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

BY

Dr. Fatma Farrag Ali

Associate Professor of Medical Physiology

Faculty of Medicine-Mutah University

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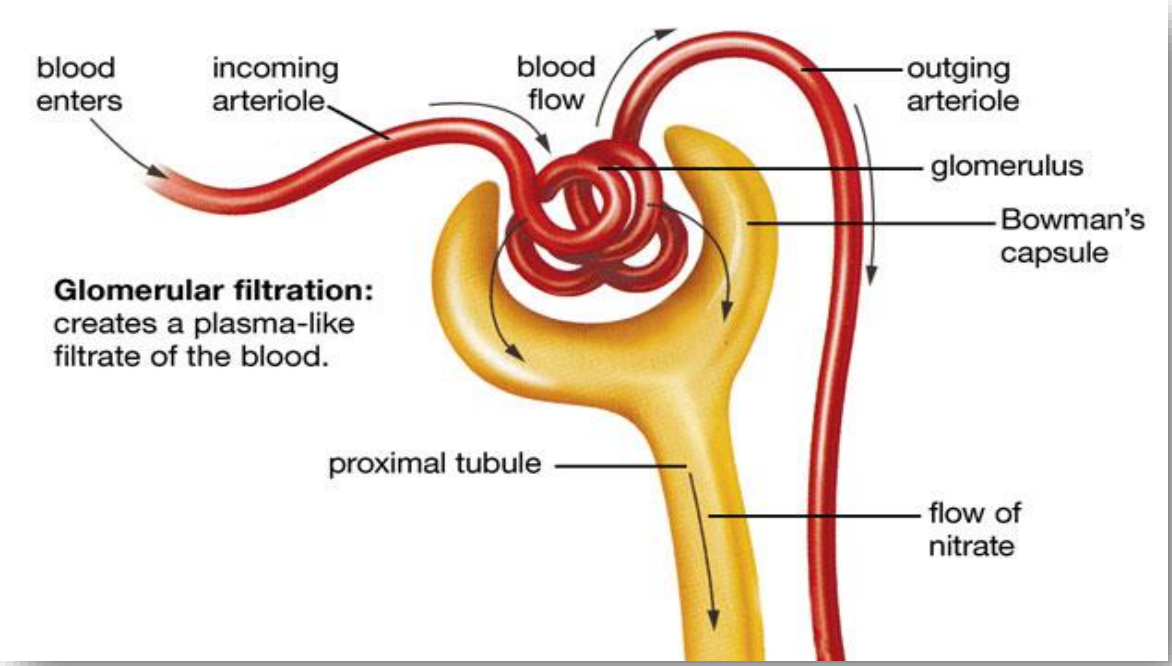

Innervation of the kidney:

The kidneys receive sympathetic efferent fibers from greater splanchnic nerve.

Sympathetic fibers are distributed to:

glomerular arterioles and juxtaglomerular cells.

Functions of Sympathetic fibers:

1-Sympathetic stimulation (noradrenaline)→ constrict afferent arterioles →↓ RBF and GFR.

2-Stimulate renin secretion from juxtaglomerular cells.

Factors affecting GFR

Factors that affect the GFR:

I) Renal blood flow (RBF): The **GFR is generally directly proportional to the RBF**.

II) Glomerular capillary pressure (GCP): The GFR is generally 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, whereas VD produces the opposite effects.

***b. Efferent arteriolar diameter*:**

- VD decreases GCP, so GFR is reduced.
- While, **efferent arteriolar constriction has a biphasic effect on GFR**.
- At moderate levels of constriction, there is a slight increase in GFR, but with severe constriction, there is a decrease in GFR. The primary cause of the eventual decrease in GFR is as follows:
- As efferent constriction becomes severe and as plasma protein concentration increases, there is a rapid, increase in colloid osmotic pressure which exceeds the increase in glomerular capillary hydrostatic pressure caused by efferent arteriolar constriction. When this occurs, the net force for filtration actually decreases, causing a reduction in GFR.

To summarize;

- Constriction of afferent arterioles reduces GFR.
- However, the effect of efferent arteriolar constriction depends on the severity of the constriction; modest efferent arteriole constriction raises GFR, but severe efferent constriction tends to reduce GFR.

c. Sympathetic stimulation:

- Mild stimulation produces almost no effect due to the autoregulatory mechanisms.
- However, strong stimulation (as in severe hemorrhage) causes marked VC in all glomerular arterioles **(especially afferent arteriole)** leading to **reduction in both RBF and GFR**.

d. Arterial blood pressure (ABP):

Variation in the mean ABP within the range 80-160 mmHg affects GFR only slightly by autoregulatory mechanisms. However beyond that range, marked changes occur in both RBF and GFR.

III) 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 located between the glomerular capillary endothelium and the basement membrane. They are contractile. Their contraction decreases K_f largely due to a reduction in the area available for filtration.

IV) 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 nephritis due to damage of capillary walls and reduction of their negative charges).

V) The colloid osmotic pressure in glomerular capillaries (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 about 20 %.
- Thus an increase in GOP (as in dehydration) reduces GFR. While, a decrease in GOP (e.g. due to hypoproteinemia) increases the GFR.

VI) Bowman's capsule pressure; intracapsular pressure (CP):

- **The GFR is inversely proportional to CP.**
- Thus an increase in the CP due to stricture or stone in the ureter (obstructing outflow of urinary tract) reduces GFR which stops completely if CP increases to 28 mmHg, because in this case the filtering forces will be balanced by the opposing forces.

VII) <u>Hormonal and autacoids influence on RBF & GFR:</u>

a) **<u>Prostaglandins:</u>** PGE_2 and PGI_2 (both produced in the kidneys) cause **dilatation of afferent > efferent arterioles**, thereby **increasing RBF and GFR**.

b) **<u>Angiotensin II:</u>** Angiotensin II constricts both afferent and efferent arterioles, but preferentially **constricts the efferent arteriole**, thus increasing or maintaining the pressure in the glomerulus. Angiotensin II maintains the GFR even in the face of decreased overall renal blood flow.

c) **Norepinephrine and Epinephrine:** Hormones that constrict afferent and efferent arterioles **(afferent > efferent)**, causing reductions in RBF and GFR. In general, blood levels of these hormones parallel the activity of the sympathetic nervous system; thus, norepinephrine and epinephrine have little influence on renal hemodynamics except under extreme conditions, such as severe hemorrhage.

AUTOREGULATION OF GFR & RBF

-This is an **intrinsic mechanism** in the kidney that keeps GFR and RBF nearly constant despite changes in mean ABP between 80 – 160 mmHg.

Importance:

- If GFR is excessively decreased, the tubular fluid will pass slowly in tubules allowing maximal reabsorption, so the waste products will be insufficiently eliminated.
- On the other hand, if the GFR is much increased, the tubular fluid would pass rapidly in the tubules allowing minimal reabsorption of the essential substances (which will be lost in the urine).

Mechanism of autoregulation of GFR and RBF

I. When the ABP rises from 100 to 160 mmHg:

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

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

1. Myogenic mechanism:

↑ ABP → 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:

Rise of BP 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 thromboxane A_2).

II. When the ABP falls from 100 to 80 mmHg:

In this condition, **VD of afferent arterioles and VC of efferent arterioles occur.** The former increases the RBF while the latter increases the renal vascular resistance (RVR), and both effects tend to increase the GCP (particularly the latter effect), so the GFR is kept relatively constant (or decreases slightly) in spite of the decreased ABP.

Such arteriolar responses are produced by a **tubuloglomerular feedback mechanism** (a feedback mechanism that links changes in sodium chloride concentration at the macula densa with the control of renal arteriolar resistance) as follows:

1. The afferent arteriolar VD (involved in autoregulation of both GFR and RBF).

- Dilatation (widening) of afferent arterioles occurs so the RBF and GFR are kept relatively constant (or decreases slightly) in spite of the decreased BP.
- This is produced as follows:
- The fall of BP 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**) which produces VD of the afferent arterioles by releasing a **prostaglandin (most probably PGI_2)**.

2. The efferent arteriolar VC (for only GFR autoregulation).

- It occurs by the same signal from **macula densa** that leads to afferent arteriolar VD.
- This signal leads also to secretion of **renin** and this catalyzes formation of **angiotensin II,** which specifically causes **VC in the efferent arterioles**.
- Since efferent arteriolar VC is more important than afferent arteriolar VD 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).

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

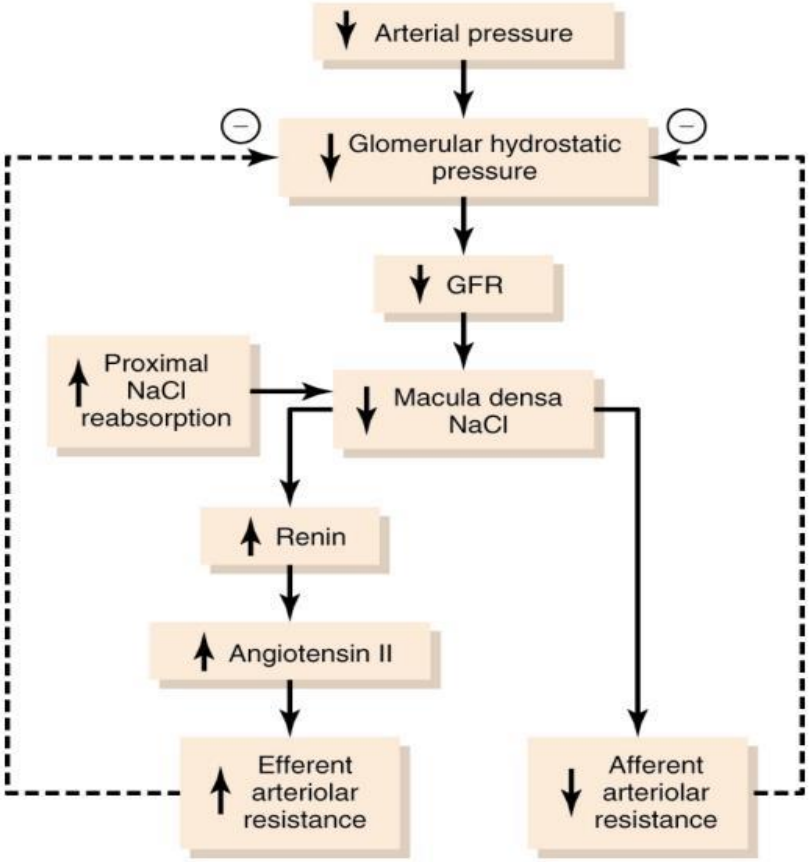

Figure 26-18;
Guyton and Hall

- In spite of the slight changes that occur in GFR with alterations of ABP between 80-160 mmHg, the urine volume is markedly changed.
- This indicates that the urine volume is not subjected to autoregulation, thus a fall of 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) or diodrast; commonly PAH.

***Para*-aminohippuric acid (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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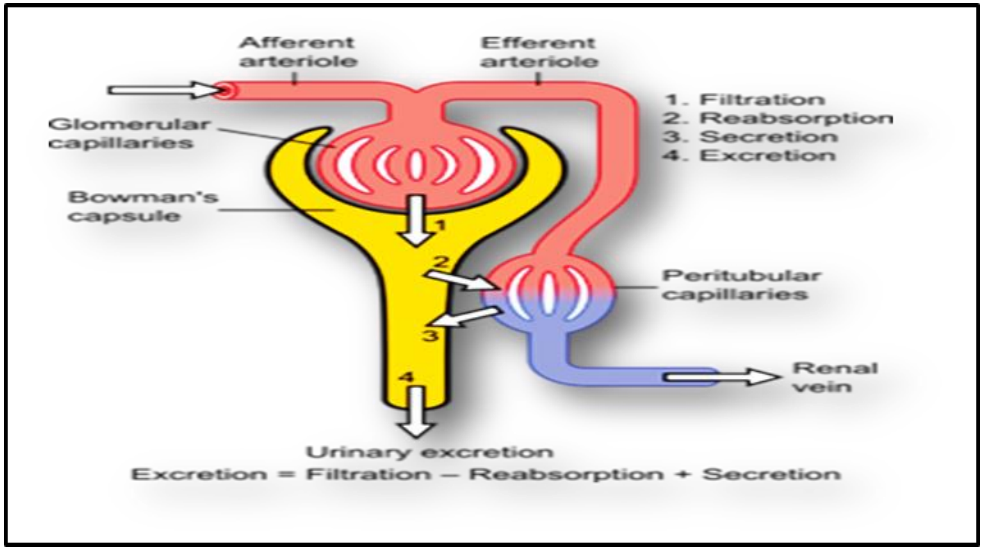

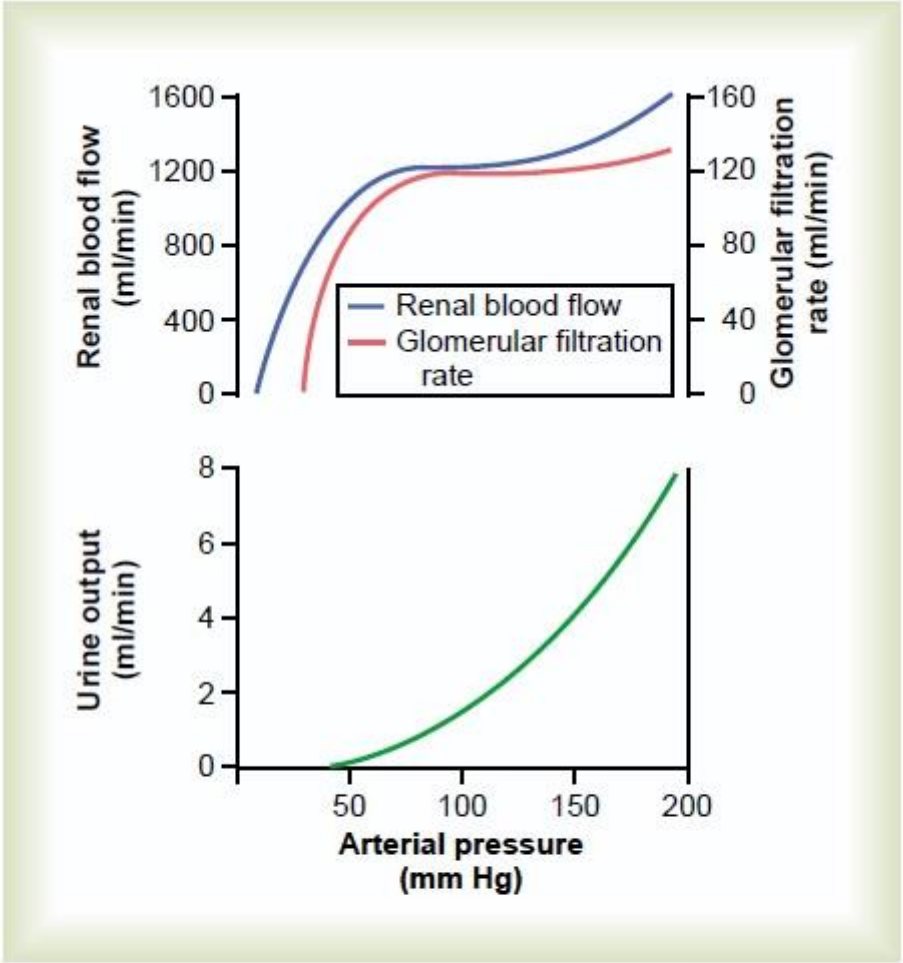

Figure 26–16

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


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