the afferent arteriole, they're adjacent to the juxtaglomerular cells of the arterioles
- Macula densa cells + juxtaglomerular cells consist the juxtaglomerular apparatus (which is the control center)

Increased GFR → results in increase in the delivery of NaCl and water to the tubules
The juxtaglomerular apparatus detects this increase
Output/net result: to decrease the synthesis and secretion of nitric oxide
Lowering NO → causes vasoconstriction in the afferent arterioles → reduction of RBF → reduction of GFR

Tubuloglomerular: the tubules will dedicate the changes and then glomerular function will be affected.

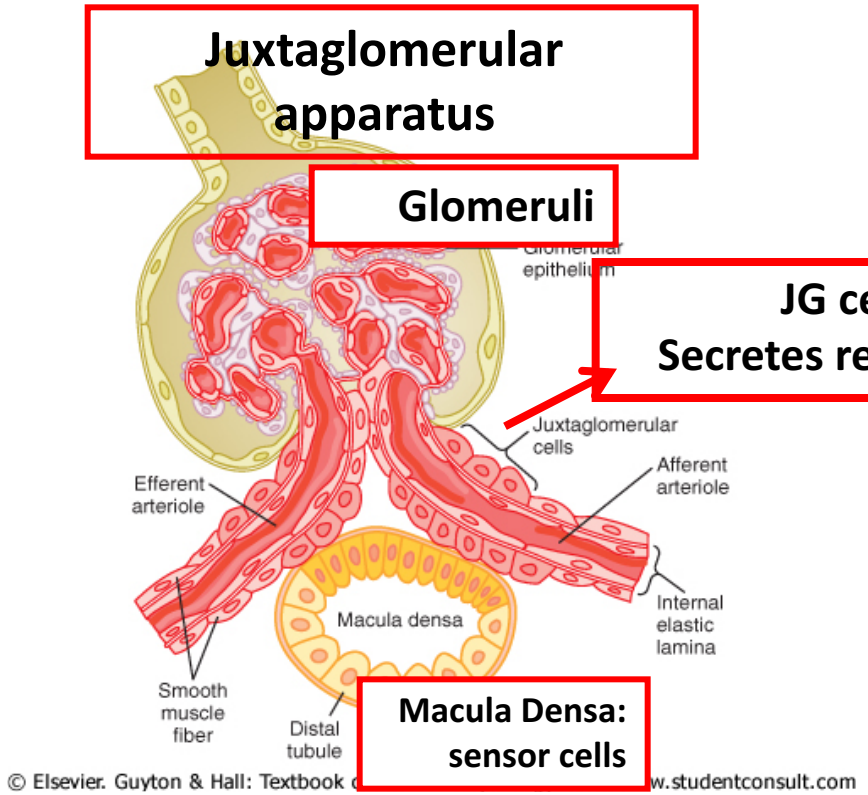


Renin secretion regulation

When Renin is secreted, it reaches the circulation and converts angiotensinogen into the deca-peptide angiotensin 1 which will be converted into **angiotensin 2** by ACE (angiotensin-converting enzyme) in the pulmonary vessels.
Angiotensin 2 is a potent vasoactive peptide hormone, which will cause systemic constriction to all vessels in the body. In the kidneys, it causes constriction of the efferent arterioles more than of the afferent arterioles → enhancing the GFR

So renin and angiotensin 2 play a role in the tubuloglomerular feedback mechanism, especially in hypotension

- They protect against the reduction of GFR in hypotension caused by hemorrhage or volume depletion



Tubuloglomerular Feedback

Renin secretion regulation

Renin enzyme is synthesized and secreted by the juxtaglomerular cells according to these conditions:

1- Perfusion Pressure

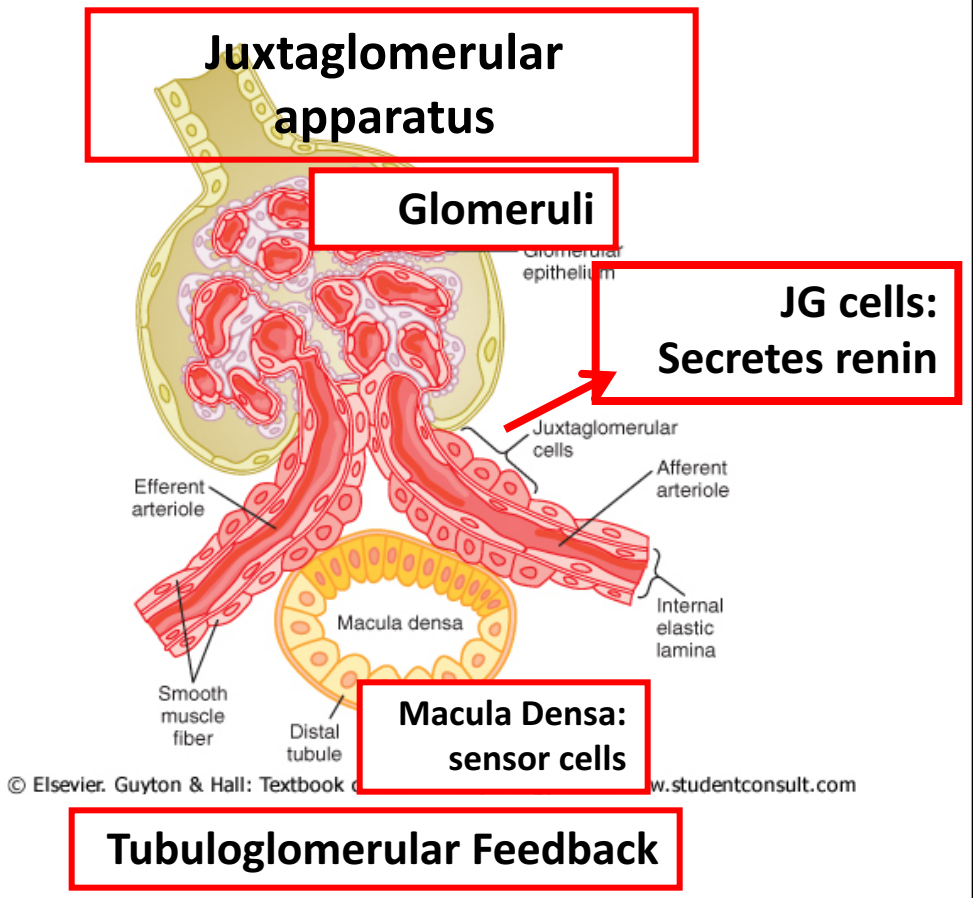
low perfusion in afferent arterioles (low flow & low hydrostatic pressure) stimulates renin secretion while high perfusion inhibits renin secretion.

2- Sympathetic nerve activity

Activation of the sympathetic nerve fibers in the afferent arterioles increases renin secretion.

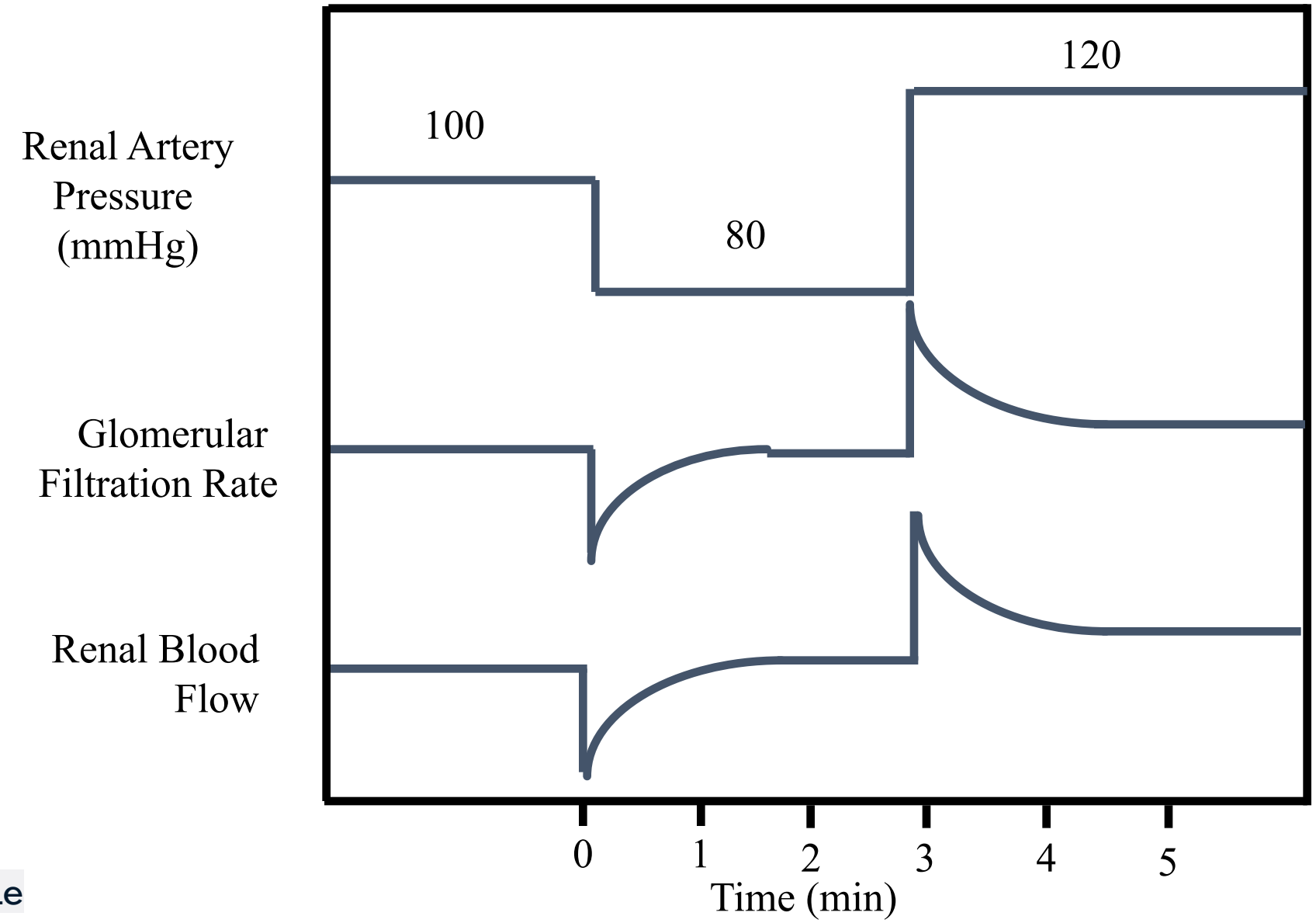
3- NaCl delivery to macula densa:

When NaCl is decreased (GFR is reduced), Renin secretion is stimulated and vice versa. **(Tubuloglomerular Feedback)**



Tubuloglomerular Feedback

Renal Autoregulation



Check next slide

Explanation for the previous slide

If the renal artery pressure drops from 100 to 80,

- There'll be acute drop in the GFR in the first min, but the rate goes back to normal fast within a minute (because of the renal autoregulation)
- Also, there'll be acute drop in the RBF, but there'll be correction and the flow goes back to normal within a minute (also because of the renal autoregulation)

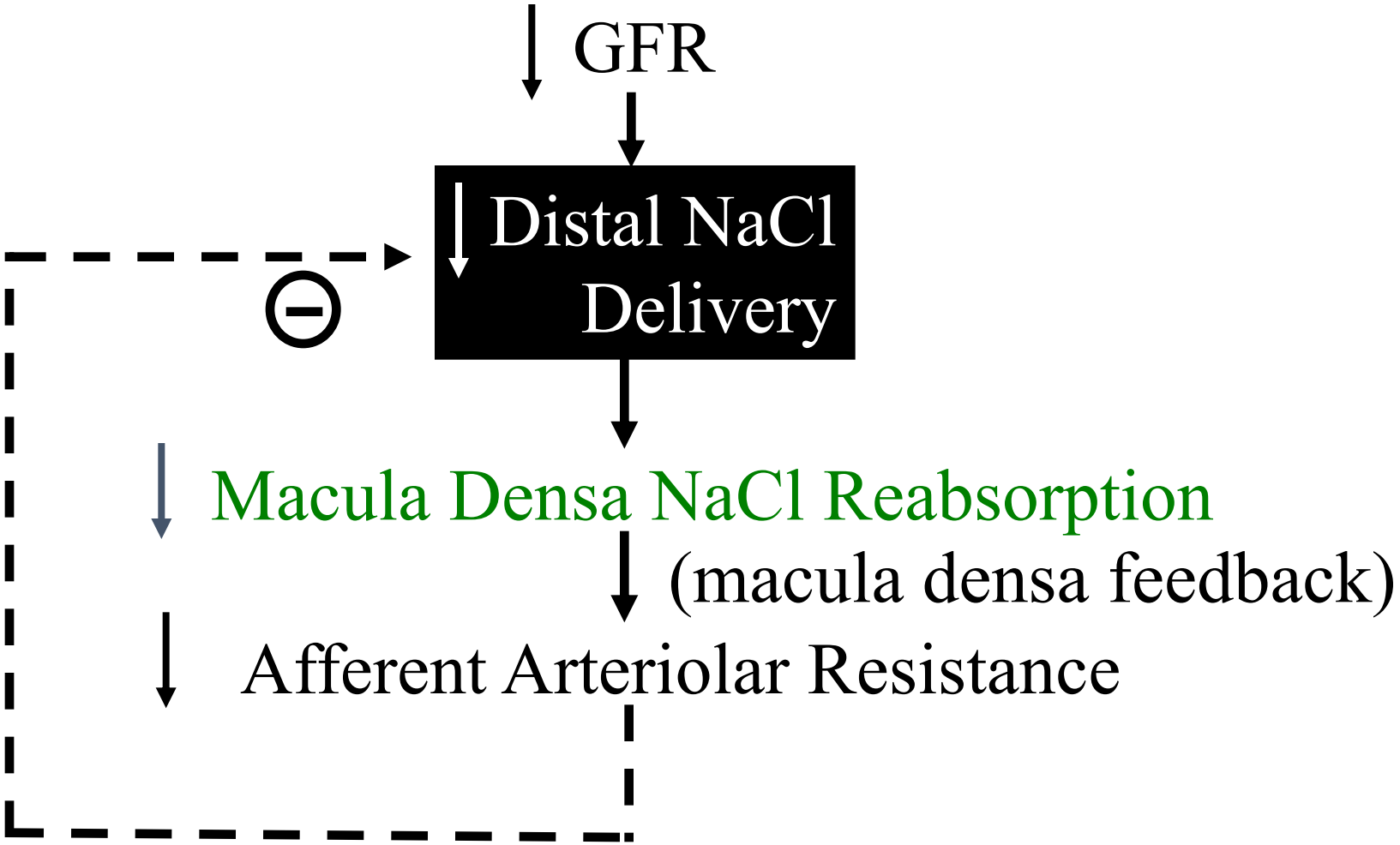
even if the renal artery pressure stays lower than normal

If the renal artery pressure increases to 120,

- There'll be acute increase in the GFR, and the rate goes back to normal fast within a minute (because of the renal autoregulation)
- Also, there'll be acute increase in the RBF, and within a minute the flow goes back to normal even if the renal artery pressure stays higher than normal

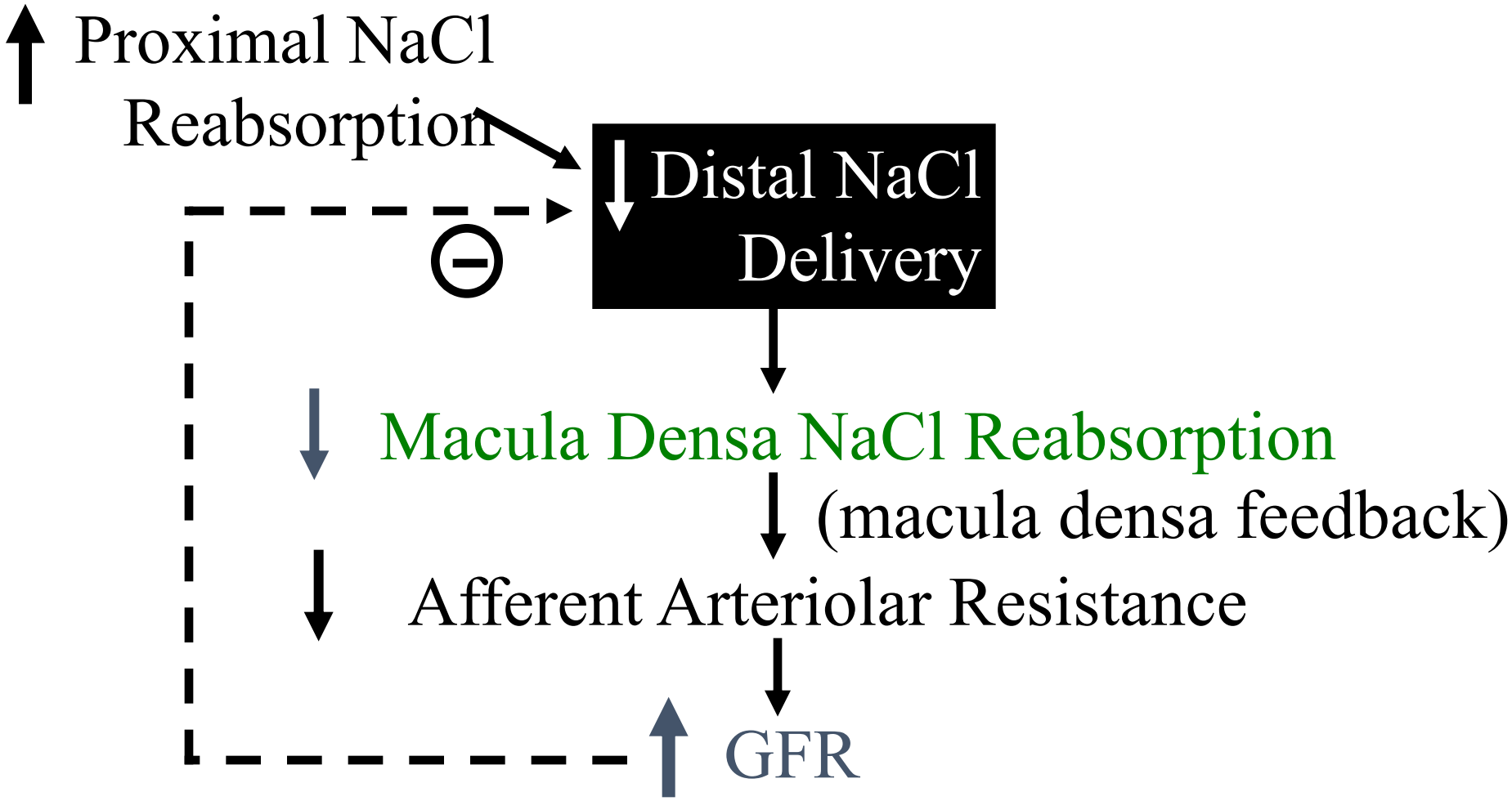
Macula Densa Feedback

When GFR is reduced → NaCl delivered to distal tubules or thick loop of Henle decreases → causing less reabsorption of NaCl in the macula densa → which tells the control center to increase synthesis of nitric oxide → decreasing the resistance in the afferent arterioles (vasodilation) → enhancing the GFR → increasing NaCl delivery

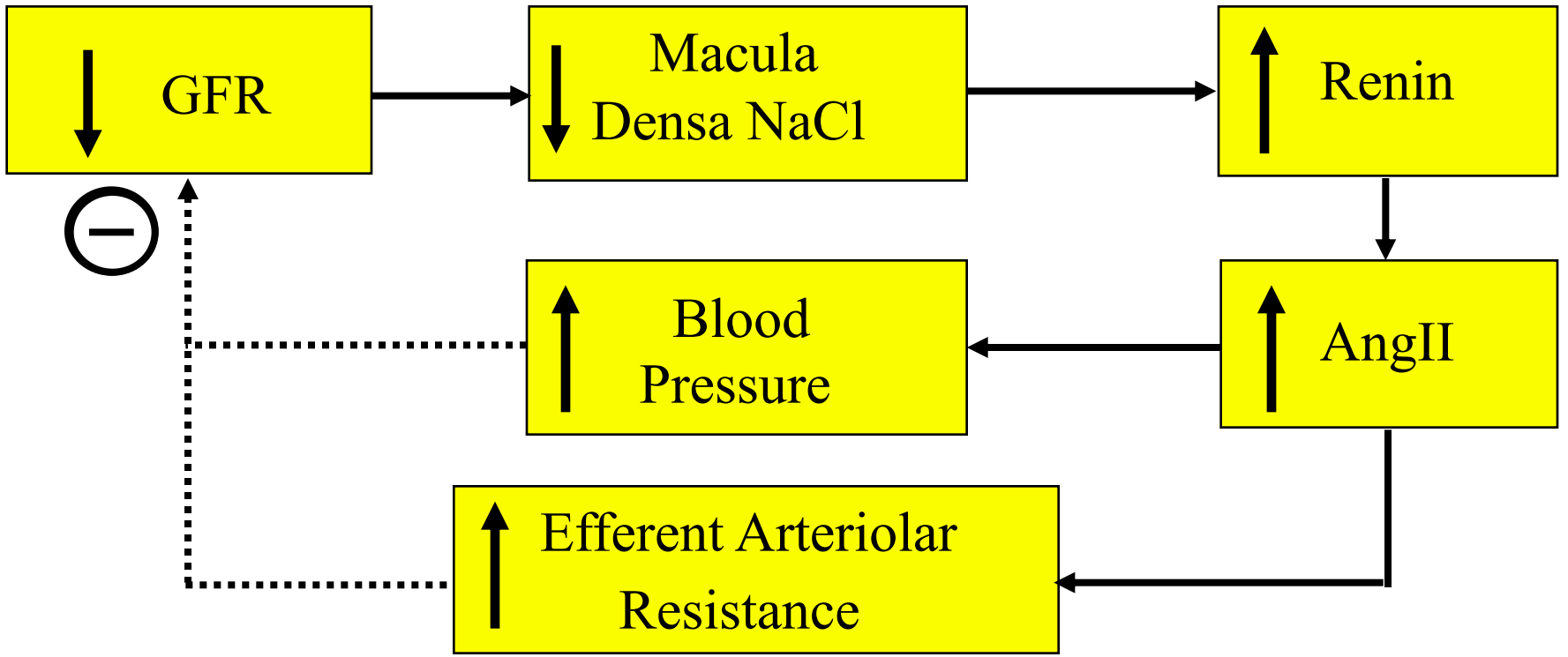


Macula Densa Feedback

If the proximal NaCl reabsorption increases → the distal NaCl delivery will decrease → causing less reabsorption of NaCl in the macula densa → increase synthesis of nitric oxide → decreasing the resistance in the afferent arterioles (vasodilation) → increasing the GFR



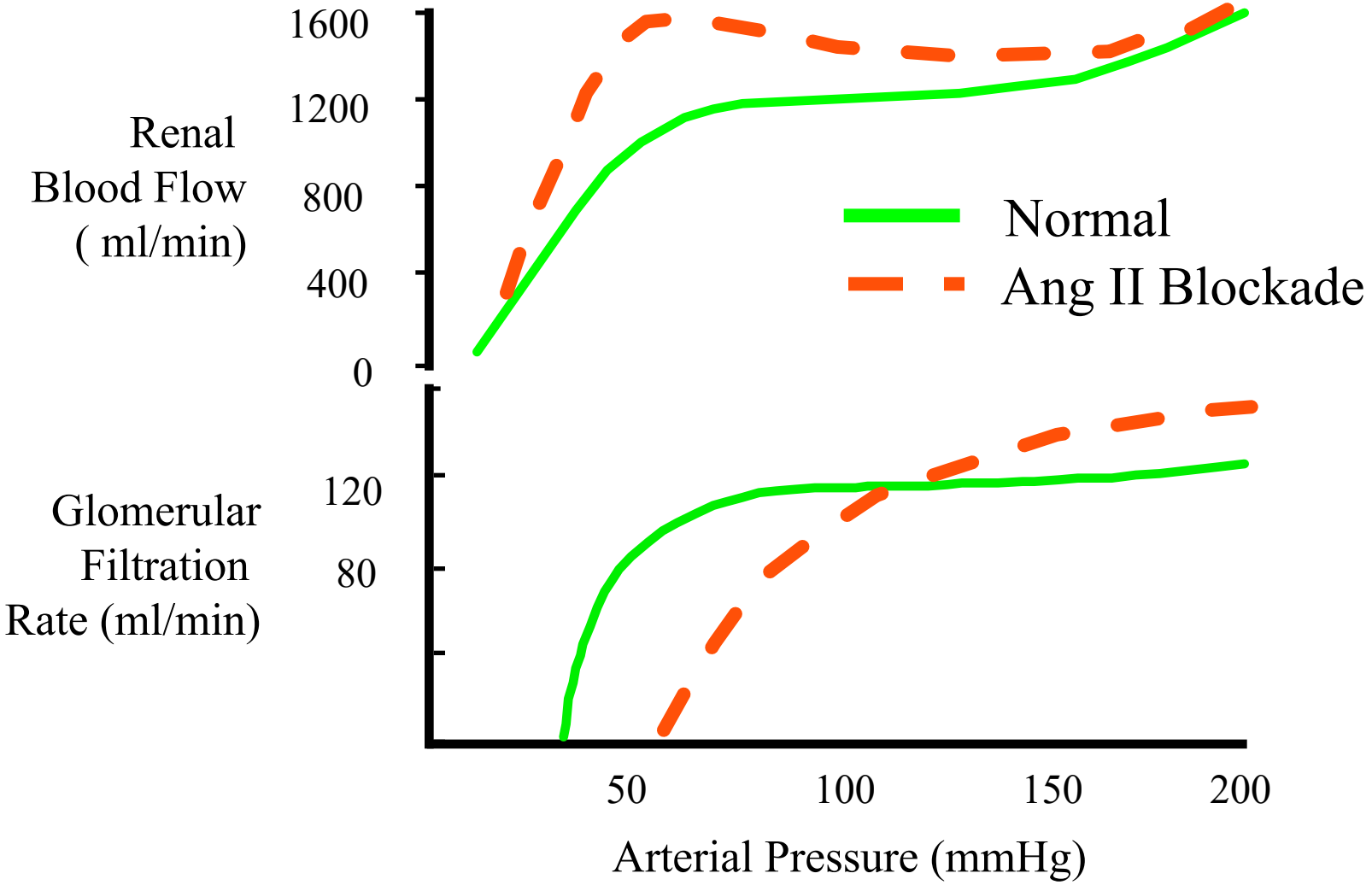
Regulation of GFR by Ang II



GFR decreases → NaCl delivery decreases → stimulation of renin → increase in angiotensin 2 →

- Angiotensin 2 increases the efferent arteriolar resistance preferentially (more in efferent arterioles than the afferent) → increasing the glomerular hydrostatic pressure → increasing the GFR
- Angiotensin 2 increases the blood pressure in the body (because it causes systemic vasoconstriction increasing the total peripheral resistance increasing the mean arterial blood pressure) → increasing the GFR

Ang II Blockade Impairs GFR Autoregulation



Some of the drugs hypertensive patients take inhibit angiotensin 2 either by inhibiting its synthesis (ACE inhibitors) prevent its binding with the receptor (angiotensin 2 receptors blockers)

Green: normally, higher pressure → plateau in GFR & RBF (no change)

Red: Blocking angiotensin 2 will result in impairment in the plateau, impairment in the autoregulation

Summary of what we already said

Macula densa feedback mechanism for regulating GFR

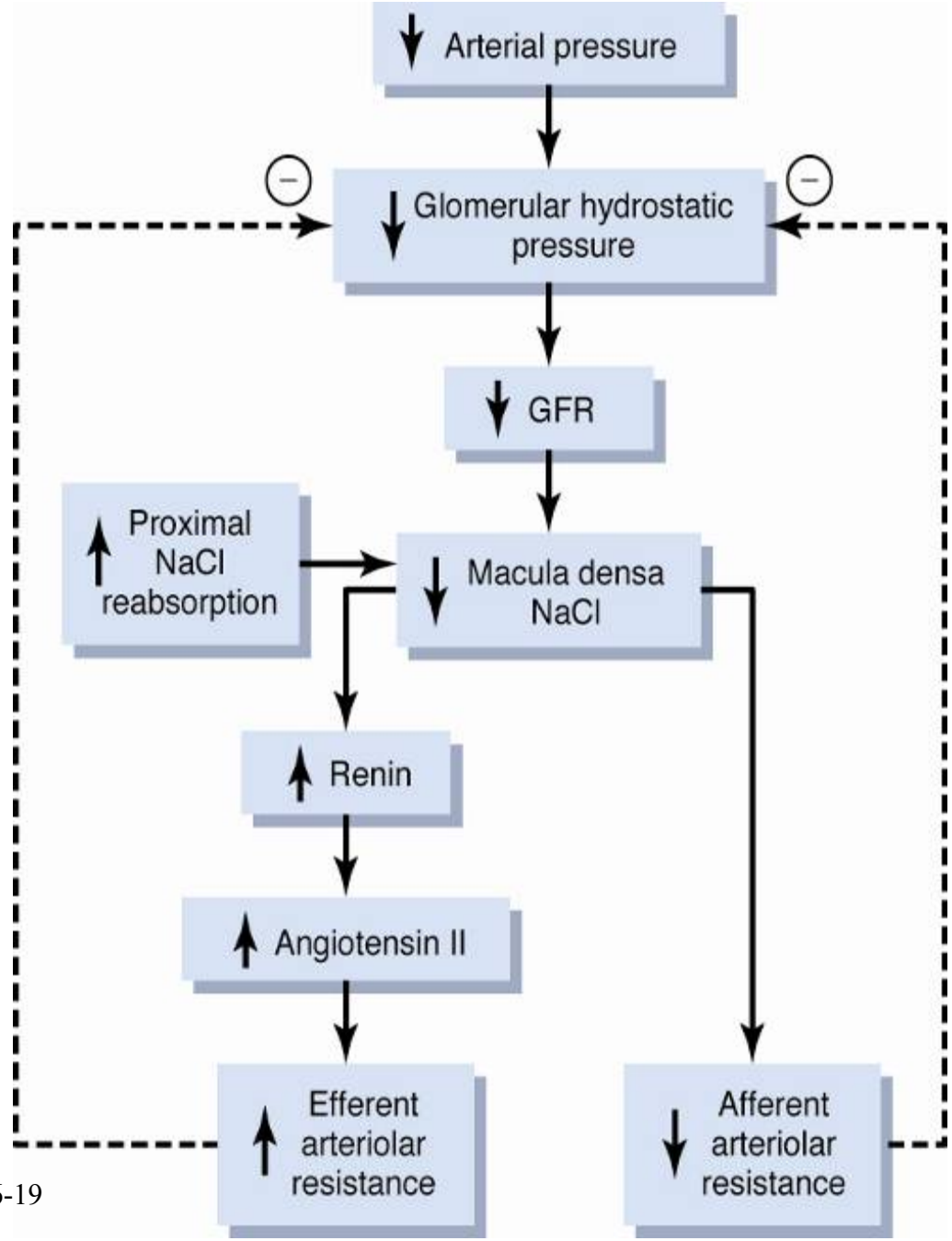


Figure 26-19

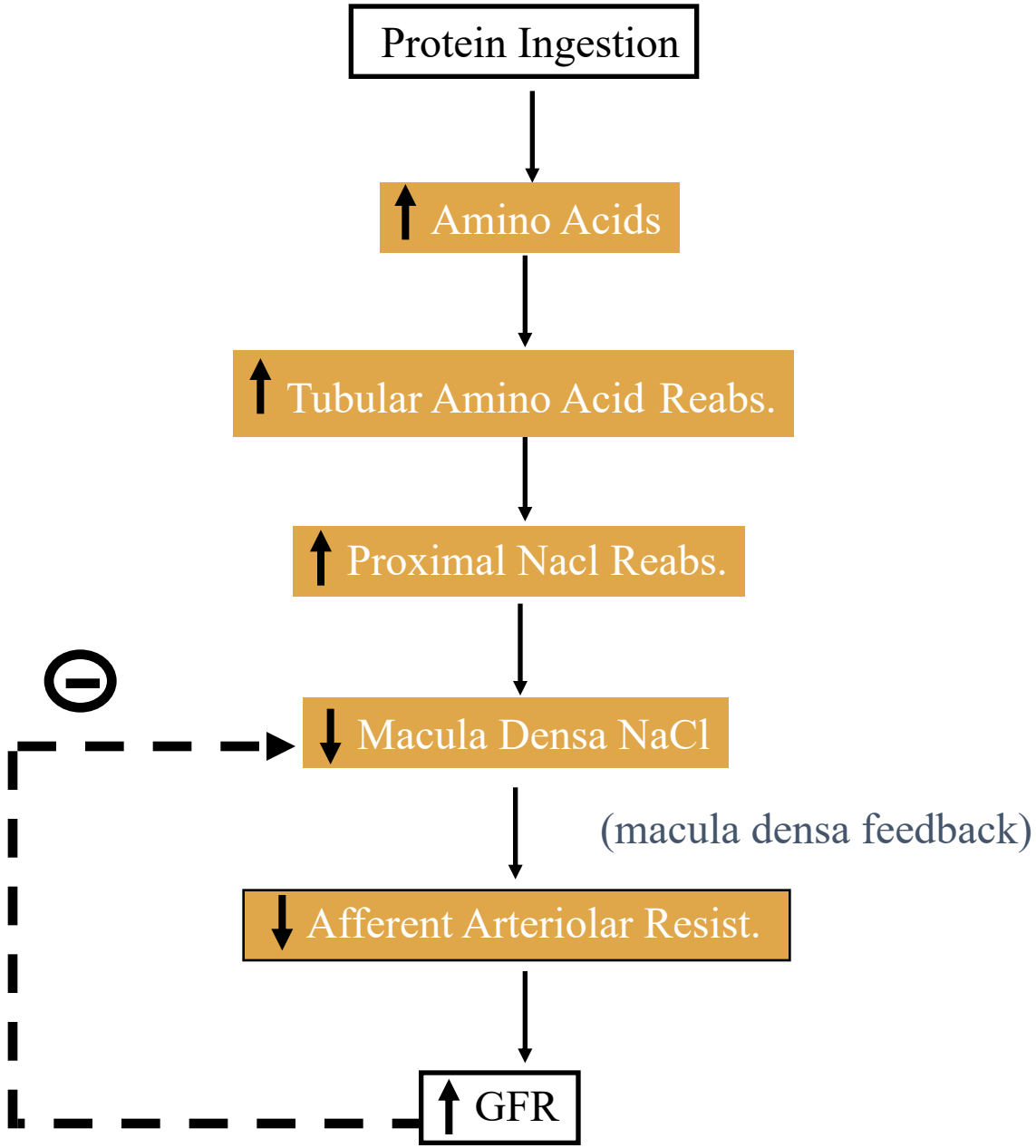
Other Factors That Influence GFR

- Fever, pyrogens: increase GFR
- Glucorticoids: increase GFR
- Aging: decreases GFR 10% / decade after 40 yrs

  Every decade after 40 is associated with 10% decrease in the GFR (because there'll be loss in the nephrons)
- Hyperglycemia: increases GFR (diabetes mellitus)
- Dietary protein: high protein increases GFR
  low protein decreases GFR

Some of these factors will be explained later

This will be explained later in the reabsorption lectures



Importance of Autoregulation

	Arterial Pressure	GFR	Reabsorption	Urine Volume
Normal	100	125	124	1.0
Poor Autoregulation + no change in tubular reabsorption				
	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

Explanation for the previous slide

Increase in the arterial pressure with poor autoregulation + no change in the tubular reabsorption (it stayed constant) → in this case, the GFR increases a lot (150 instead of 125) and the urine volume would equal 26 ml/min = 37 L/day instead of 1

On the other hand, Increase in the arterial pressure with good autoregulation + no change in the tubular reabsorption → the increase in the GFR would be less (130 instead of 150 [but still not completely normal]) and the urine volume would equal 5 ml/min

But the best scenario: Increase in the arterial pressure with good autoregulation + adaptation/correction in the tubular reabsorption → the GFR would be 130 and the reabsorption increases (128) and the urine volume would equal 1.2 ml/min [which is close to normal]