Glomerular Filtration Rate and its control-cont.

Lecture-3

31/3/2015

Kidney Function

- It is important to assess Kidney function in many clinical settings.
- A commonly performed test is creatinine clearance as a measure of GFR.
- Twenty four hour urine collection is required for accurate creatinine testing.
- However, this is not always possible as in the case of demented elderly, small children, uncooperative patients, etc...
- Consequently, scientists used different methods and equations to estimate GFR (the value obtained thus labeled eGFR).

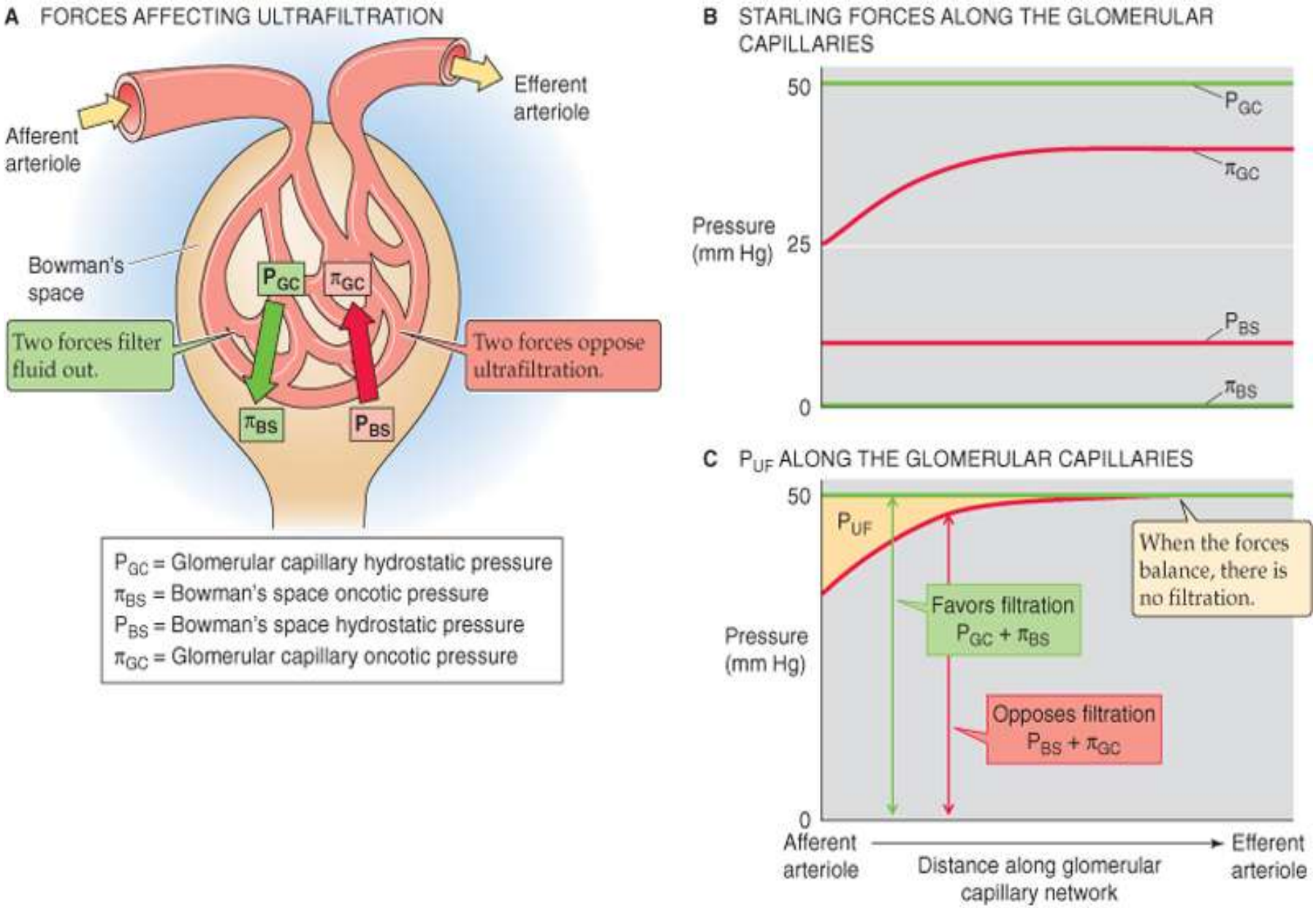
KFT: blood tests to assess kidney function:
Urea, Creatinine and Electrolytes.
- Sometimes, creatinine increases above the given range, only if we have too much damage to the kidney, so if [creatinine] is within normal range does not exclude kidney impairment.

*** Still, creatinine is the best indicator as KFT. It is more important than urea because urea is subjected to other variables. (Like in cases of dehydration or GI bleeding), it's level changes.**

*** Creatinine also rises due to increase muscle mass.**
*** In old age we have less muscle mass**

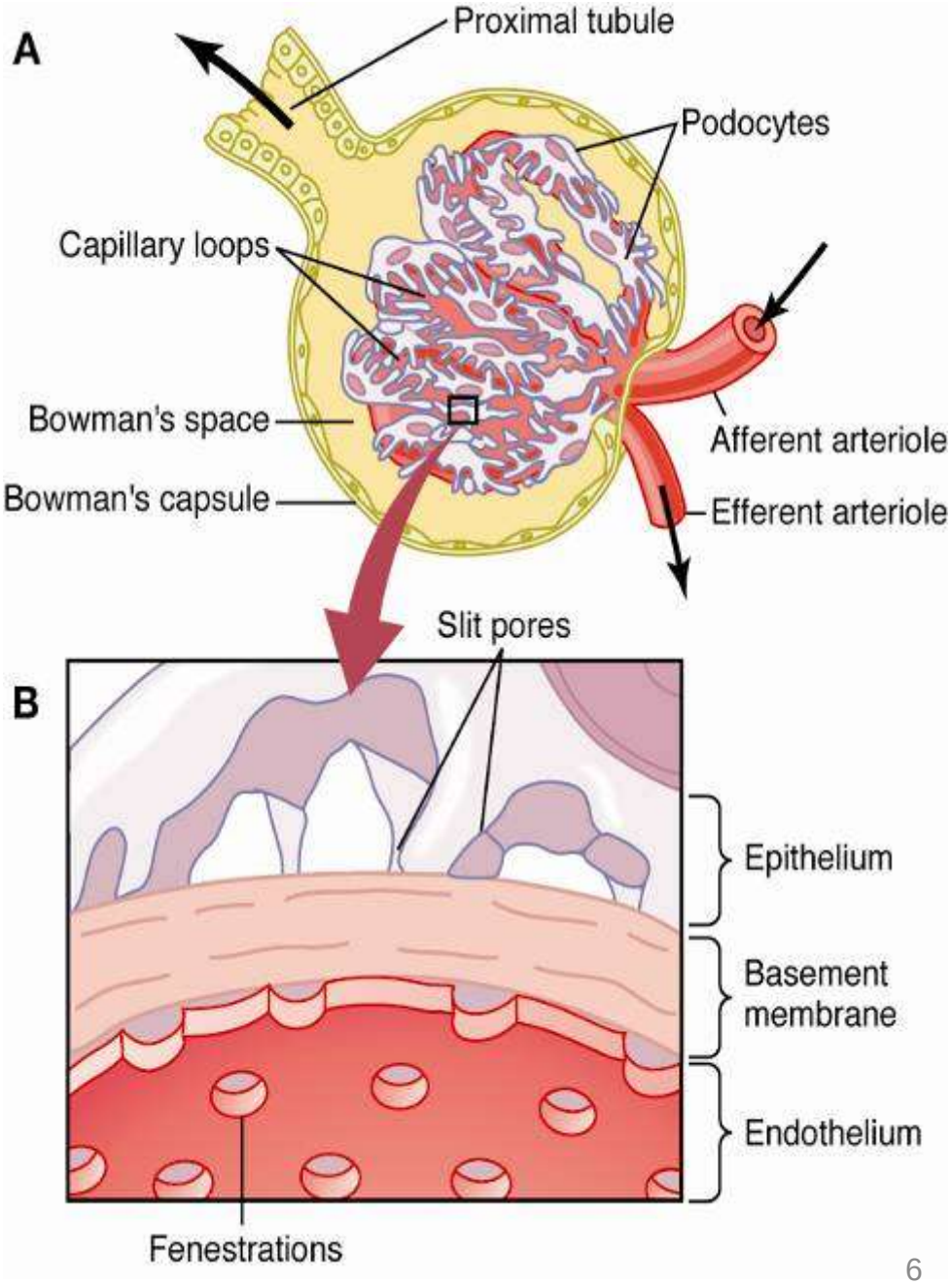
Comparison between Filtration in systemic capillary beds VS. Glomerular Filtration

- filtration across the systemic capillaries (kidneys are excluded) is 20L/day ;17L is reabsorbed by veins and 3L by lymphatics (remember: This is a subject of question I asked you in the lecture).
- GFR is 180L/day ;i.e., 9 times more than the systemic filtration. Why?



Boron & Boulpaep: Medical Physiology, 2nd Edition.

Glomerular capillary filtration barrier



Glomerular Filtration

GFR = 125 ml/min = 180 liters/day

- Plasma volume is filtered 60 times per day
- Glomerular filtrate composition is about the same as plasma, except for large proteins
- Filtration fraction (GFR ÷ Renal Plasma Flow) = 0.2 (i.e. 20% of plasma is filtered)

$$GFR = Kf.[(P_{GC} - P_{BS}) - (\Pi_{GC} - \Pi_{BS})] = K_f * P_{eff}$$

(Ohm's law again)

- The driving force is the summation of Starling forces which are 2 forces inside and only one force outside.
- The inside ones are:

1. Capillary hydrostatic pressure (**P_{GC}**)=60 mmHg
2. Colloid capillary pressure (Π_{GC}) provided by albumin and globulin (mostly by albumin WHY?)=32 mmHg.

- The outside ones are:

1. P_{BS}= 18 mmHg opposes filtration.

Summary of Driving Forces affecting Filtration

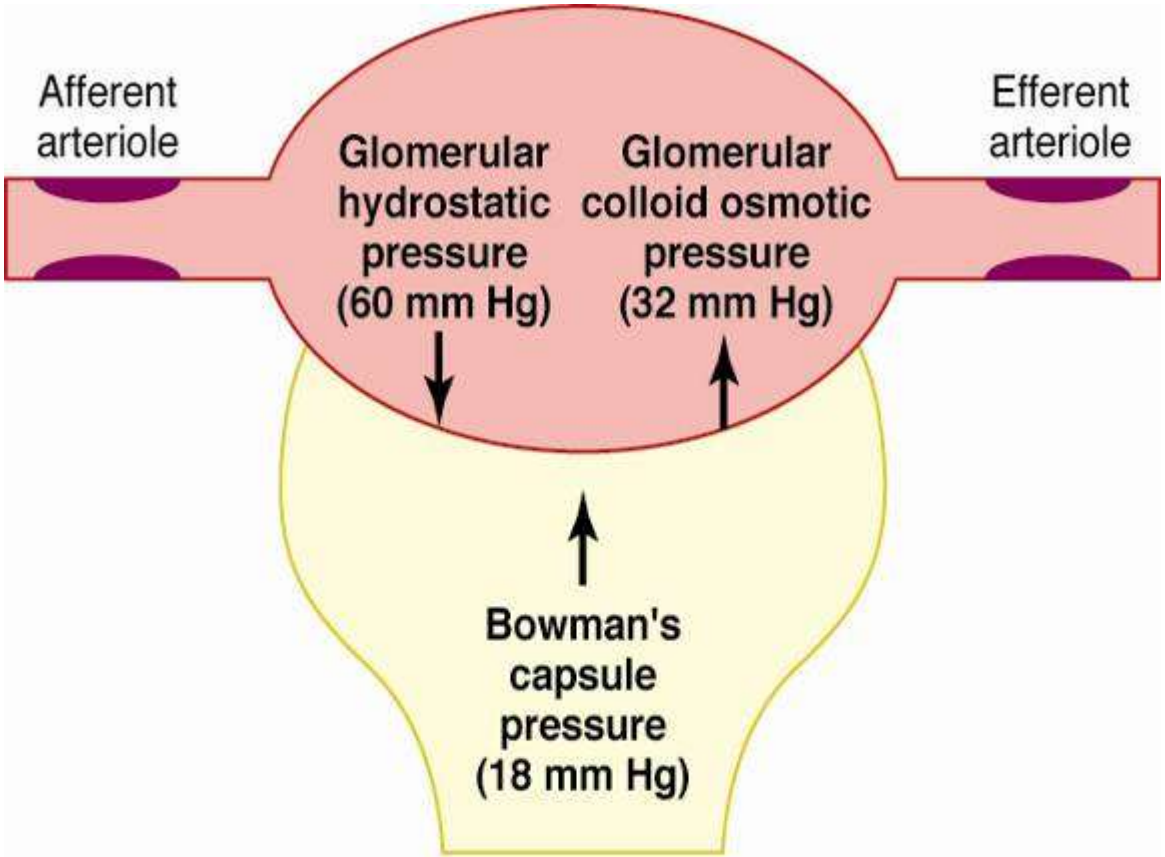
- Favoring Filtration:

1. Hydrostatic Pressure in the Glomerular capillaries. ($\mathbf{P_{GC}}$)
2. Oncotic (Colloid) Pressure of the filtrate in the Bowman's capsule. ($\Pi_{\mathbf{BS}}$)= zero mmHg

- Opposing Filtration:

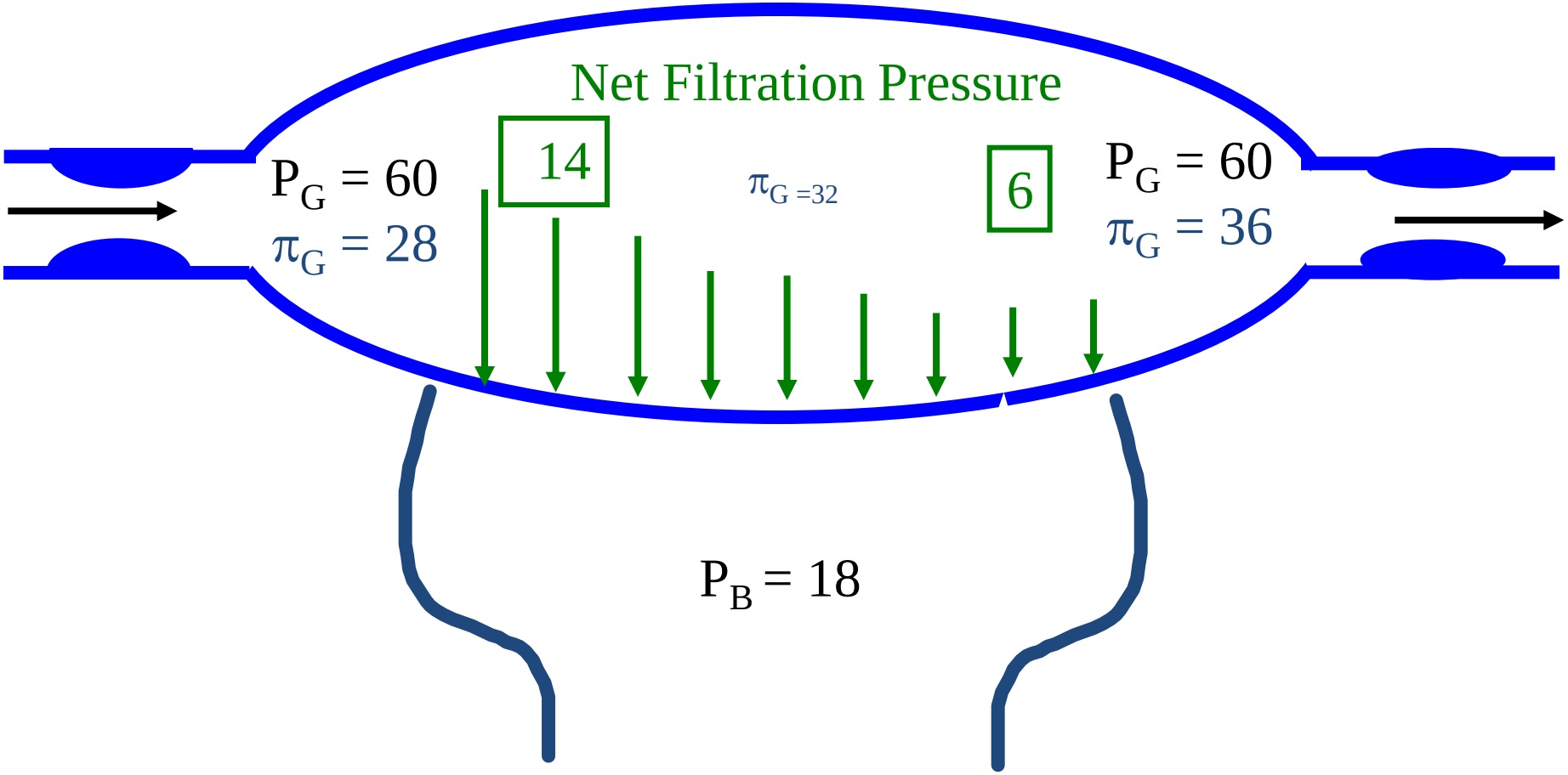
1. Hydrostatic Pressure in the Bowman's capsule.($\mathbf{P_{BS}}$)
2. ($\Pi_{\mathbf{GC}}$)

Determinants of Glomerular Filtration Rate



Net filtration pressure (10 mm Hg)	=	Glomerular hydrostatic pressure (60 mm Hg)	–	Bowman's capsule pressure (18 mm Hg)	–	Glomerular oncotic pressure (32 mm Hg)

Net Filtration Pressure Decreases Along the Glomerulus Because of Increasing Glomerular Colloid Osmotic Pressure



I.

Glomerular Hydrostatic Pressure:

- The difference between 20L/day and the 180L/day is either due to increased $\mathbf{P_{eff}}$ or increased Kf or both.
- The $\mathbf{P_{GC}}$ here is 60-59 mmHg as opposed to 30-15 mmHg in systemic…..WHY?
- If we look at systemic capillaries they have an arterial end and a venous end but glomerular capillaries have both arteriolar ends afferent and efferent arterioles. This makes the pressure much more so the driving force is also much more (60 mmHg).

Arteriolar diameter effect on GFR:

- Afferent **dilatation** means an increase in the blood coming to the capillaries so increased Pc and GFR.
- **Constriction** of efferent arteriole increases P_{GC} to a limit. If it goes over this limit filtration will decrease as no more blood entering the capillaries.
- To regulate P_{GC} you either control the afferent arteriolar dilatation or the efferent arteriolar constriction.

II. Glomerular Capillaries Oncotic(colloid) Pressure:

- In the **systemic** capillaries the Π_{GC} stays 28mm Hg at both the arterial and venous ends .

<u>Answer of the question I asked you earlier</u>: Because what is filtered is 0.5% from the whole fluid, so it does not affect the concentration of proteins at both ends.

- But filtration in the **kidneys** is 20% so it must have an effect on Π_{GC} and thus increases from 28 to 36 and the average is 32 mmHg..

III. Interstitial forces (Bowman's Space) :

- Bowman's Space contains protein free glomerular filtrate; i.e, too small Π_{GC} .

So in the kidneys Starling forces have been reduced to 3 forces from the normal 4.

- And Hydrostatic Pressure (P) of Bowman's space is 18 due to the fluids filtered.
- **Net Driving forces favoring filtration=**

60 – (32 + 18) = 10 mmHg

- **Knowing that P = 10mmHg and GFR is 125 then:**
- **K_f =12.5 ml/min.mmHg**
- **(125 ml/min=10 mmHg*KF)**

Glomerular Capillary Filtration Coefficient (K_f)

- K_f = hydraulic conductivity * surface area. Cannot b measured directly

- Normally is <u>not</u> highly variable. It is however,
- 400 times as high as Kf of systemic capillaries

- Diseases that can reduce K_f and GFR
  - chronic hypertension
  - obesity / diabetes mellitus increases the thickness of the basement membrane
  - glomerulonephritis

Renal K_f.

cont.

- The cause of ↑ Kf?

Loosing the negative charge of the basement membrane as in minimal change nephrotic syndrome causes albumin loss and edema.

- (Remember that albumin might be decreased as a result of malabsorption, malnutrition or malproduction from the liver and increased loss from the kidney).
- Hypoalbuminemia → ↑ GFR.

Bowman's Capsule hydrostatic Pressure (P_B)

- Normally changes as a function of GFR, not a physiological regulator of GFR
- Tubular Obstruction
  - kidney stones
  - tubular necrosis
- Urinary tract obstruction:
  Prostate hypertrophy/cancer

Factors Influencing Glomerular Capillary Oncotic Pressure (π_G)

- Arterial Plasma Oncotic Pressure (π_A)

$$\uparrow \pi_A \longrightarrow \uparrow \pi_G$$

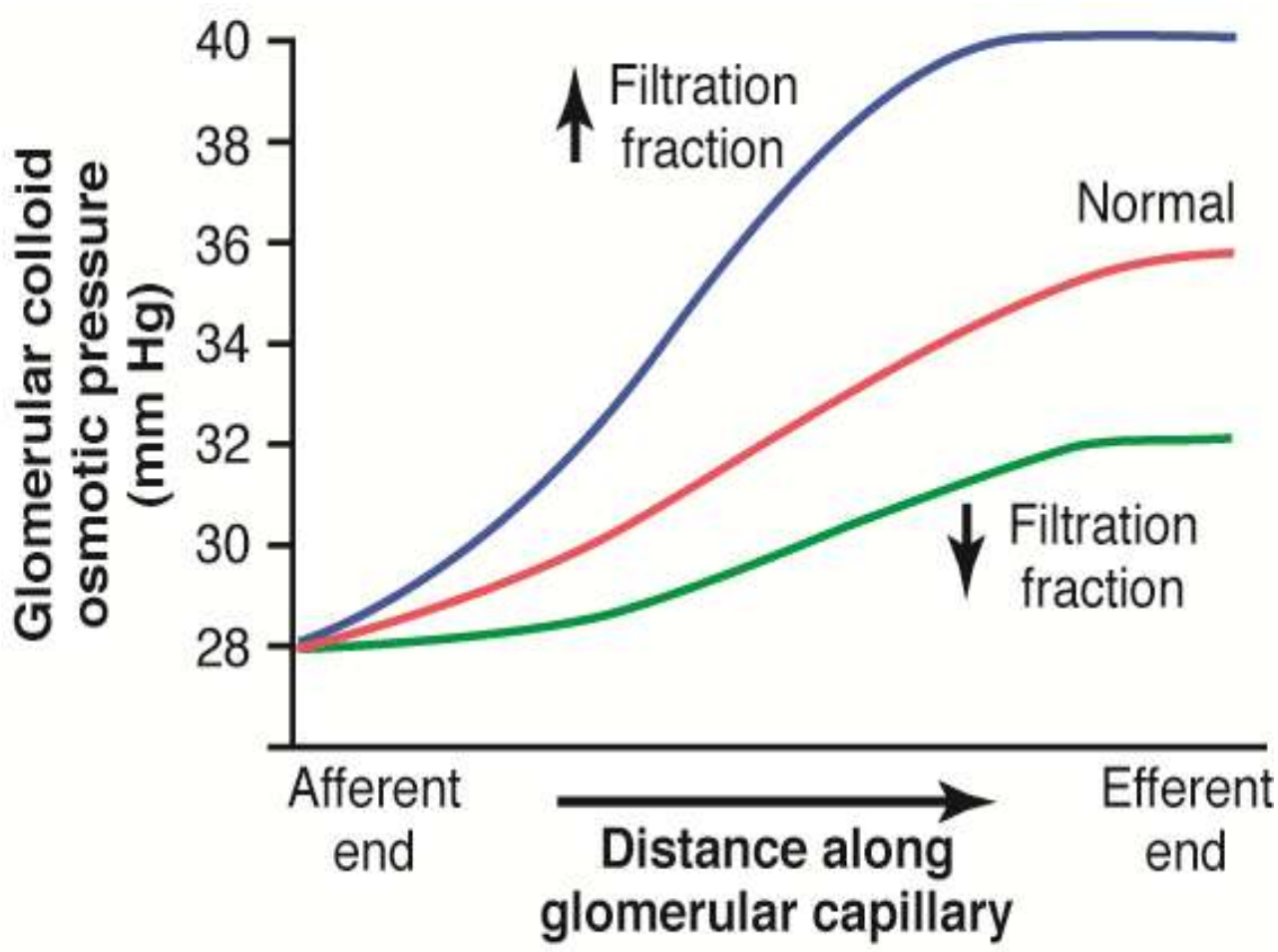
- Filtration Fraction (FF)

$$\uparrow FF \longrightarrow \uparrow \pi_G$$

Remember: FF = GFR ÷ RPF

= 125÷650 ~ 0.2 (or 20%)

Increase in colloid osmotic pressure in plasma flowing through glomerular capillary



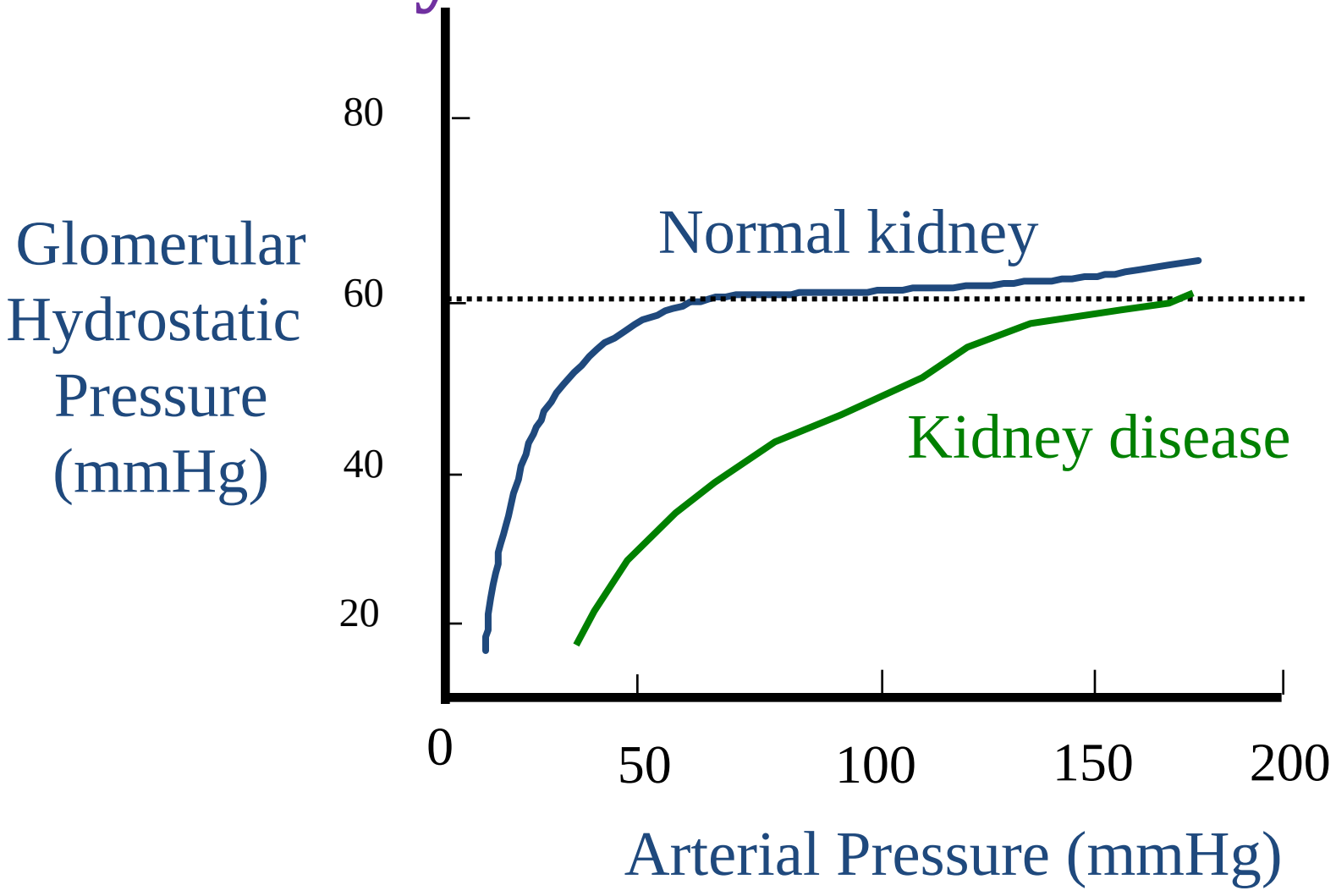
Renal Autoregulation

- **Autoregulation of GFR**
- Expressed in the following figures
- UOP increases greatly.
- GFR increases slightly in relation to arterial blood pressure but this is translated in a significnt increase in urine output… why is that?
- GFR = 125m1/min and UOP is only = 1m/min = 1.5L/day which means 124ml/min is reabsorbed (more than 99% is reabsorbed and only 0.6% is excreted) so a little change in GFR changed the urine output a lot.
- GFR must be regulated and this is achieved mainly by the vascular factor (glomerular capillary hydrostatic pressure) and this is controlled by afferent or efferent arterioles

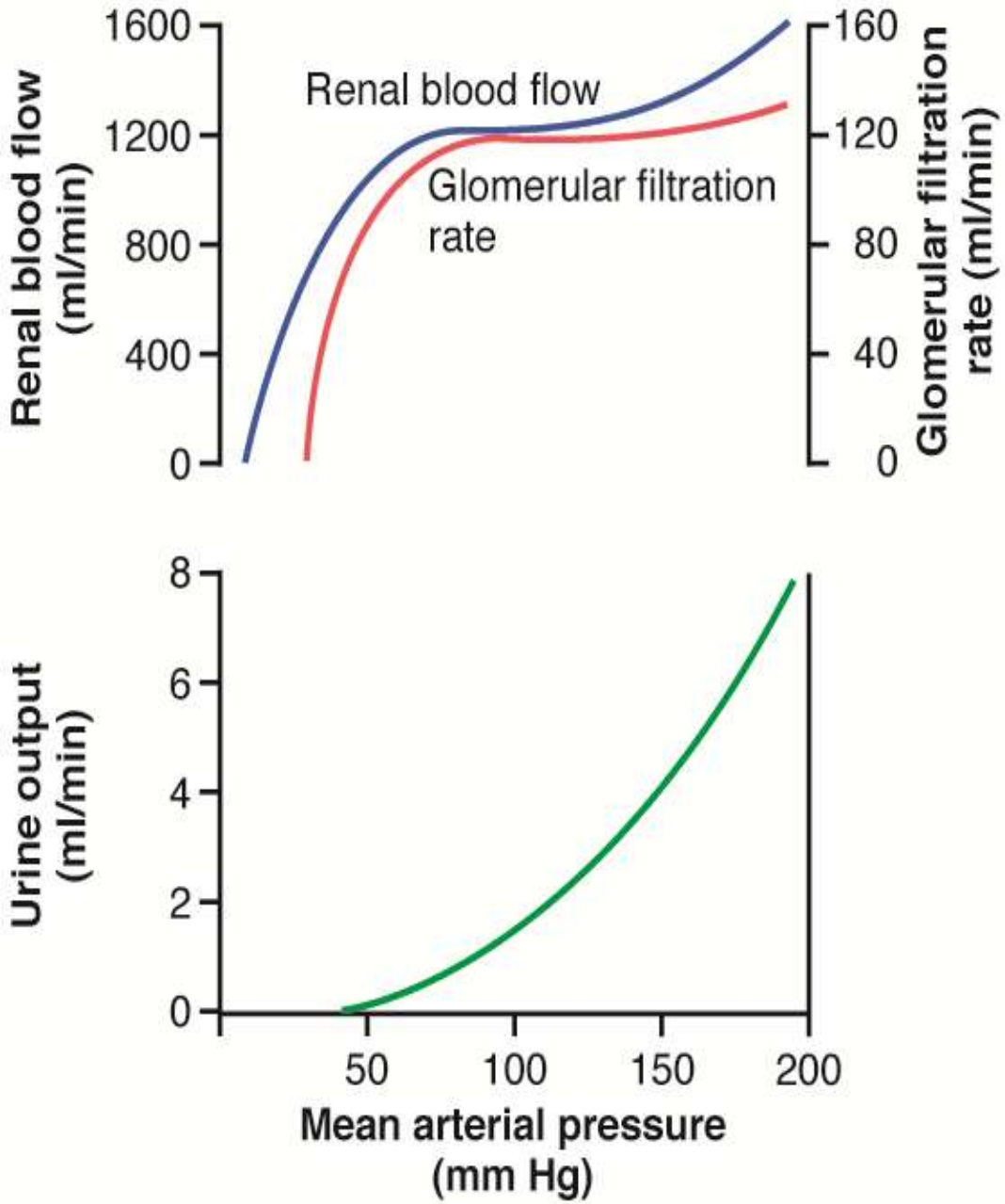
Importance of Autoregulation

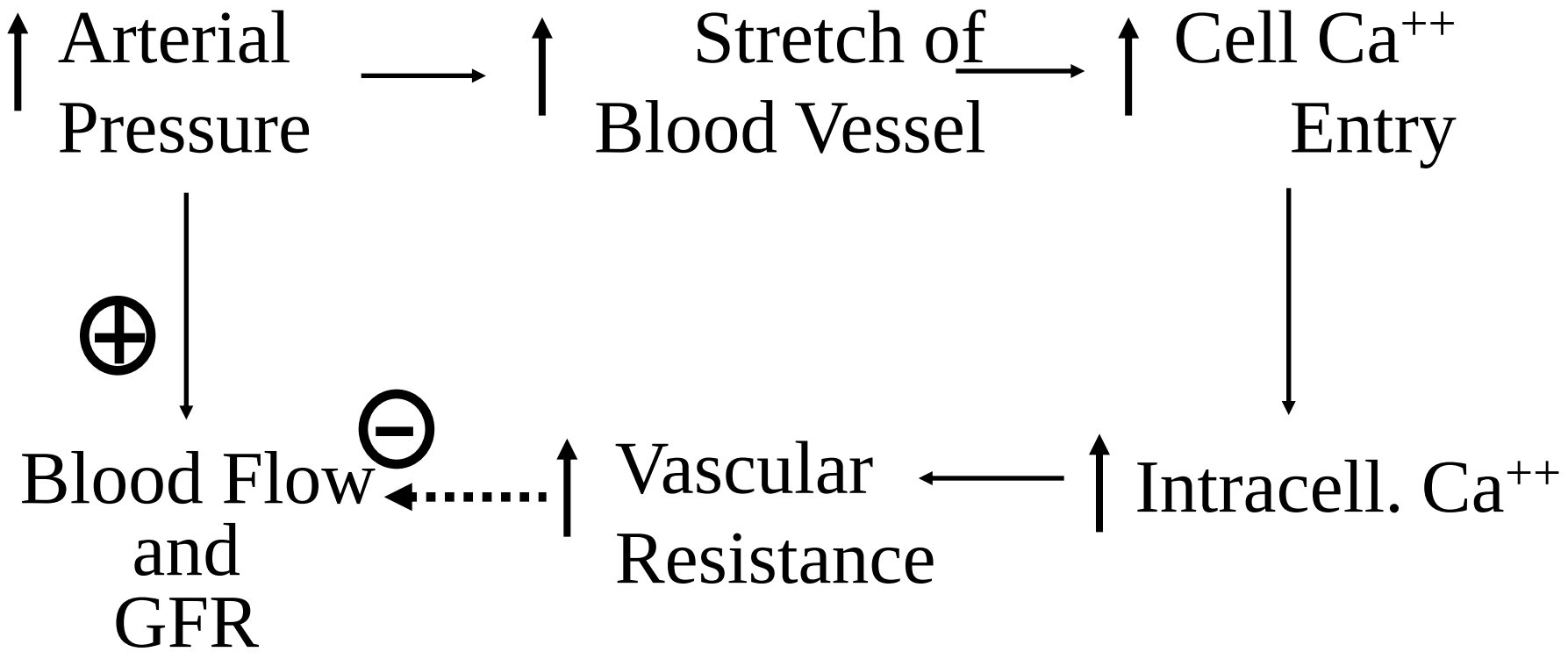
Arterial Pressure	GFR	Reabsorption	Urine Volume
1- Poor Autoregulation + no change in tubular reabsorption			
100	125	124	1.0
120	150	124	26.0 = 37.4 L/day!
2- Good Autoregulation + no change in tubular reabsorption			
120	130	124	6.0
3 Good Autoregulation+adaptive increase in tubular reabsorption			
120	130	128.8	1.2

Autoregulation of Glomerular Hydrostatic Pressure

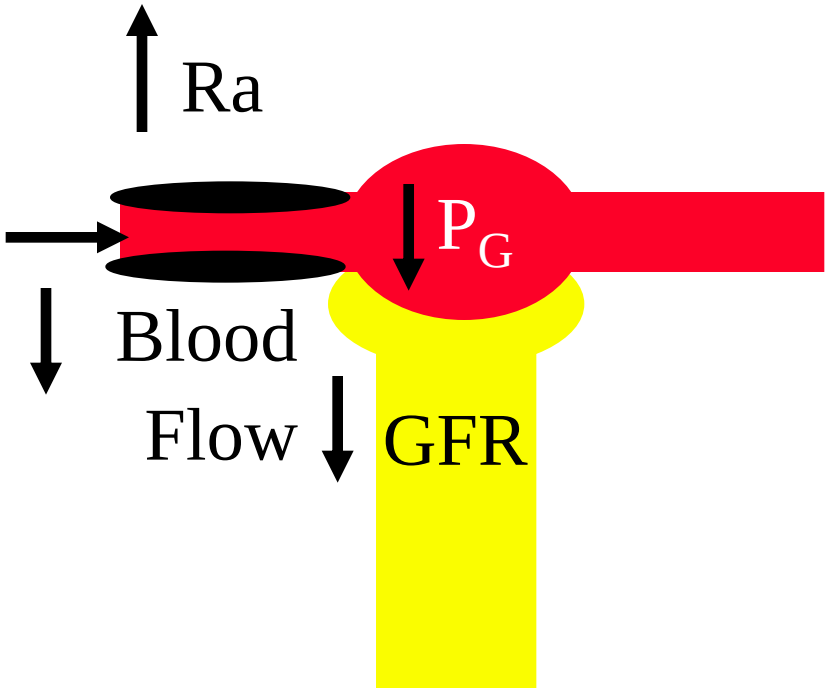


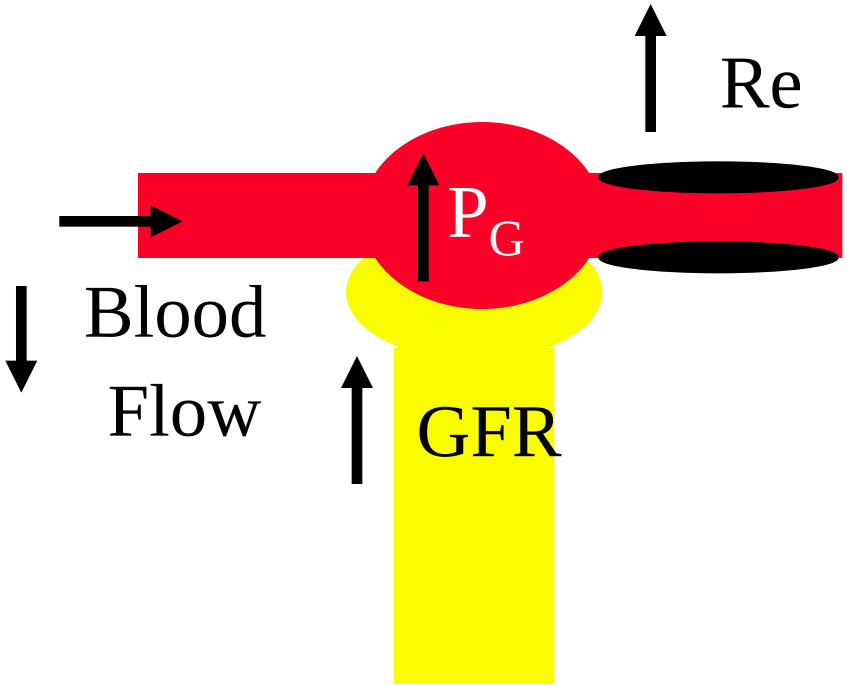
Autoregulation of renal blood flow and GFR but not urine flow




↑ Arterial Pressure
↑ Stretch of Blood Vessel
↑ Cell Ca++ Entry
⊕
Blood Flow and GFR
⊖
↑ Vascular Resistance
↑ Intracell. Ca++

Effect of afferent and efferent arteriolar constriction on glomerular pressure

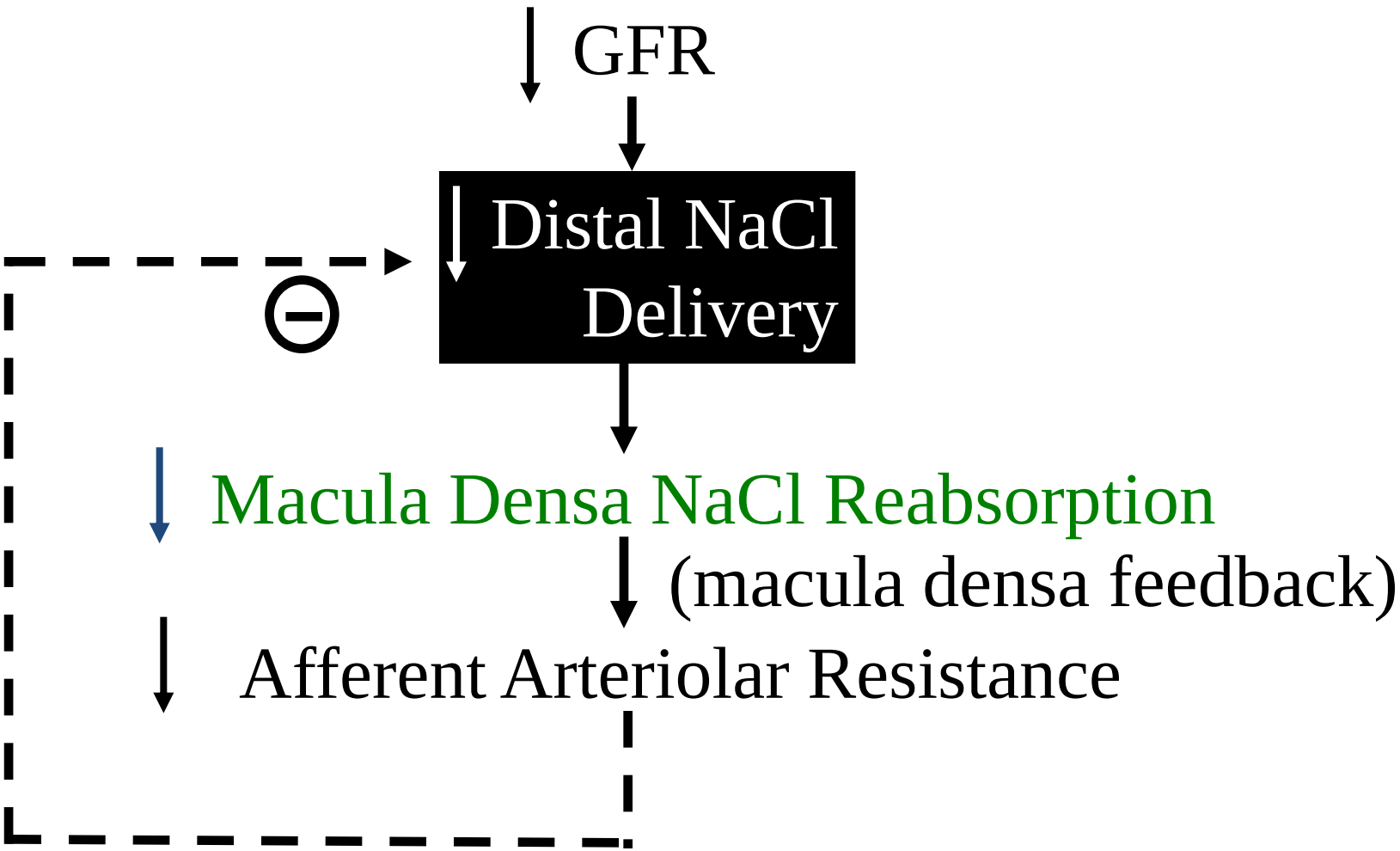




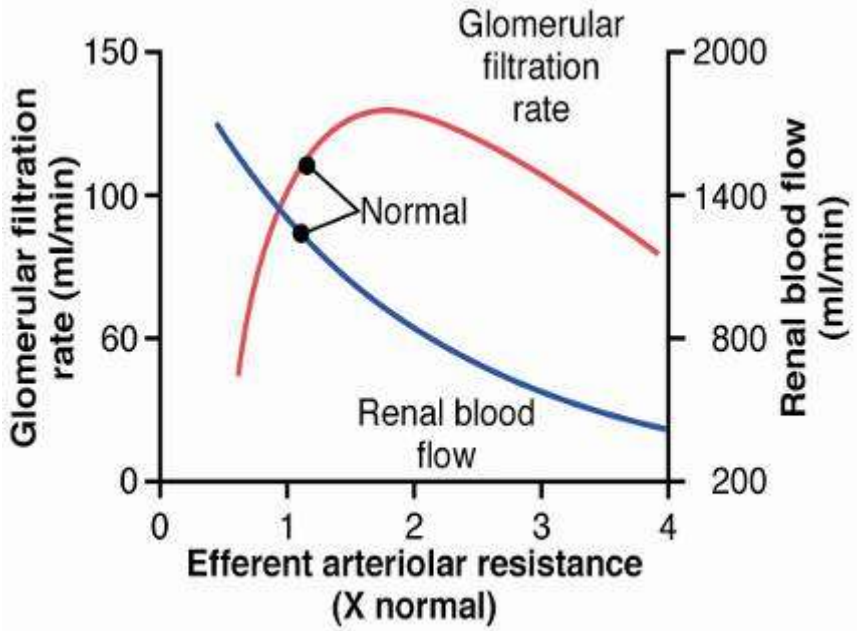
↑ Ra → ↓ GFR + ↓ Renal Blood

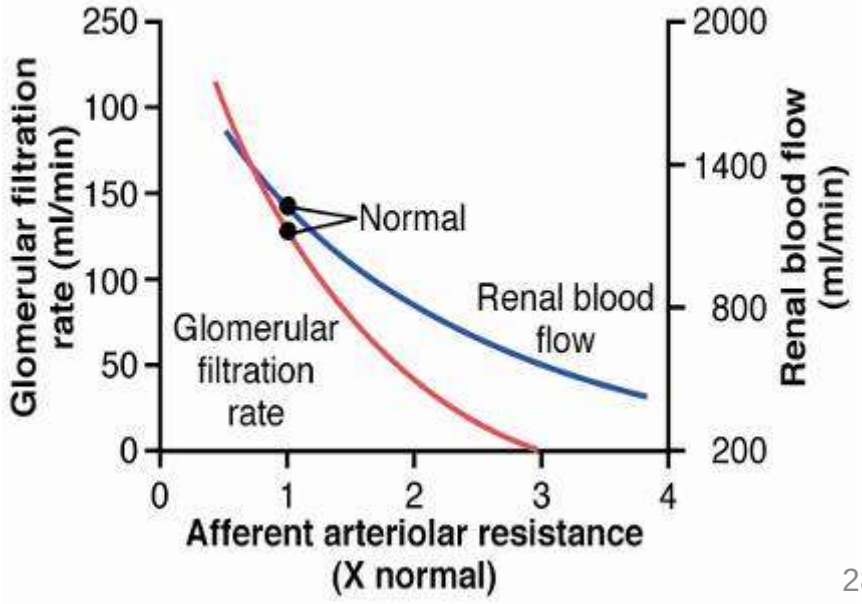
↑ Re → ↑ GFR + ↓ Renal Blood

Macula Densa Feedback



Effect of changes in afferent arteriolar or efferent arteriolar resistance. Biphasic Effect





Summary of Determinants of GFR

↑ K_f → ↑ GFR Renal Disease, DM,HP

↑ P_B → ↓ GFR Renal stones

↑ π_G → ↓ GFR Decrease RBF

↑ π_A → ↑ π_G → ↓ GFR

↑ FF → ↑ π_G

↑ P_G → ↑ GFR

↑ R_A → ↓ P_G → ↓ GFR

↑ R_E → ↑ P_G → ↑ GFR

(as long as R_E < 3-4 X normal)

Determinants of Renal Blood Flow (RBF)

$$RBF = \Delta P / R$$

ΔP = difference between renal artery pressure and renal vein pressure = 100-4 mmHg

R = total renal vascular resistance

= Ra + Re + Rv

= sum of all resistances in kidney vasculature

Table 26-3. Approximate Pressure and Vascular Resistances in the Circulation of Normal Kidney

Afferent + efferent contribute to about 70% of the intrarenal vascular resistance (mainly efferent).

	Pressure mmHg		% Total Vascular R
	Beginning	End	
Renal Artery	100	100	0
Interlobar, arcuate and interlolbular arteries	100	85	15
Afferent	85	60	25
Glomerular capillaries	60	59	1 only 1mmHg which means little resistance
Efferent	59	18	43 resistance mainly resides her
Peritubular Capillaries	18	8	10
Interlobar, arcuate and interlolbular veins	8	4	4
Renal vein	4	≈4	0

Tubuloglomerular Feedback

- In the distal tubule few cells in its wall sense the content of NaCl in the Tf and send two messages.

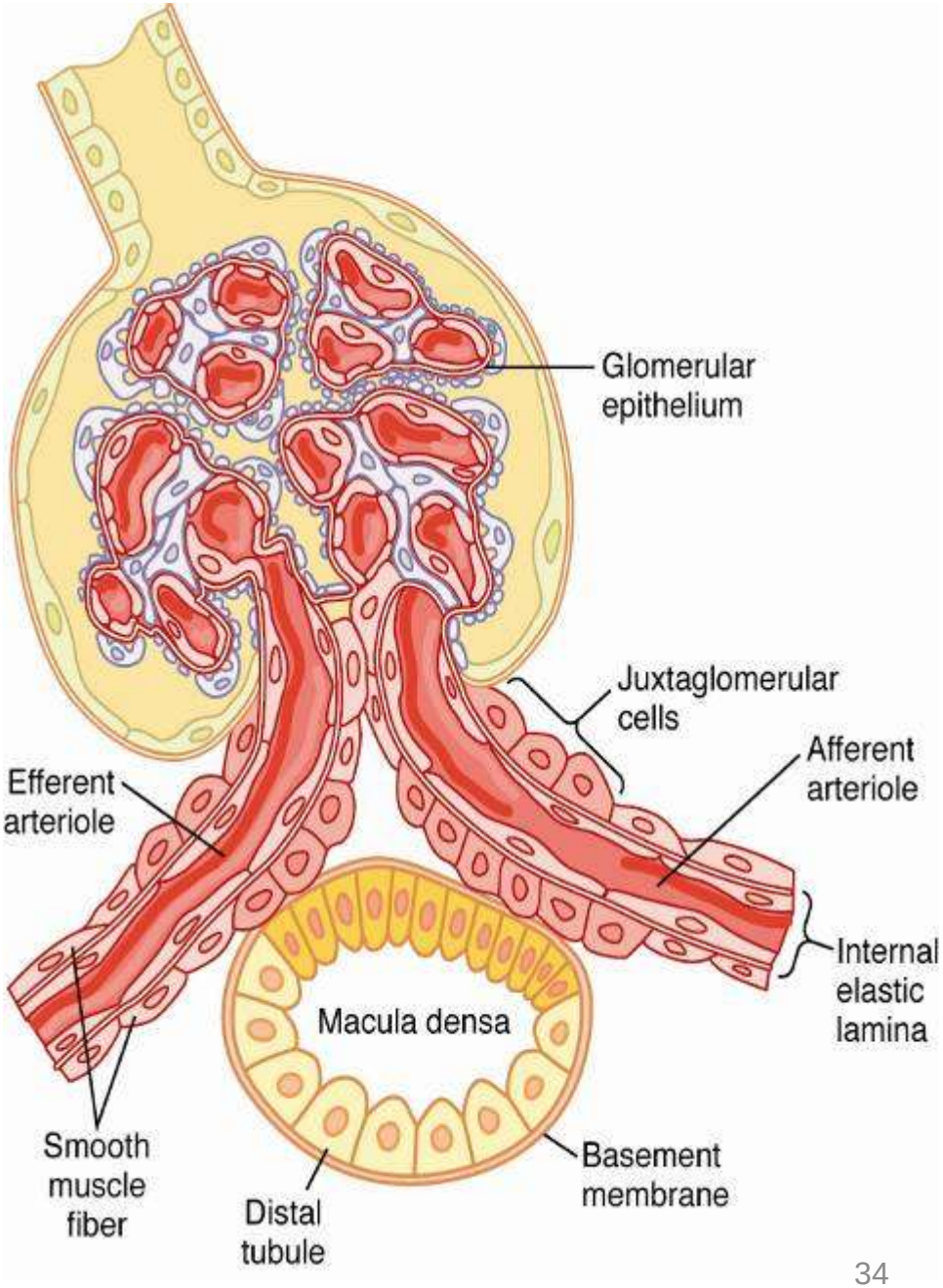
1. **The first message**: dilatation of the afferent arteriole and therefore increases blood flow to glomerular capillaries. (Myogenic Response)
2. **The second message**: is to the granular cell in the afferent and efferent arterioles to secret rennin.

- Rennin goes to the circulation where it convert angiotensinogen (produced by the liver) to AI (decapeptide) and then by the lungs converting enzyme into AII (octapeptide).
- Now remember that we have bleeding so we have to protect the kidneys and keep the GFR up but if we increase the GFR we might loose more urine and get yet more hypotension (contradicted situation) but angiotensin can do it both. (Next slide)

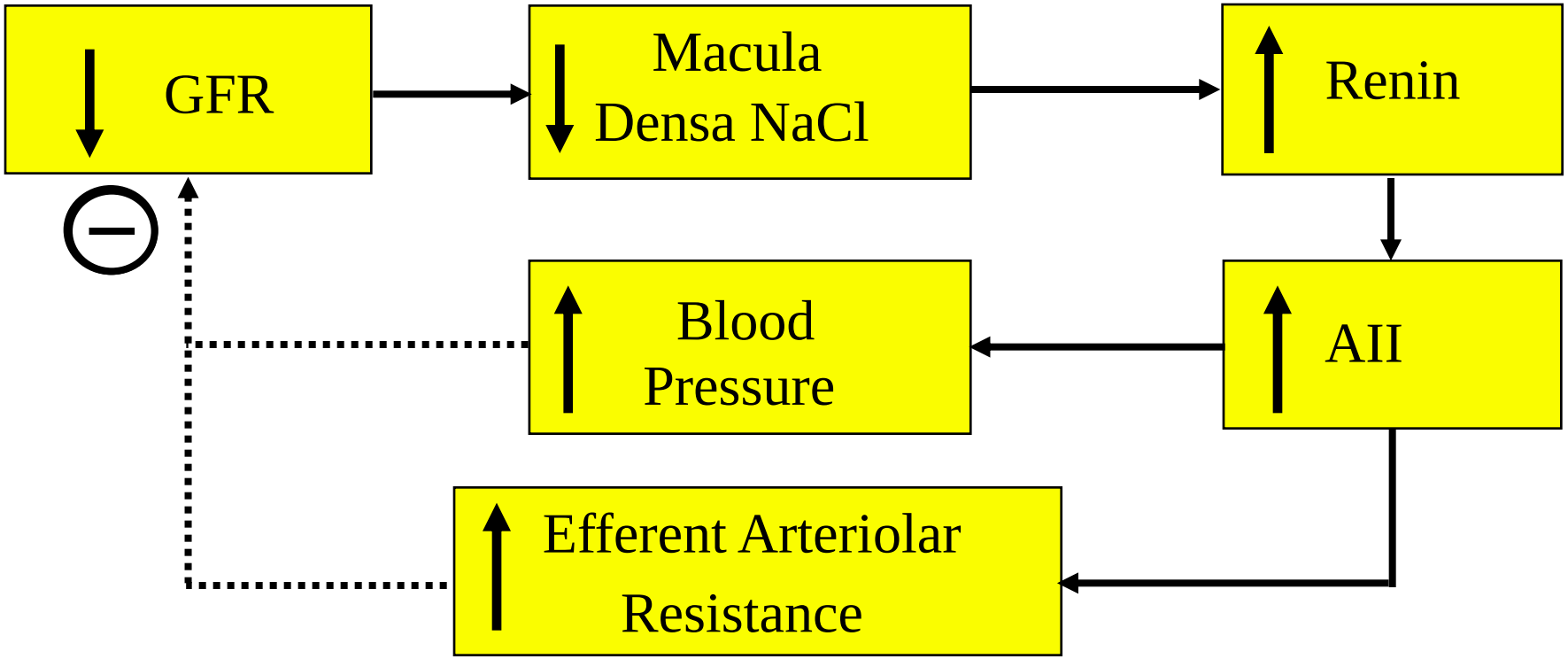
Tubuloglomerular Feedback

- **First**: constriction of efferent arteriole leading to increased GFR and at the same time the pressure in the peritubular capillaries decreases giving a better chance for reabsorbing to get the minimal urine output which is 0.5L/day. below this volume is oligourea.
- **Second**: AII acts directly on the adrenal cortex to secret aldosterone that enhances the reabsorption of Na from the distal tubule and sodium bring with it water.
- **Third**: angiotensin itself act directly to enhance sodium reabsorption in the proximal tubule.
- **Now these three functions of AII in addition to the first message (afferent dilatation) are responsible for the autoregulation of GFR**

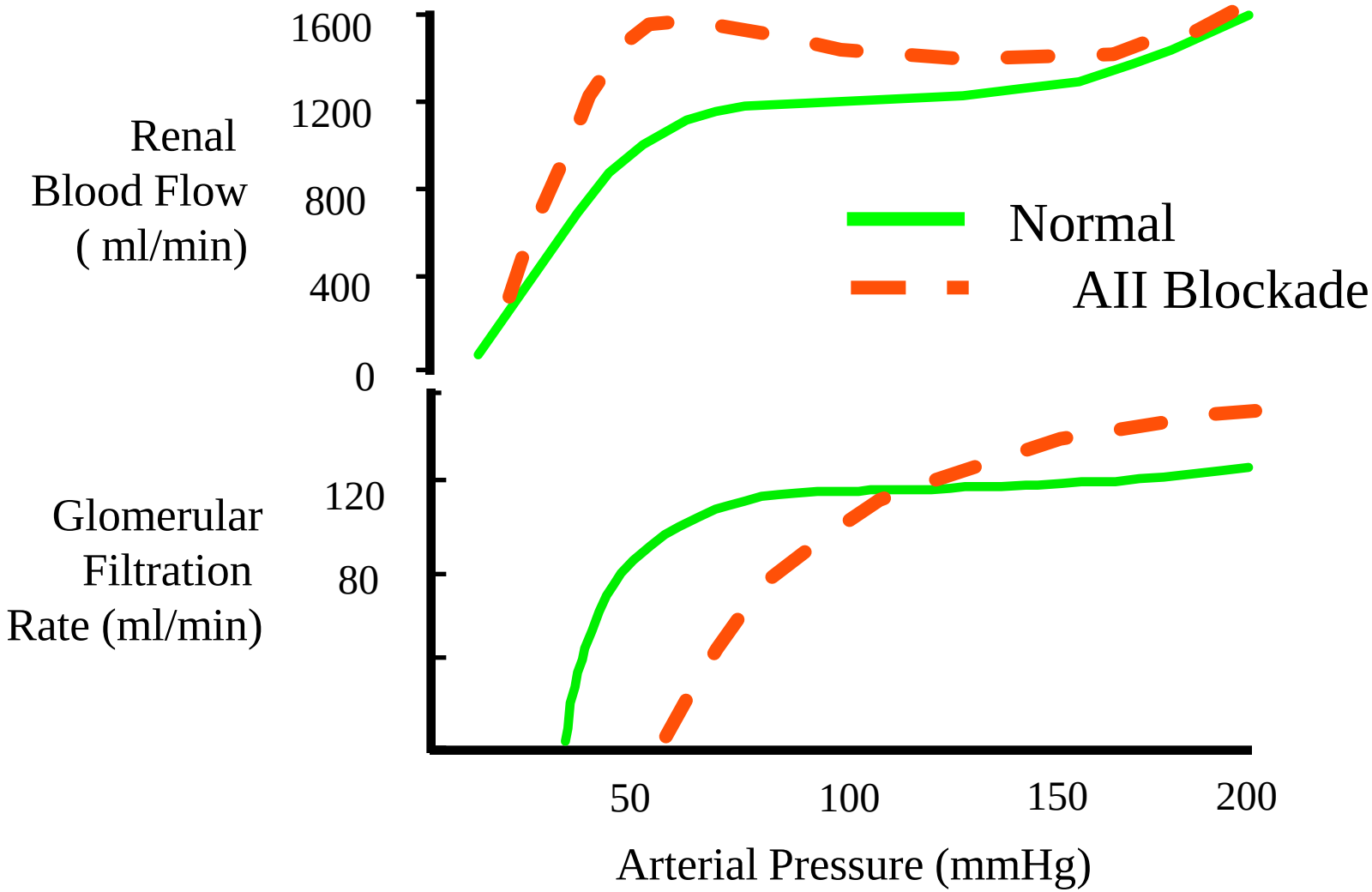
Structure of the juxtaglomerular apparatus: macula densa



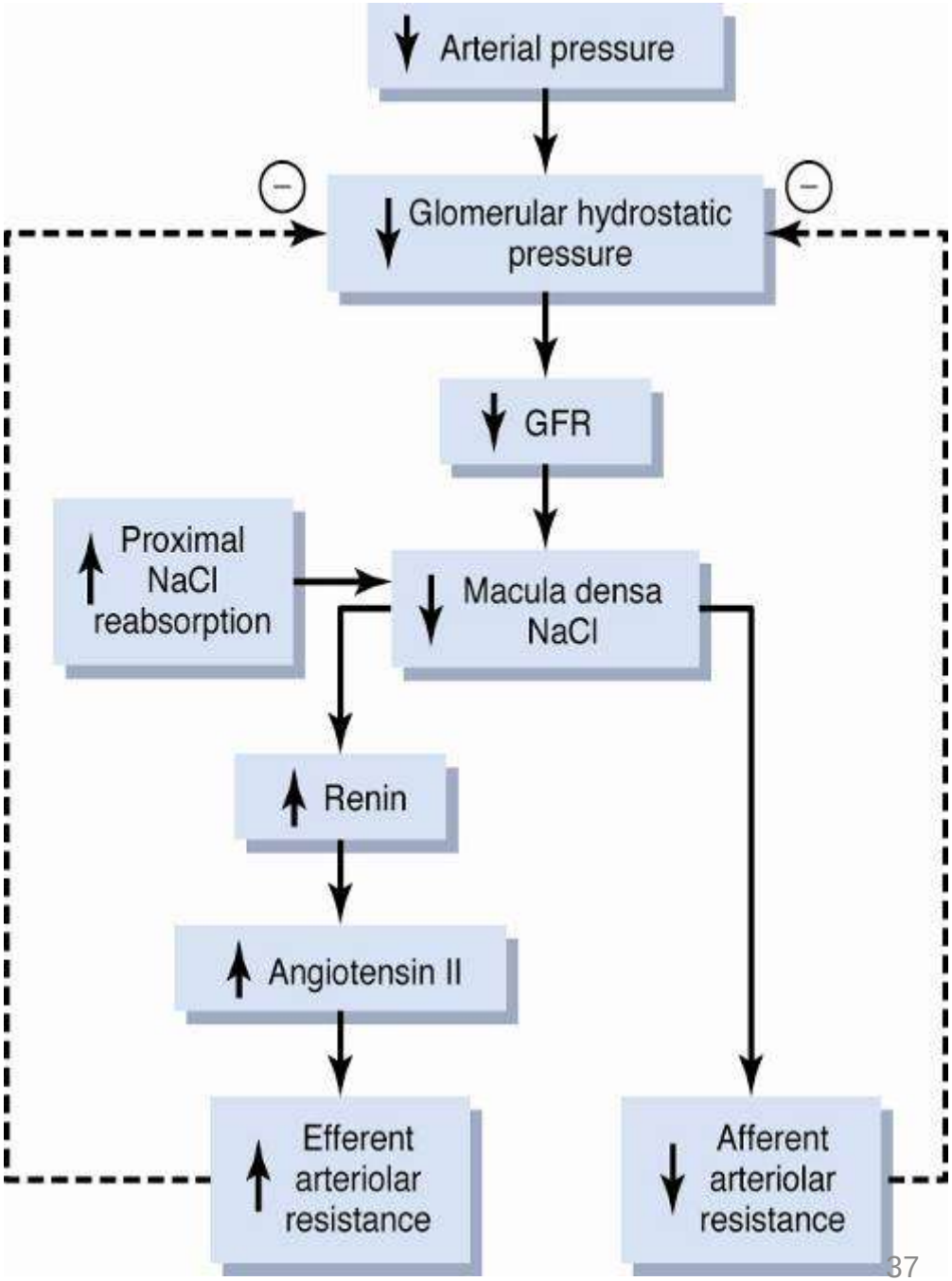
Regulation of GFR by AII

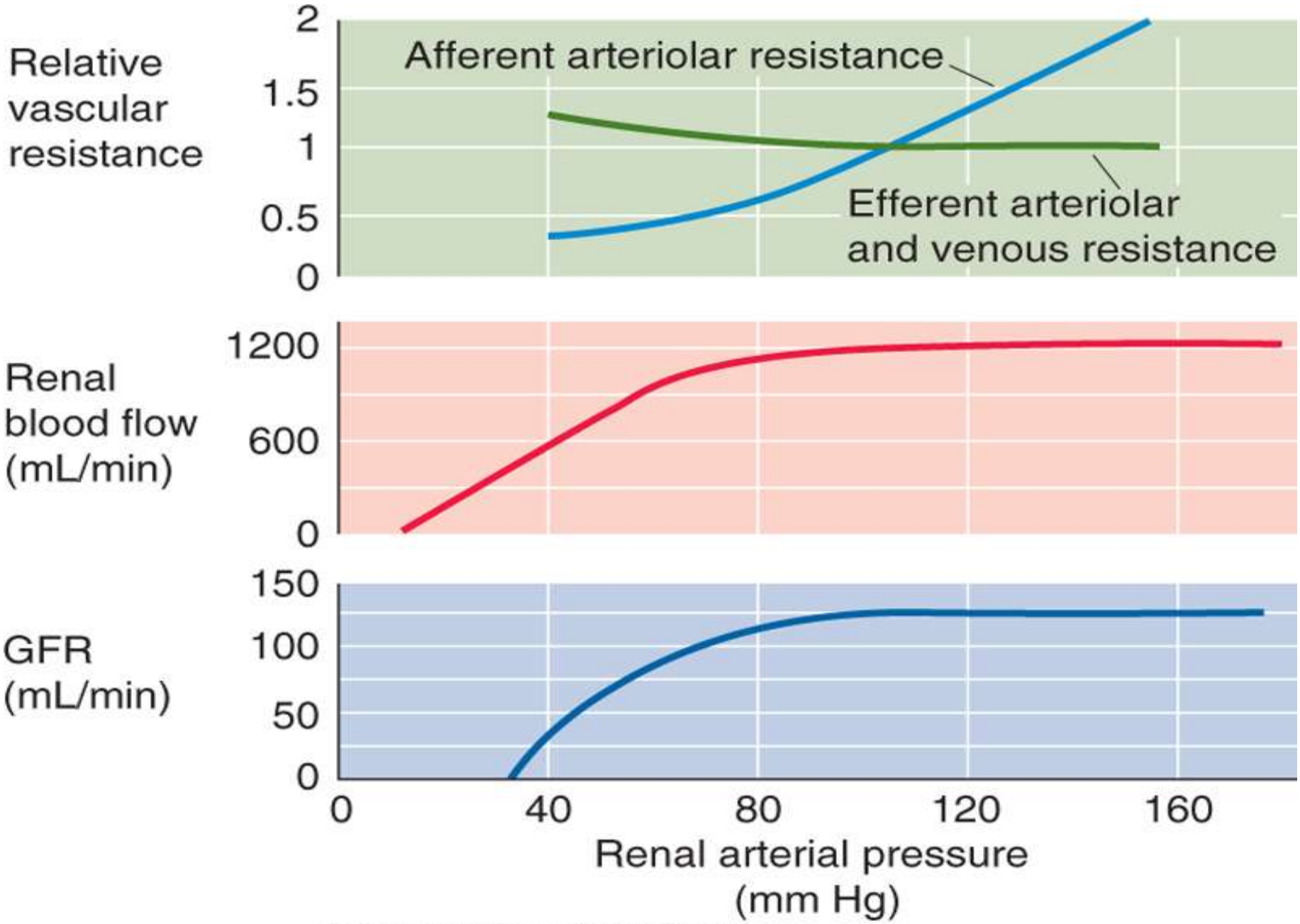


AII Blockade Impairs GFR Autoregulation

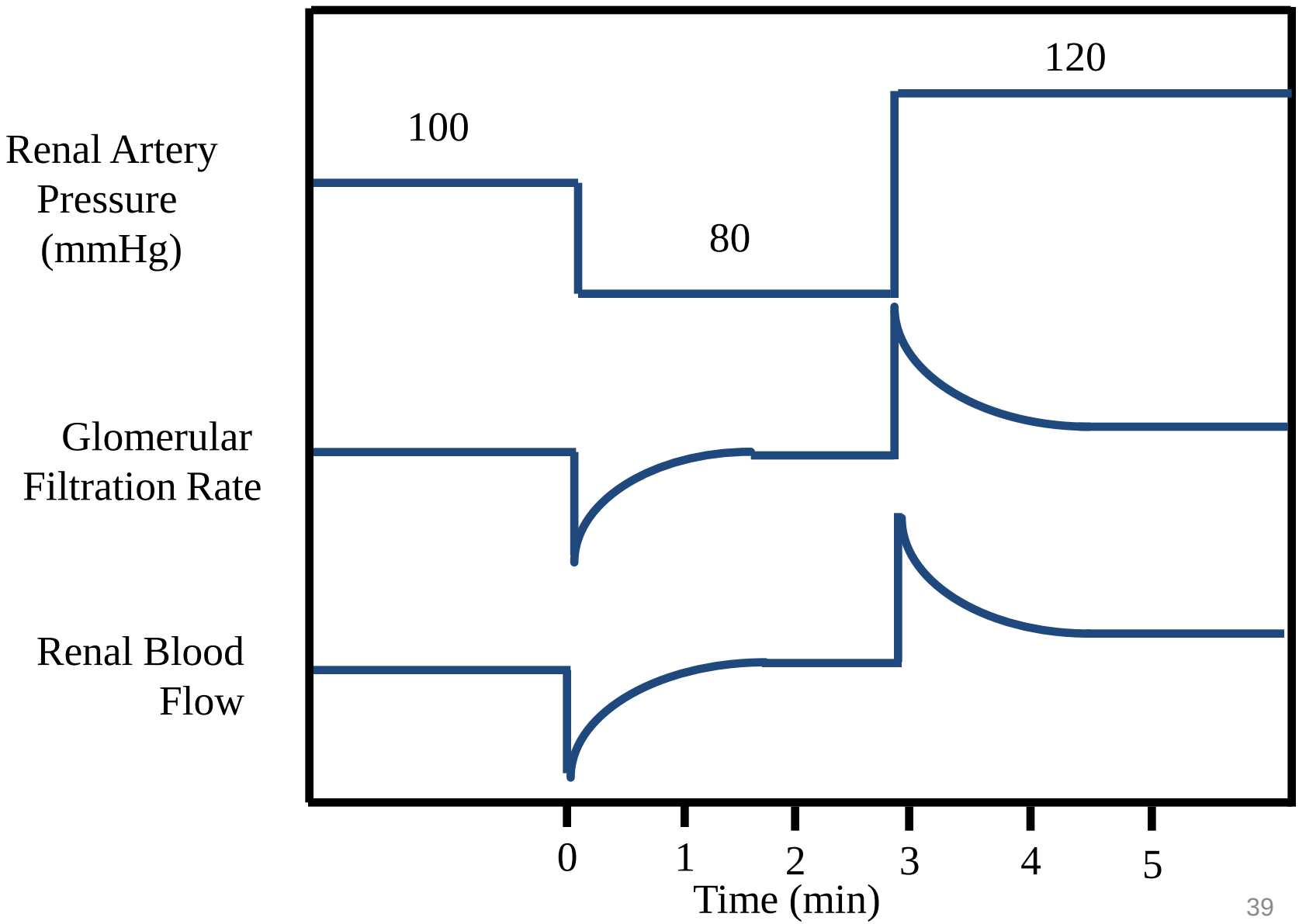


Macula densa feedback mechanism for regulating GFR





Renal Autoregulation



Control of GFR and renal blood flow

- Neurohumoral
- Local (Intrinsic)

Control of GFR and renal blood flow

1. Sympathetic Nervous System /catecholamines

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

e.g. severe hemorrhage.

Under normal conditions Sympathetic tone have little influence on RBF.

Sympathetic system may not influence RBF under normal circumstances, but in severe sympathetic stimulation it may decrease RBF significantly

2. Angiotensin II

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

(prevents a decrease in GFR)

e.g. low sodium diet, volume depletion

3. Prostaglandins

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

Blockade of prostaglandin synthesis → ↓ GFR

This is usually important only when there are other disturbances that are already tending to lower GFR. If Aspirin is administered which suppresses PGs then a severe decrease in GFR might occur.

e.g. nonsteroidal antiinflammatory drugs NDAID in a volume depleted patient, or a patient with heart failure, cirrhosis, etc

Control of GFR and renal blood flow

4. Endothelial-Derived Nitric Oxide (EDRF)

$\downarrow\downarrow$ R_A + $\downarrow$ R_E $\longrightarrow$ $\uparrow$ GFR + $\uparrow\uparrow$ 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

Control of GFR and renal blood flow

5. Endothelin

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

- 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

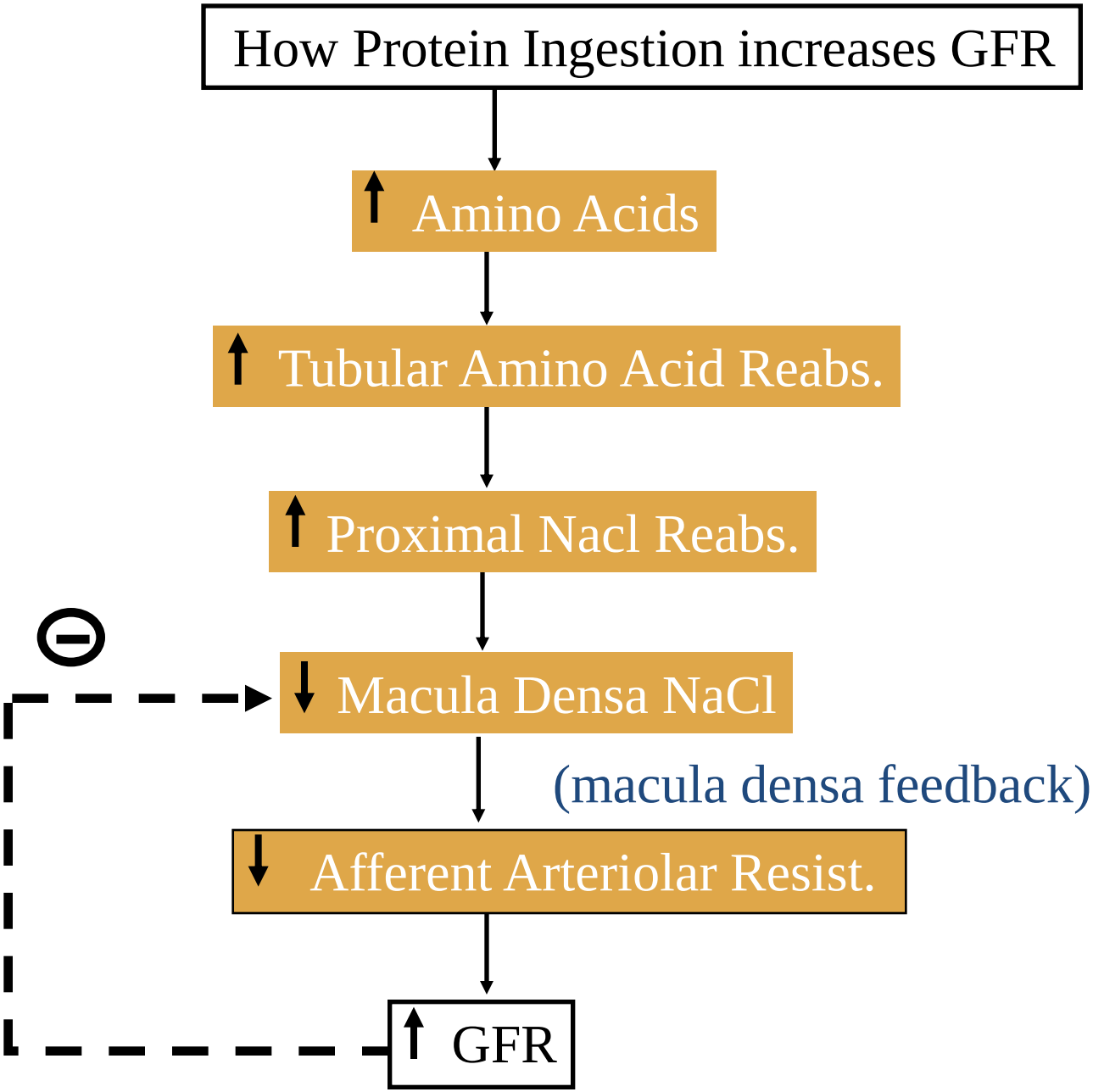
Summary of neurohumoral control of GFR and renal blood flow

	Effect on RBF	Effect on GFR
↑ Sympathetic activity	↓	↓
↑ Catecholamines	↓	↓
↑ Angiotensin II	↓	↔
↑ EDRF (NO)	↑	↑
↑ Endothelin	↓	↓
↑ Prostaglandins	↑	↑

↑ increase ↓ decrease ↔ no change

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


How Protein Ingestion increases GFR
Amino Acids
Tubular Amino Acid Reabs.
Proximal Nacl Reabs.
Macula Densa NaCl
(macula densa feedback)
Afferent Arteriolar Resist.
GFR