UGS MODULE
PHYSIOLOGY(LECTURE 2)
Regulation of GFR and RBF

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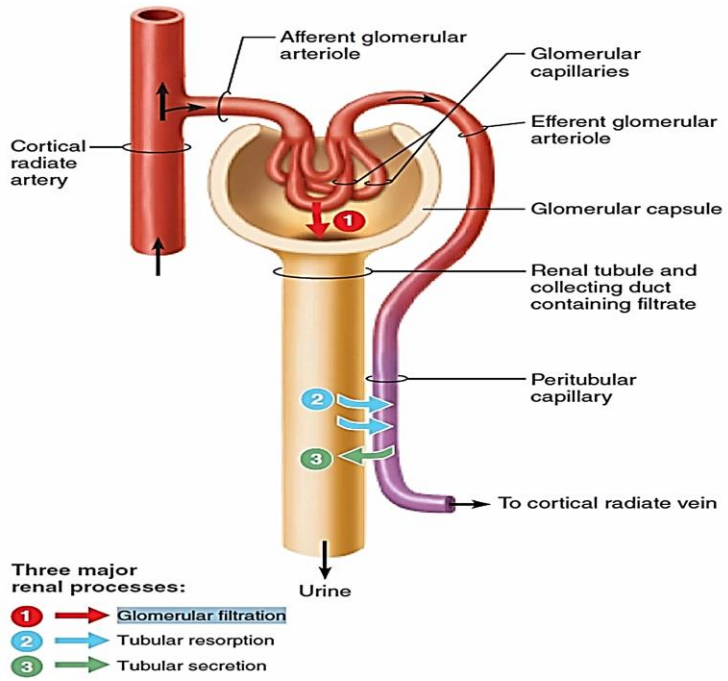


Determinants of GFR

I) Renal blood flow (RBF):

The **GFR is generally directly proportional to the RBF**.

II) Glomerular capillary pressure (GCP):

The GFR is directly proportional to the GCP which is affected by the following factors:

A. Afferent arteriolar diameter:

- **VC decreases both RBF and GCP, so GFR is reduced.**
- **VD increases both RBF and GCP, so GFR is increased.**

***B. Efferent arteriolar diameter*:**

- **VD decreases GCP, so GFR is reduced.**
- **VC increases GCP, so GFR is increased.**

C. ABP

Increased mean ABP (MAP) tends to raise glomerular capillary hydrostatic pressure and, therefore, to increase GFR. (However, this effect is buffered by autoregulatory mechanisms that maintain a relatively constant glomerular pressure as blood pressure fluctuates within a certain range.)

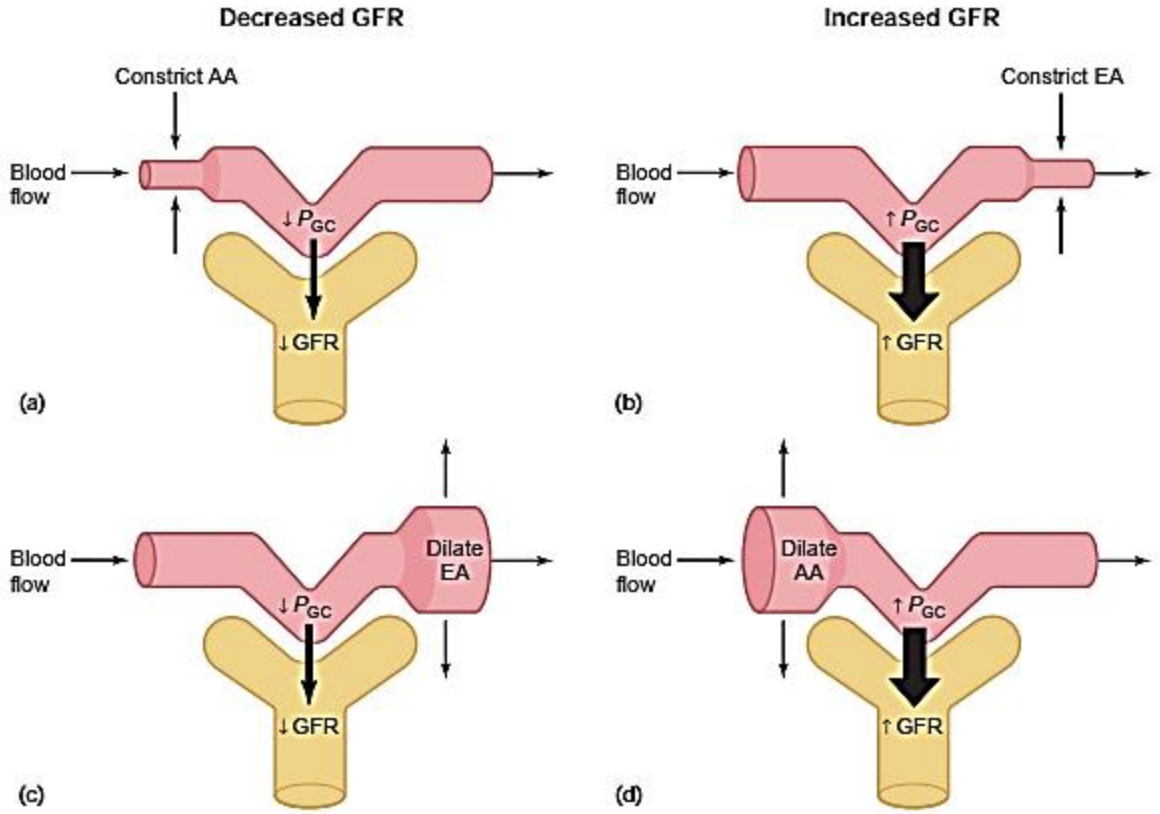


Figure 14.9 AP|R Control of GFR by constriction or dilation of afferent arterioles (AA) or efferent arterioles (EA). (a) Constriction of the afferent arteriole or (c) dilation of the efferent arteriole reduces P_{GC}, thus decreasing GFR. (b) Constriction of the efferent arteriole or (d) dilation of the afferent arteriole increases P_{GC}, thus increasing GFR.

III) The glomerular colloid osmotic pressure (GOP):

- **The GFR is inversely proportional to GOP.**
- As blood passes from the afferent arteriole through the glomerular capillaries to the efferent arterioles, the plasma protein concentration increases.
- **Thus an increase in GOP (as in dehydration) reduces GFR. While, a decrease in GOP (e.g. due to hypoproteinemia) increases the GFR.**

IV) Bowman's capsule pressure; capsular pressure (CP):

- **The GFR is inversely proportional to CP.**
- Thus **an increase in the CP due to stone in the ureter (obstructing outflow of urinary tract) reduces GFR.**

V) Size of the glomerular capillary bed (the filtration surface area):

The **GFR is reduced if the glomerular surface area available for filtration is decreased**. This occurs due to either:

(a) **A decrease in functioning kidney mass** (i.e. number of nephrons) as in chronic renal failure and after nephrectomy.

(b) **Contraction of the mesangial cells** (stellate cells that surround the glomerular capillaries between the glomerular capillary endothelium and basal lamina). Contraction of these cells **reduces the surface area** of the capillaries, which causes **a decrease in GFR.**

VI) The glomerular capillary permeability:

- **The GFR is directly proportional to glomerular capillary permeability.**
- Glomerular capillary permeability is altered in renal diseases (e.g. it is increased in glomerulonephritis due to damage of capillary walls and reduction of their negative charges).

Regulation of GFR (Renal Hemodynamics)

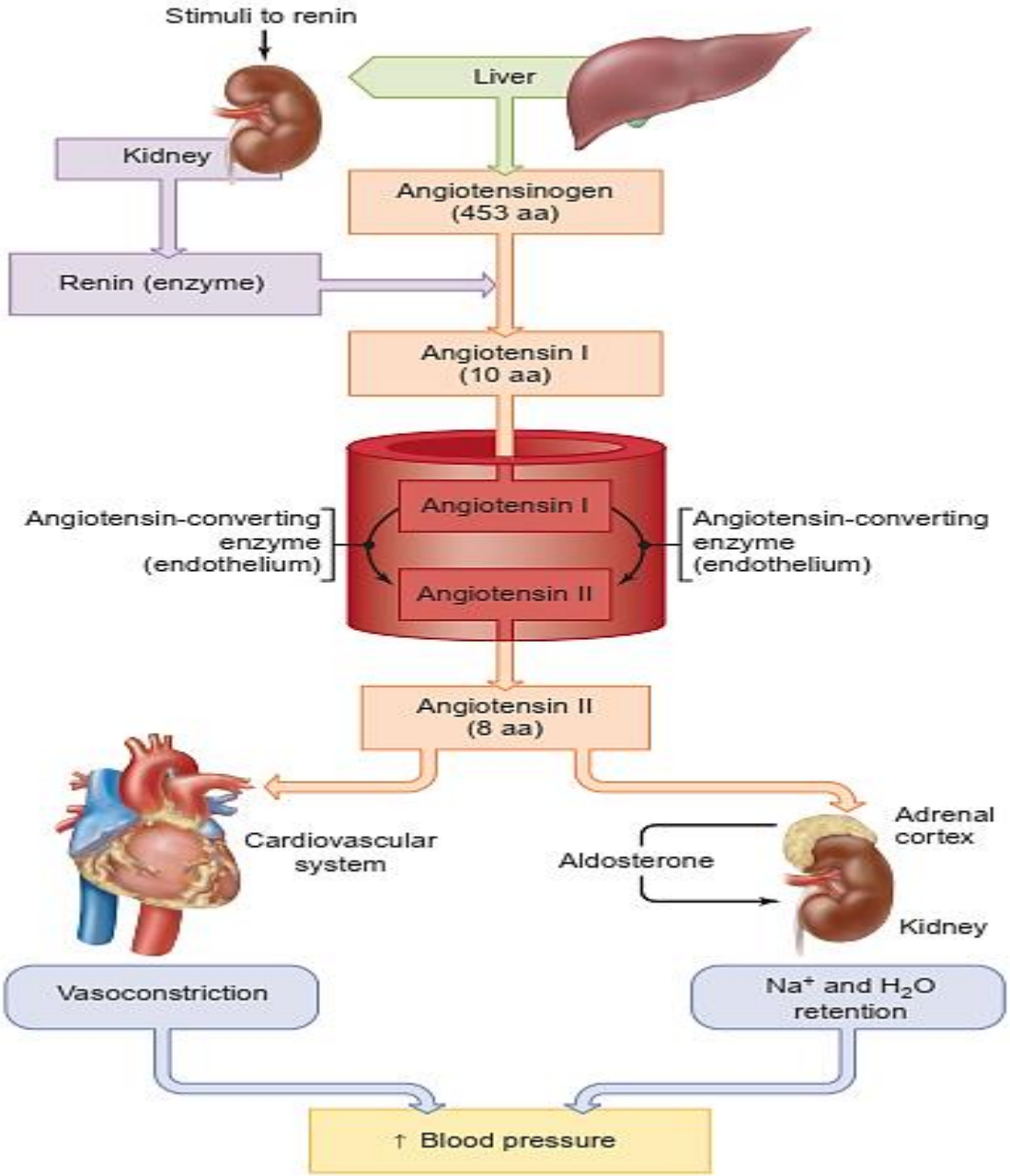
Control of renal hemodynamics occurs through the following mechanisms:

The renin-angiotensin-aldosterone system (RAAS):

- ✓ It is activated in response to **low renal vascular flow (renal ischemia)** which stimulates **renin** secretion by the **juxtaglomerular cells** at the ends of the **afferent arterioles**.
- ✓ This, in addition to the **modulation of renin secretion by the macula densa**, will **activate the RAAS**.
- ✓ **The renin will act on angiotensinogen to produce angiotensin I which is converted to angiotensin II by ACE and thus control GFR**.

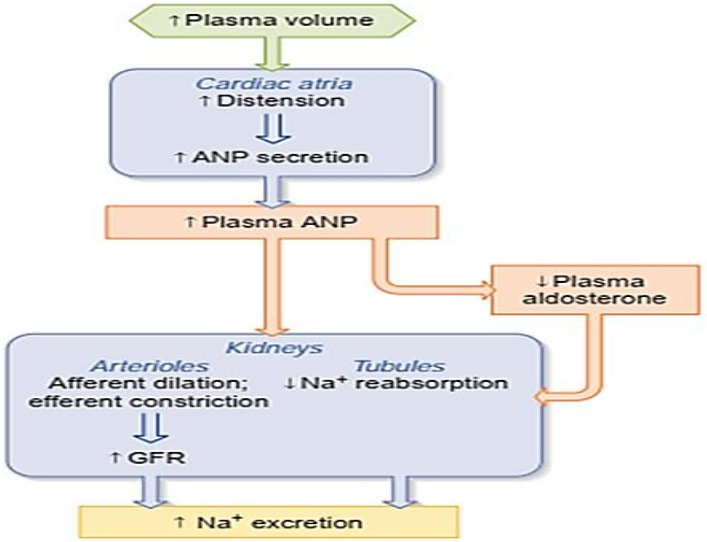
Angiotensin II:

- o It is a **vasoconstrictor**, and in the kidneys, it acts directly on the renal arteries, and to a greater extent at the **afferent and efferent arterioles**, increasing resistance.
- o **Angiotensin II actually has greater effect on the efferent arteriole than afferent arteriole. Thus, increasing or maintaining the glomerular capillary pressure in the glomerulus and GFR**.
- o **Angiotensin II maintains the GFR** even in the face of decreased overall RBF.


Stimuli to renin
Liver
Kidney
Angiotensinogen
(453 aa)
Renin (enzyme)
Angiotensin I
(10 aa)
Angiotensin-converting
enzyme
(endothelium)
Angiotensin I
Angiotensin II
Angiotensin-converting
enzyme
(endothelium)
Angiotensin II
(8 aa)
Cardiovascular
system
Aldosterone
Adrenal
cortex
Kidney
Vasoconstriction
Na+ and H2O
retention
↑ Blood pressure

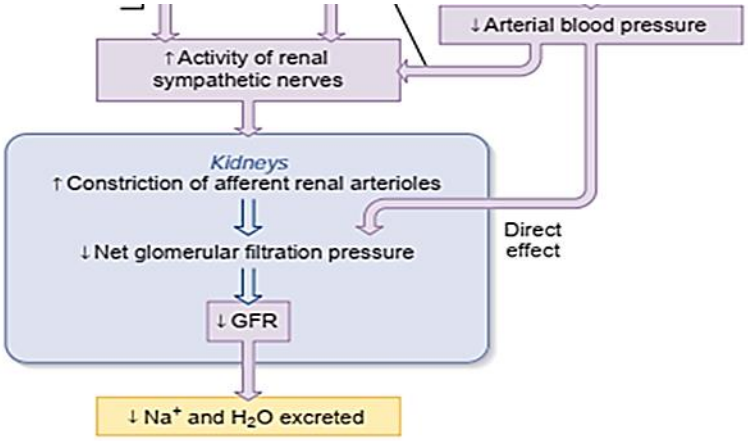
Atrial natriuretic peptide (ANP):

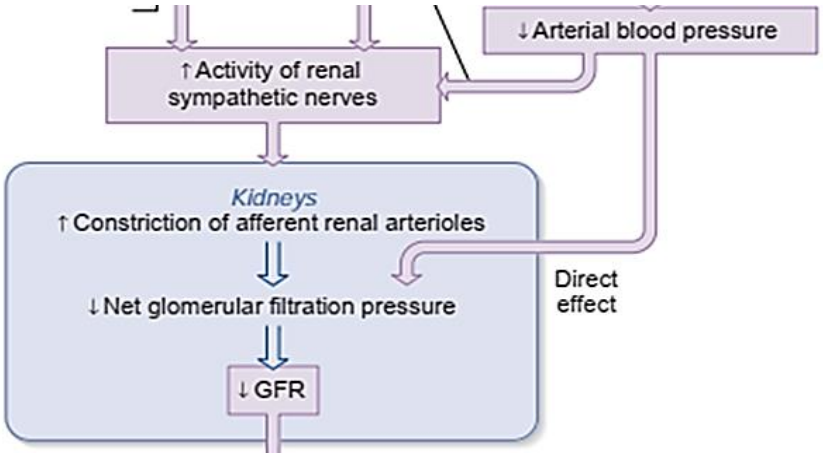
- Cells in the **cardiac atria synthesize and secrete ANP in response to stretch; atrial distension (at high blood volume)**.
- **ANP acts on several tubular segments to inhibit Na^+ reabsorption.**
- **ANP also directly inhibits aldosterone secretion, which leads to an increase in Na^+ excretion.**
- **ANP causes natriuresis and diuresis, reducing ECF volume.**
- **ANP also causes VD of renal afferent arteriole and VC of efferent arteriole increasing glomerular capillary pressure, and thus, GFR. The enhanced flow increases sodium and water excretion, reducing blood volume.**



Sympathetic nerves and catecholamines (NE and Epi):

- ✓ They are **stimulated in response to reductions in systemic blood pressure.**
- ✓ They cause **vasoconstriction of the renal arteries and arterioles (afferent > efferent)**.
- ✓ **Mild stimulation of sympathetic nerve activity produces almost no effect, the intrarenal systems will counteract this effect, to ensure the kidney vasculature remains dilated, preserving GFR.**
- ✓ **During high sympathetic nerve activity (severe hemorrhage), sympathetic nerve activity overrides the intrarenal regulatory mechanisms and reduces RBF and GFR.**





Endothelial-Derived Nitric Oxide (NO):

- **NO is an autacoid that decreases the renal vascular resistance and increases GFR.**
- It is released by the vascular endothelium throughout the body.
- A basal level of nitric oxide production appears to be important for maintaining vasodilation of the kidneys.
- Therefore, administration of drugs that inhibit this normal formation of nitric oxide increases renal vascular resistance and decreases GFR and urinary sodium excretion, eventually causing high blood pressure.
- In some hypertensive patients, impaired nitric oxide production could be the cause of increased renal vasoconstriction and increased blood pressure.

Intrarenal prostaglandins: (PGE_2 and PGI_2)

- **They are vasodilators**, acting at the level of the arterioles and glomerular mesangial cells.
- They cause **dilation of afferent arterioles > efferent arterioles**, thereby **increasing RBF and GFR**.
- Nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin will block prostaglandin synthesis and restrict the compensatory renal vasodilation.

AUTOREGULATION OF GFR & RBF

- This is an **intrinsic mechanism in the kidney that keeps GFR and RBF nearly constant despite changes in mean ABP (MAP) between 80 – 180 mmHg.**
- **Intrinsic systems include the myogenic and tubuloglomerular feedback (TGF) mechanisms.**
- These systems allow regulation of GFR over a wide range of systemic blood pressure (MAP 80 to 180 mm Hg).

Mechanism of autoregulation of GFR and RBF

I. When the mean ABP rises to 180 mmHg:

In this condition, **constriction of afferent arterioles occurs, so both RBF and GFR are kept relatively constant (or increase slightly) in spite of the increased MAP.**

This is produced by either **myogenic mechanism or tubuloglomerular feedback mechanism**.

1. Myogenic mechanism:

↑ Mean ABP (MAP) → stretch afferent arterioles→ entry of Ca^{2+} from extracellular fluid into cells→ vasoconstriction of the afferent arteriole → increasing vascular resistance to prevent excessive increases in RBF and GFR.

2. Tubuloglomerular feedback mechanism:

(**A feedback mechanism that links changes in sodium chloride concentration at the macula densa with the control of renal arteriolar resistance**)

- Rise of mean ABP increases glomerular filtration, so the rate of flow through the ascending limb of LH and first part of DCT also increases.

- This initiates a signal from **macula densa** (probably as a result of the **increase of Na^+ and Cl^- concentrations**) that produces **VC of the afferent arterioles** (which may be mediated by adenosine or ATP).

- The **afferent arteriole constricts, which reduces glomerular capillary pressure, and thus decreases the pressure for filtration, reducing GFR and tubular flow.**

II. When the mean ABP (MAP) falls to 80 mmHg:

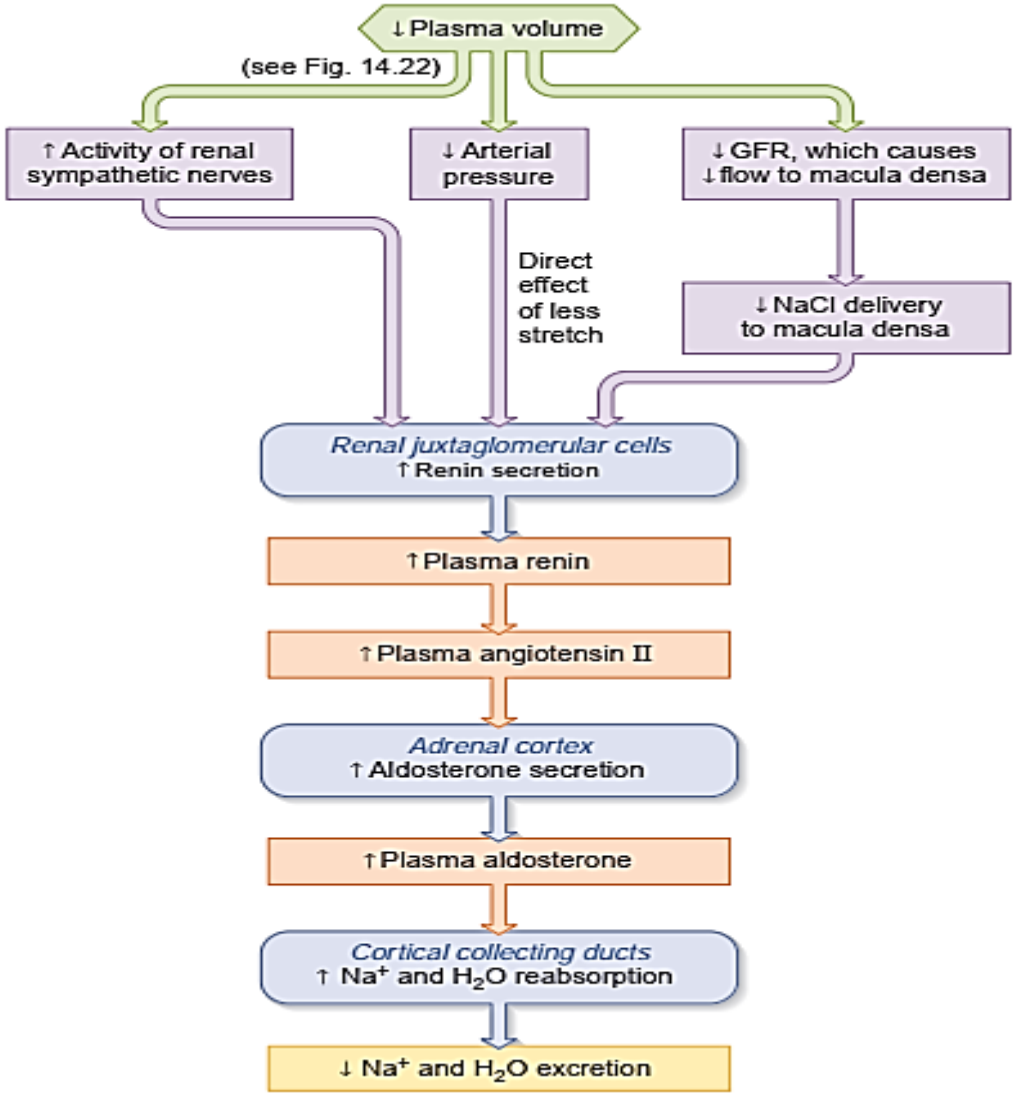
- In this condition, **VC of efferent arterioles occurs.** So, the GFR is kept relatively constant (or decreases slightly) in spite of the decreased MAP.
- **Such arteriolar response is produced by a tubuloglomerular feedback mechanism as follows:**

✓ The fall of MAP decreases glomerular filtration, so the rate of flow through the ascending limb of LH and first part of DCT also decreases.

✓ This initiates a signal from **the macula densa (probably as a result of the decrease of Na^+ and Cl^- concentrations).**

✓ **Macula densa cells activate juxtaglomerular cells causing the release of renin** and this catalyzes formation of **angiotensin II, which specifically causes VC in the efferent arterioles**.

✓ Since efferent arteriolar VC is important for stabilization of GFR when ABP falls, severe reduction of GFR (that may lead to renal failure) may occur in patients with poor renal perfusion if angiotensin II is not formed (e.g. due to use of drugs that inhibit the angiotensin-converting enzyme such as captopril or angiotensin II antagonists).


↓ Plasma volume
(see Fig. 14.22)
↑ Activity of renal sympathetic nerves
↓ Arterial pressure
↓ GFR, which causes ↓ flow to macula densa
Direct effect of less stretch
↓ NaCl delivery to macula densa
Renal juxtaglomerular cells
↑ Renin secretion
↑ Plasma renin
↑ Plasma angiotensin II
Adrenal cortex
↑ Aldosterone secretion
↑ Plasma aldosterone
Cortical collecting ducts
↑ Na+ and H2O reabsorption
↓ Na+ and H2O excretion

Macula densa feedback mechanism for GFR Autoregulation And angiotensin system augment each other

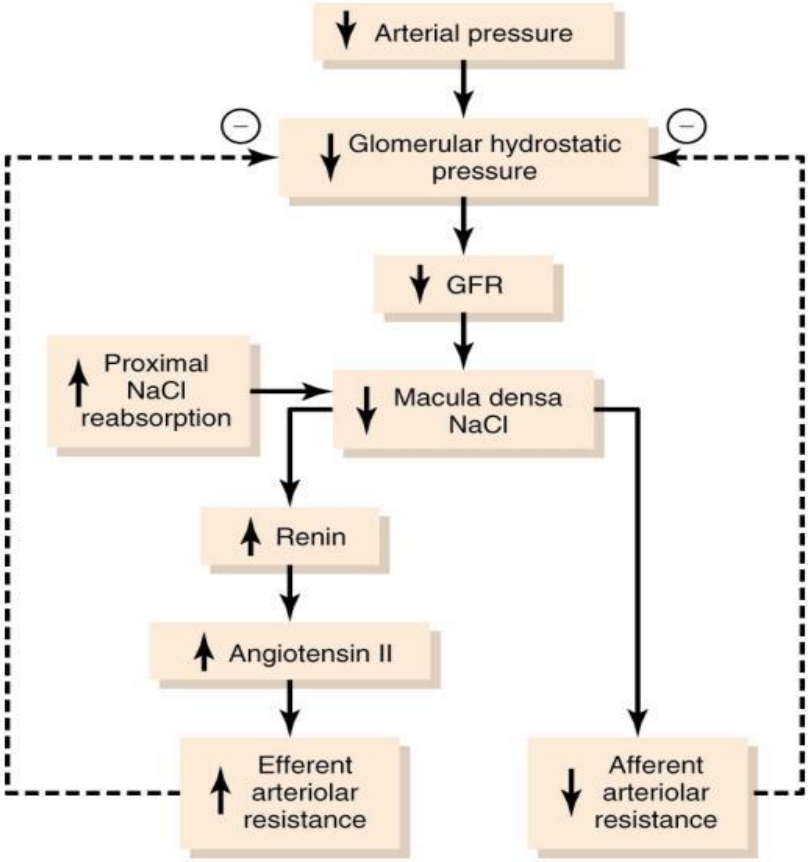


Figure 26-18;
Guyton and Hall

- In spite of the slight changes that occur in GFR with alterations of mean ABP between 80-180 mmHg, the urine volume is markedly changed.

- This indicates that the urine volume is not subjected to autoregulation, thus a fall of mean ABP to 50 mmHg may completely stop urine output, while a rise to 200 mmHg may increase the urine output 7-8 times. The latter effect is an important mechanism in control of a high ABP, and is called **pressure diuresis**.

Control of RBF

Normally, **RBF is about 1200 ml/minute**.
The **RBF is directly proportional to the mean ABP and inversely proportional to renal vascular resistance (RVR)** which is **determined mainly by diameter of glomerular afferent and efferent arterioles**.

This is shown as in:

- Catecholamines and strong sympathetic stimulation cause renal VC specially at the afferent arterioles leading to an increase of RVR and a decrease of RBF.
- Acetylcholine and other VD drugs (e.g. caffeine) decrease the RVR and increase the RBF.
- Angiotensin II causes VC particularly in the efferent arterioles leading to an increase of RVR and a decrease of RBF.

Measurement of RBF

By determination of RPF and hematocrit (Hct) value.

Determination of RPF:

By estimating clearance of para-aminohippuric acid (PAH).

PAH is a substance that is freely filtered in glomeruli and almost (90%) completely secreted in PCT and is not reabsorbed.

Therefore, the clearance rate of PAH can be used to calculate the effective renal plasma flow **(ERPF) = 585 ml/min.**

Actual RPF= 585 X100/90= 650 ml/minute.

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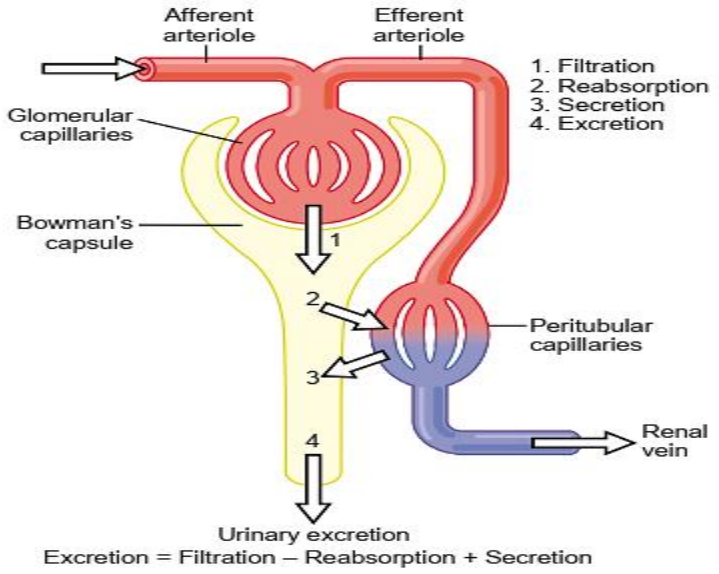

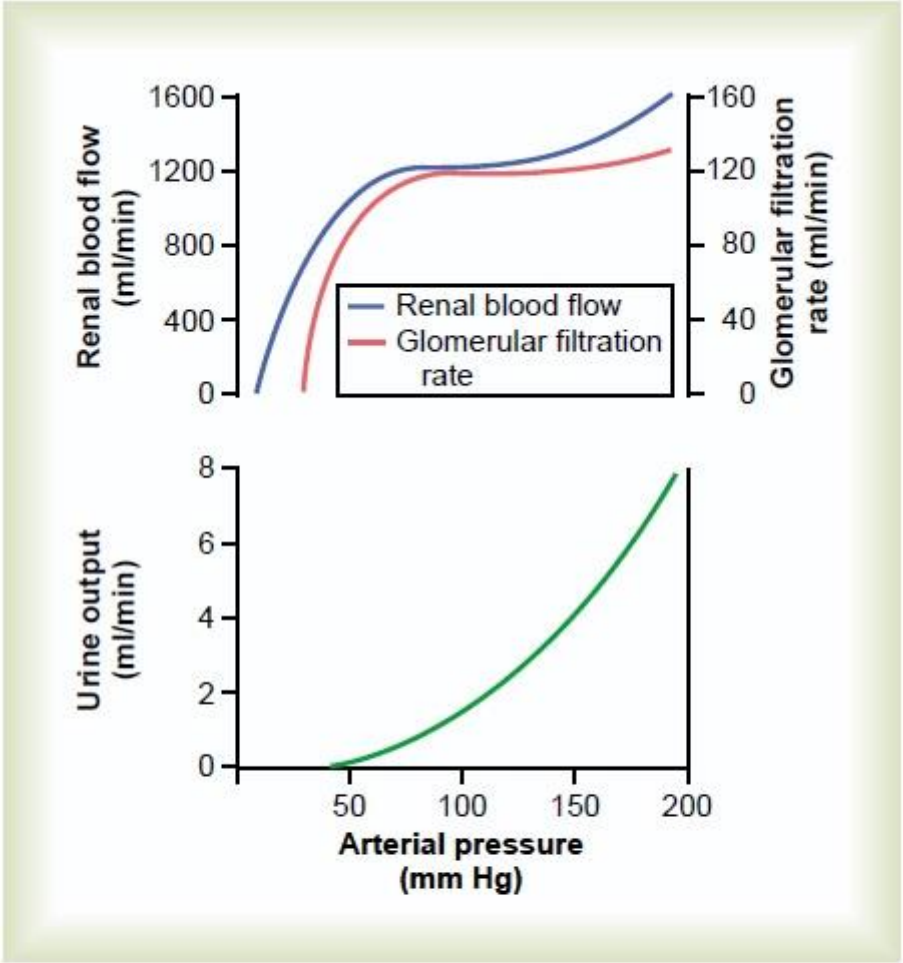

Figure 26–16

Autoregulation of renal blood flow and glomerular filtration rate but lack of autoregulation of urine flow during changes in renal arterial pressure.

THANK YOU