Glomerular Filtration Rate and Renal Perfusion

Objective

- Review the basic renal processes
- Review glomerular filtration rate and the factors that regulate it
- Emphasize the importance of fractional excretion, clearance and filtration fraction concepts

Summary of renal function

Help maintain a constant extracellular environment for adequate functioning of cells

- Excretion of some waste products of metabolism eg. Urea, uric acid.
- Excretion of water and electrolytes
- Regulate the excretion individually water and solutes
- Maintain pH, Regulate acid-base balance
- Secrete certain hormones
- Excrete drugs

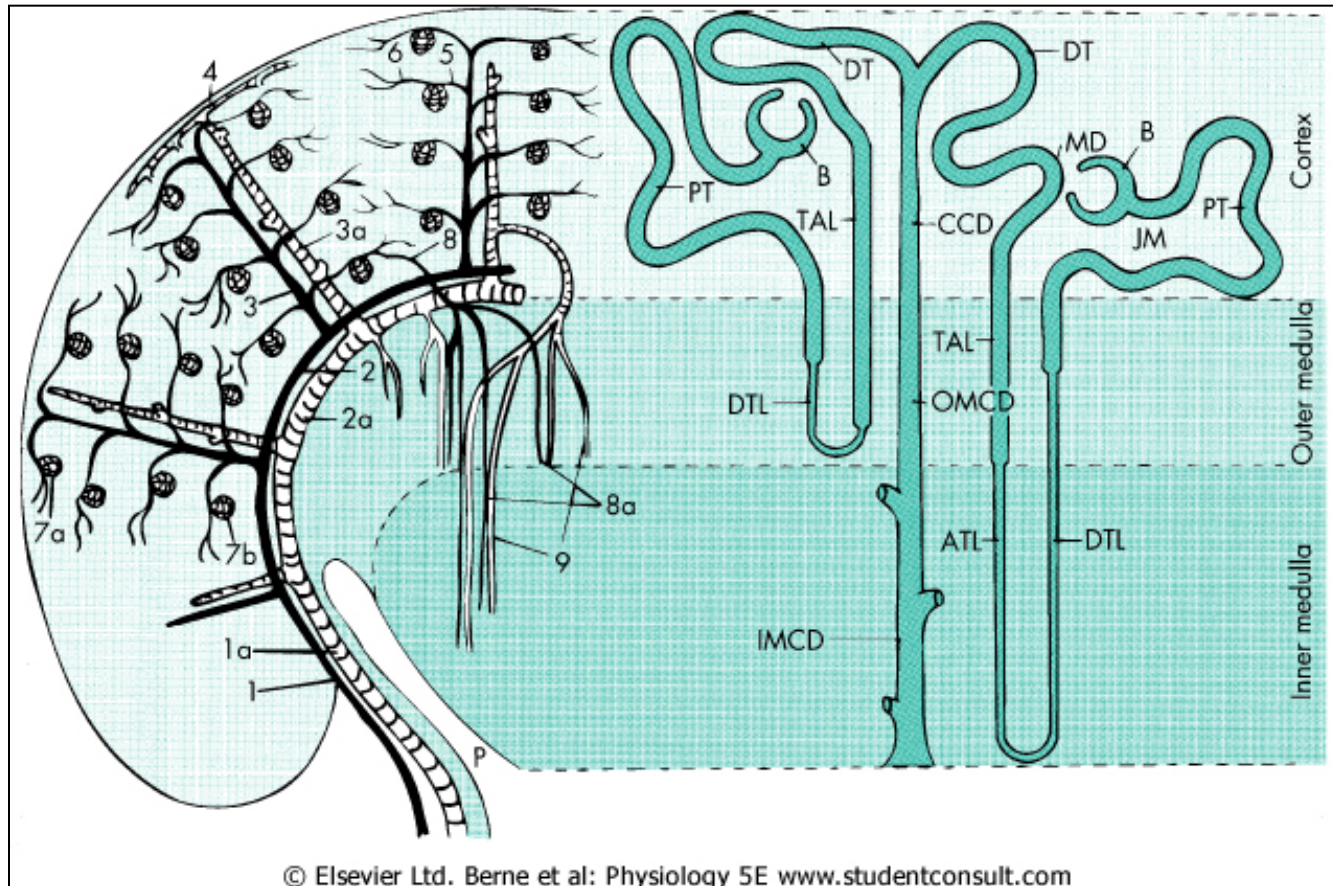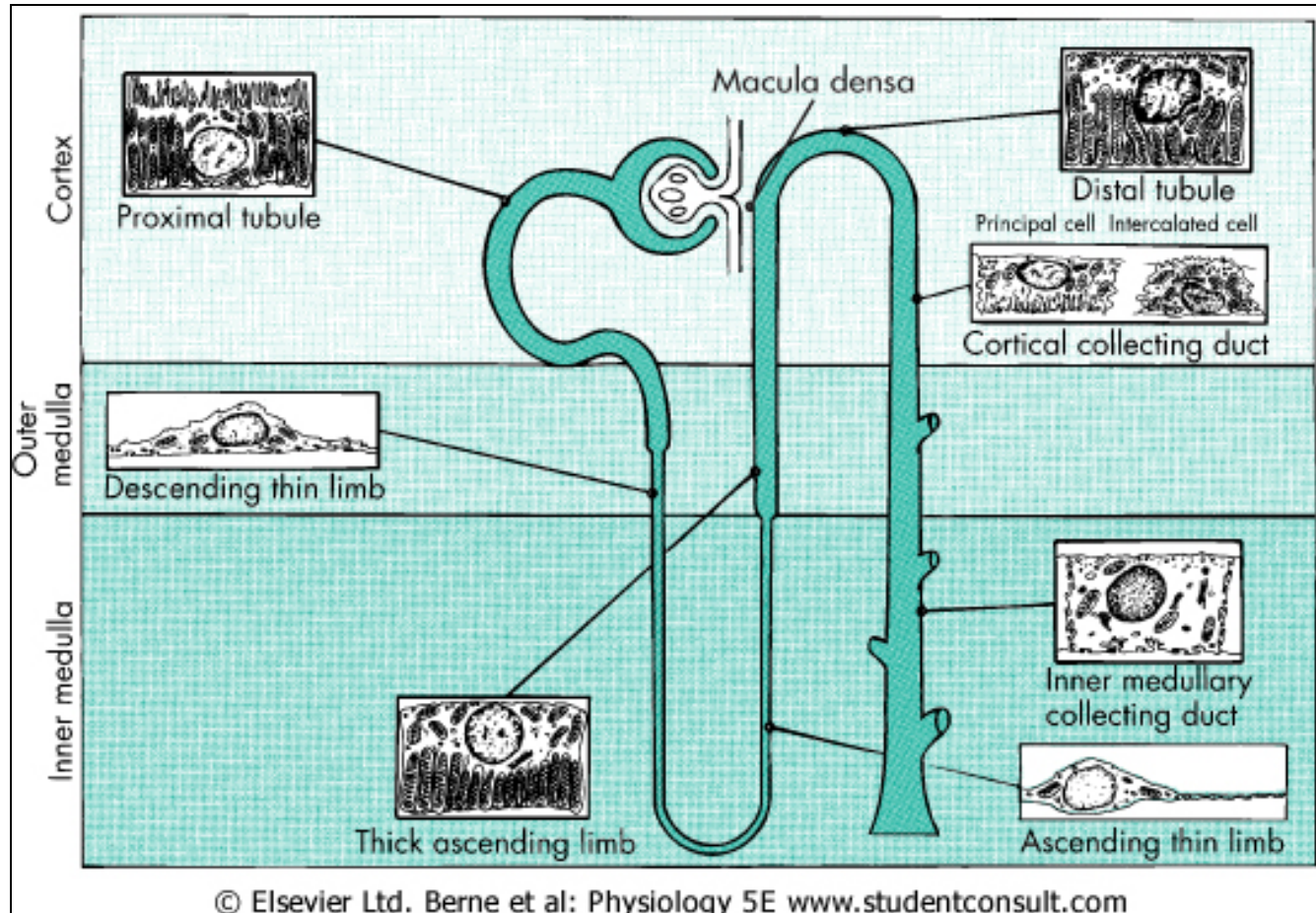Figure 1a: Organization of renal vascular system and nephron

© Elsevier Ltd. Berne et al: Physiology 5E www.studentconsult.com

Figure 1b: Parts of the Nephron

Macula densa

Cortex

Proximal tubule

Distal tubule
Principal cell Intercalated cell

Cortical collecting duct

Outer medulla

Descending thin limb

Inner medulla

Inner medullary collecting duct

Thick ascending limb

Ascending thin limb

© Elsevier Ltd. Berne et al: Physiology 5E www.studentconsult.com

- Glomerular filtration is the flow of fluid from the glomerular capillaries into the Bowman's capsule. The volume filtrate formed per unit time is called **glomerular filtration rate**

- The rate of glomerular filtration averages 135-180L/day in a normal adult.
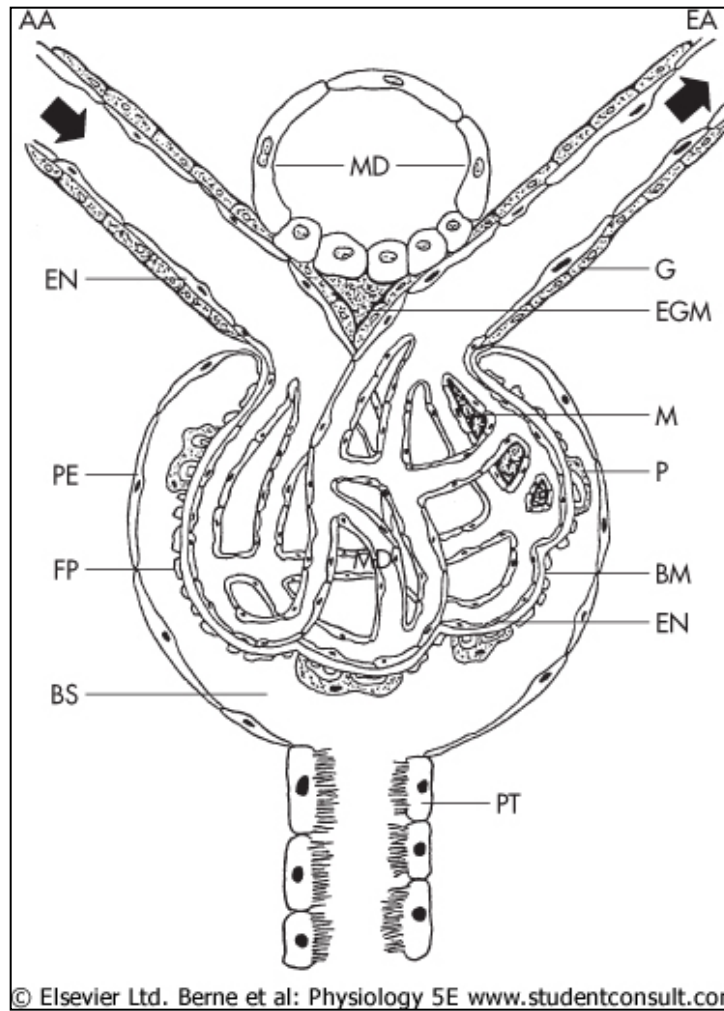
Figure 3: Filtration barrier

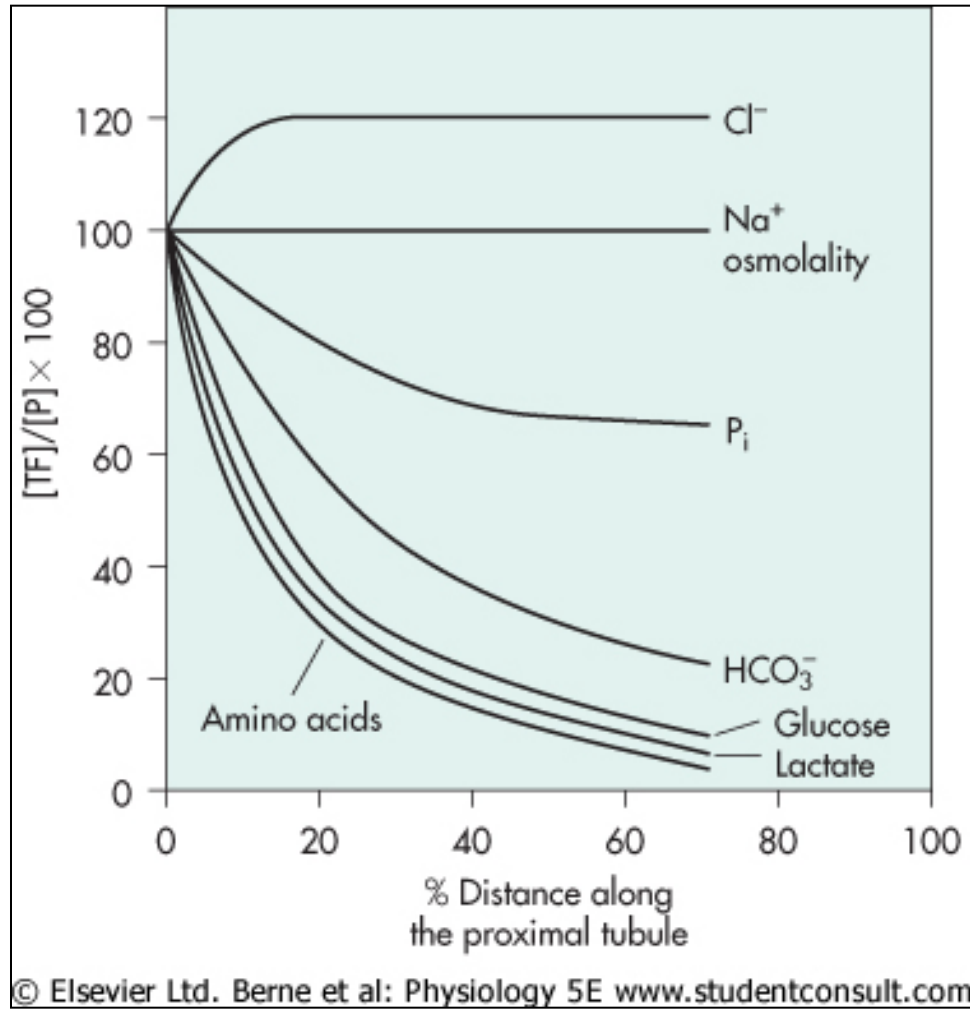Figure 2: concentration of solutes in tubular fluid in the proximal tubule
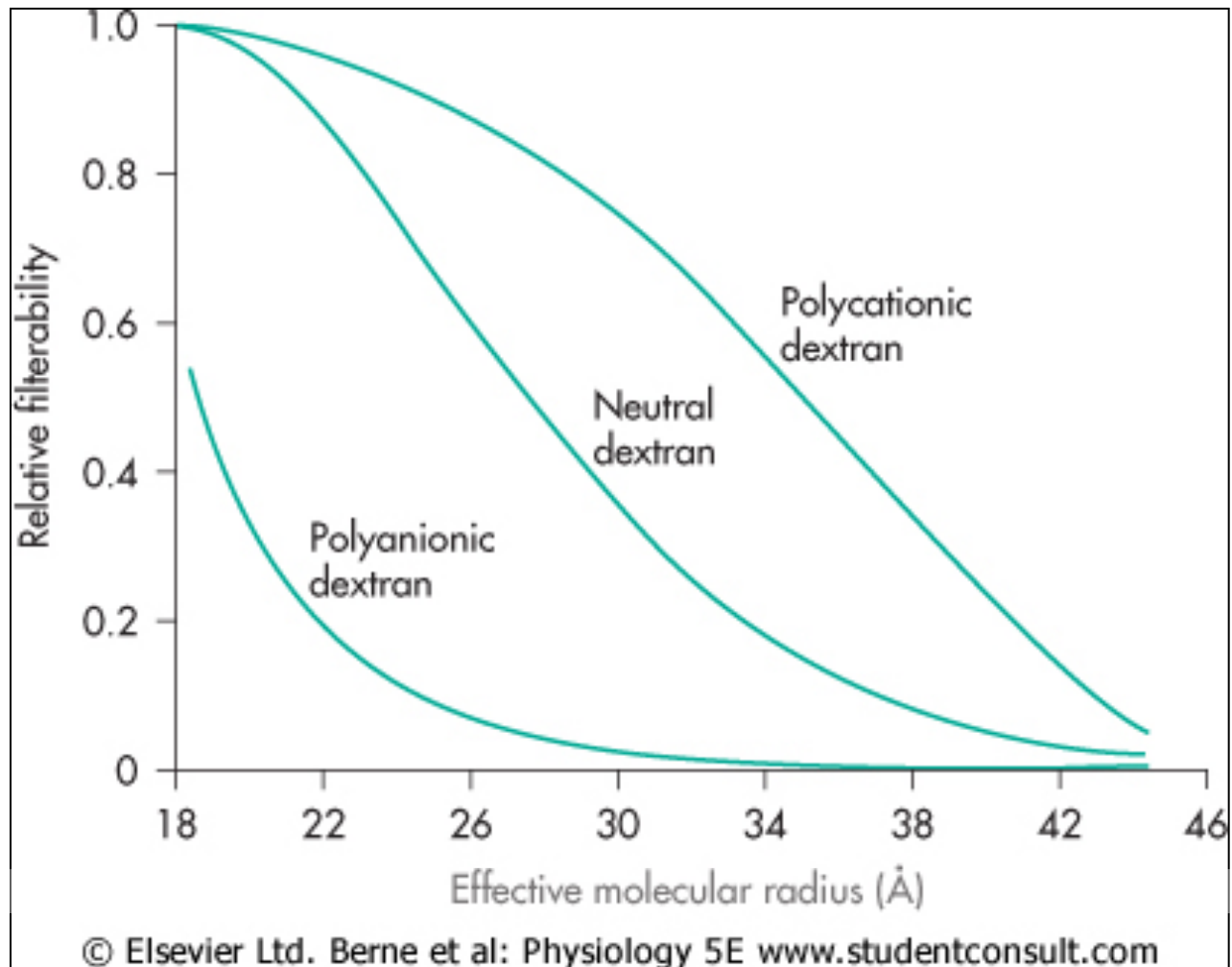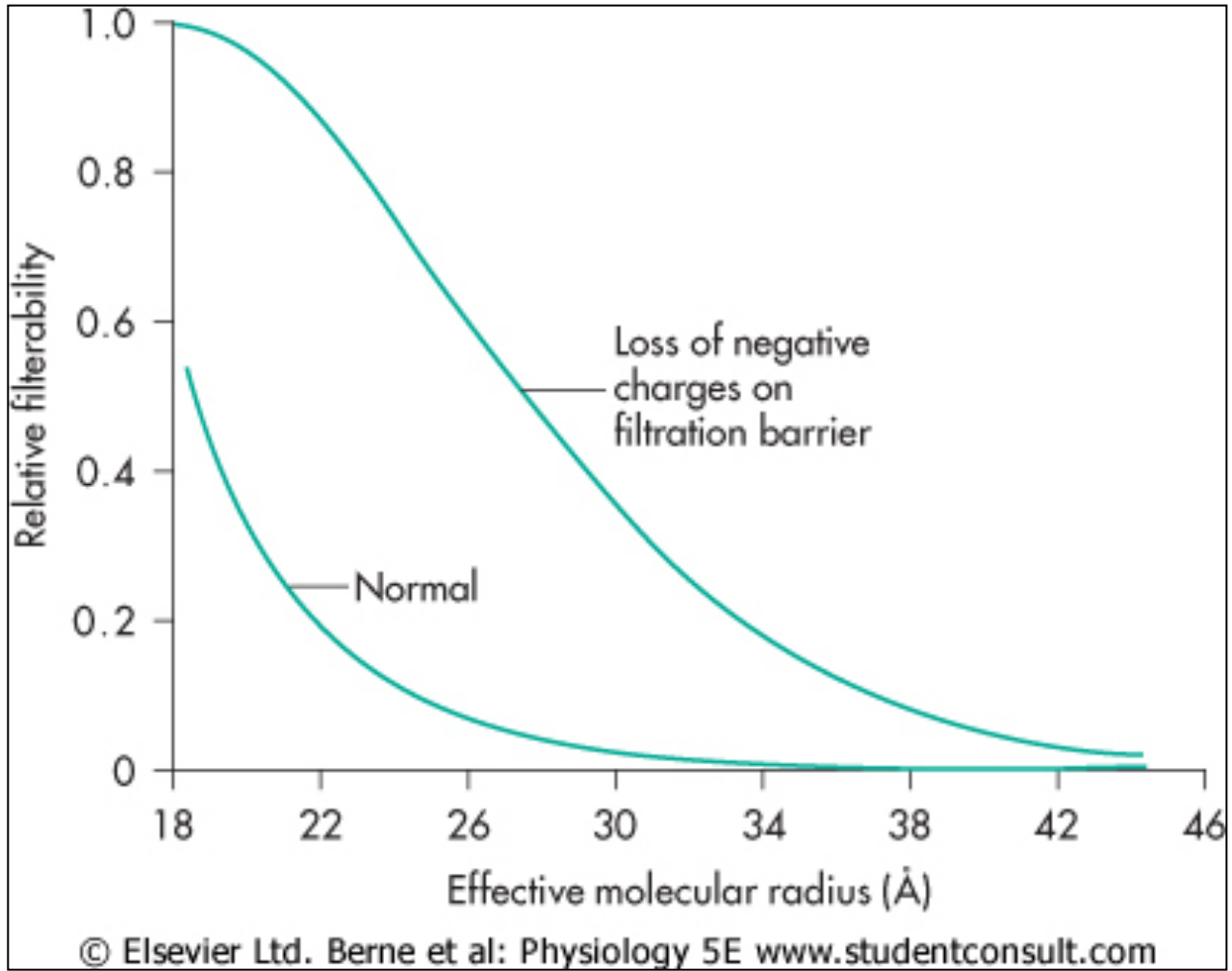
Figure 4a: Size and Charge effect on filterability

© Elsevier Ltd. Berne et al: Physiology 5E www.studentconsult.com

Figure 4b: Size and Charge effect on filterability

© Elsevier Ltd. Berne et al: Physiology 5E www.studentconsult.com

Determinants of GFR

- Fluid movement across the glomerulus is determined by Starling forces, being proportional to the permeability of the membrane and to the balance between the hydraulic and oncotic pressure gradients [Fig 4: illustration from The Renal System, Churchill Livingstone, 2001]

GFR=K_f (delta hydraulic pressure-delta oncotic pressure)

$$= K_f [(P_{GC}-P_{BS})-(\pi_{GC}- \pi_{BS})]$$
$$= K_f (P_{GC}-P_{BS}-\pi_p)$$

Kf is the product of the permeability of the capillary wall and the surface area available for filtration.

P_{GC} and P_{BS} are hydrostatic pressures in the glomerular capillary and Bowman's space, respectively.

π_p and π_{BS} are oncotic pressures in the plasma entering the glomerulus and the Bowman's space, respectively.

Fig

Forces Involved in Glomerular Filtration

Glomerular capillary

P_{gc} → +45

−10 P_t

π_{gc} ← −25

Filtration →

+10

Tubular lumen

Bowman's space
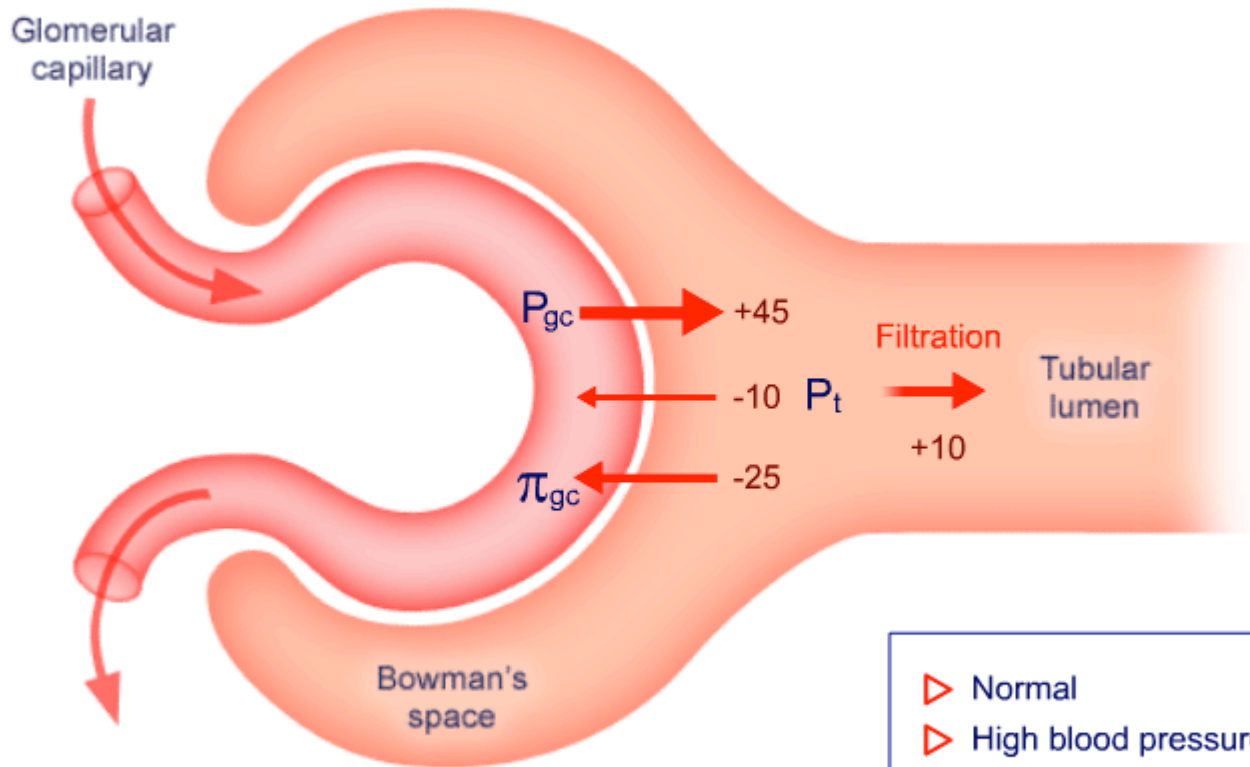
$P_{uf} = P_{gc} - P_t - \pi_{gc}$

▷ Normal
▷ High blood pressure
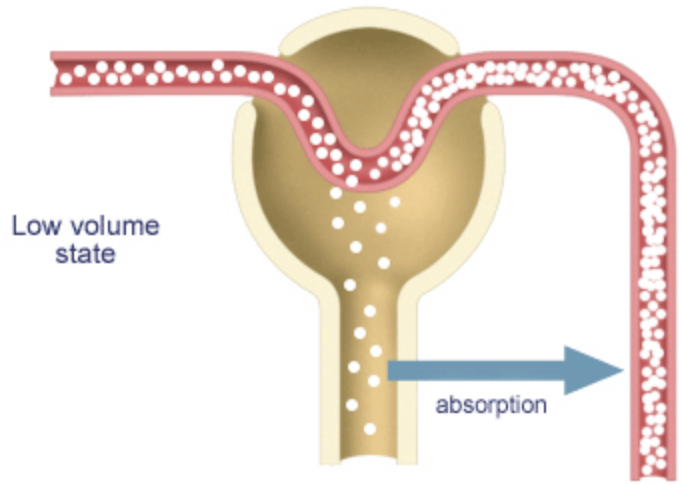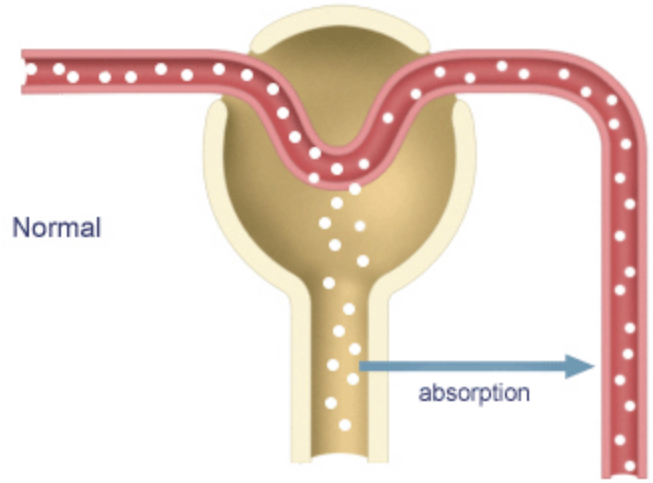▷ Low oncotic pressure
▷ Low blood pressure
● Overview

MM⚕

$P_{t} = P_{BS}$

Filtration equilibrium=is the gradient favoring filtration at the afferent arteriole but it falls before the efferent arteriole because of the elevation of plasma oncotic pressure. The hydrostatic pressures in the glomerulus in Bowman's space remains relatively constant but capillary oncotic pressure progressively rises due to the filtration of protein free fluid.

Filtration Fraction

- Filtration Fraction (FF) is GFR/RPF
- In low effective circulatory volume, FF is increased because RPF is more decreased proportionately than GFR.
- The higher FF increases the plasma oncotic pressure of the peritubular capillaries and promotes tubular reabsorption. Similarly, the hydrostatic pressure decreases in the tubules, but the hydrostatic pressure of the peritubular capillaries decrease even more and allows the tubulointerstitial gradient to be higher and favour further volume reabsorption.

Filtration Fraction

Normal

Low volume
state

absorption

absorption
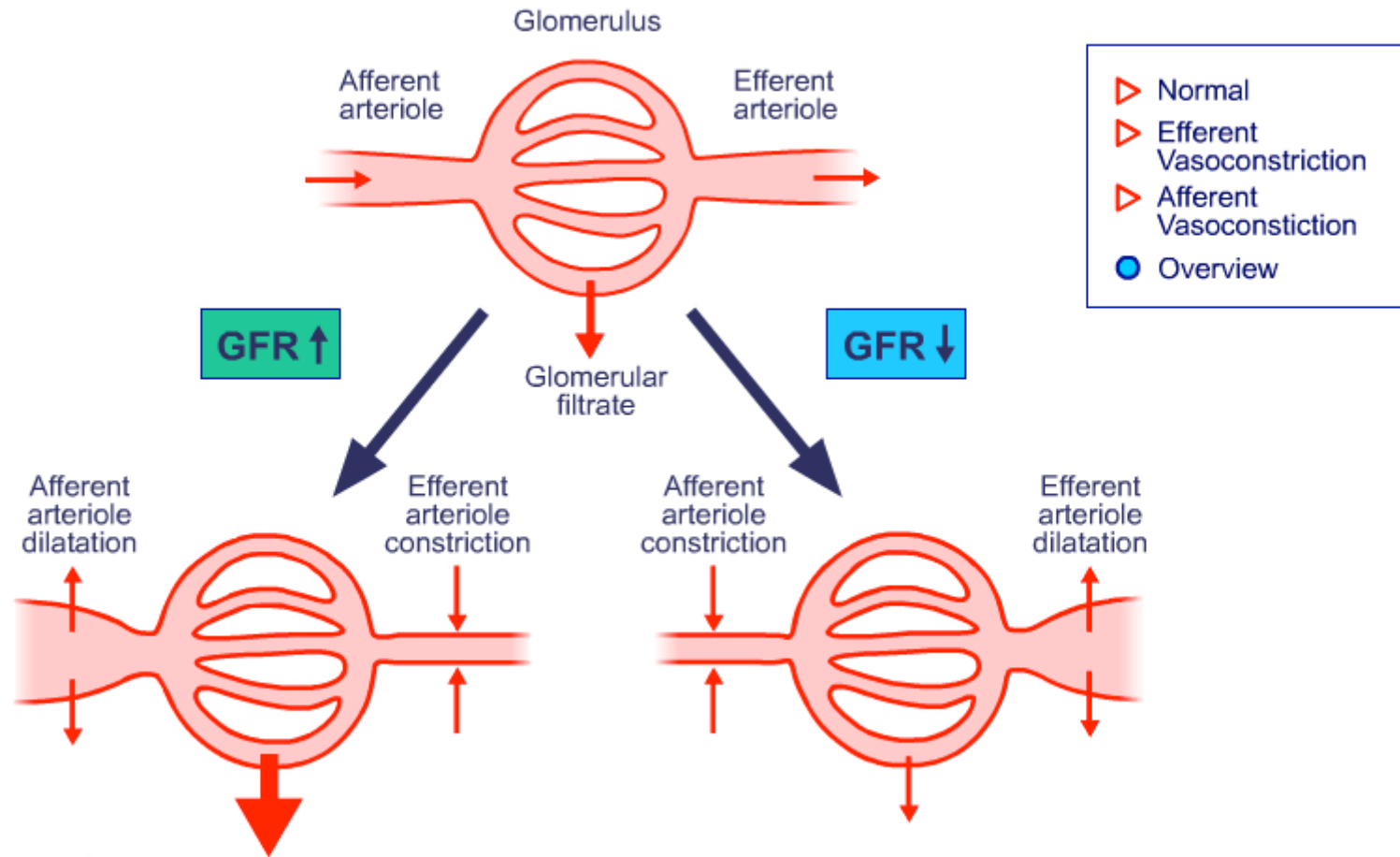
MM⚕

Regulation of GFR

What decreases GFR?

- Decrease in permeability eg. Renal disease, diabetic nephropathy, hypertension
- Increase in Bowman's space hydrostatic pressure eg urinary obstruction
- Increase in oncotic pressure of capillaries eg. High plasma protein levels
- Decrease in glomerular capillary hydrostatic pressure
    - Decrease in arterial pressure
    - Decrease in Ang II levels
    - Increase in sympathetic activity ie. vasoconstriction

- What determines glomerular capillary hydrostatic pressure?
  - Aortic pressure
  - Resistance at the afferent arteriole
  - Resistance at the efferent arteriole

- By regulating arteriolar resistance, permits the rapid regulation of GFR through changes in glomerular capillary hydrostatic pressure. [Fig 7: illustration from The Renal System, Churchill Livingstone, 2001]

Figure 7

Changes in Resistance of Afferent and Efferent Arterioles

Glomerulus

Afferent arteriole

Efferent arteriole

Normal

Efferent Vasoconstriction

Afferent Vasoconstiction

Overview

GFR ↑

GFR ↓

Glomerular filtrate

Afferent arteriole dilatation

Efferent arteriole constriction

Afferent arteriole constriction

Efferent arteriole dilatation

MM☿

What is Autoregulation?

- GFR and RPF remain almost constant over a wide range of arterial pressures [Fig 6: illustration from The Renal System, Churchill Livingstone, 2001]

- Since the GFR and RPF are maintained in parallel, autoregulation must be mediated through changes in the arteriolar resistance.

- Example, if systemic arterial pressure rises, than an increase in afferent arteriolar resistance prevents the pressure from being sensed by the glomerulus, permitting glomerular capillary hydrostatic pressure and GFR to not increase and remain constant.

- Two mechanisms responsible for autoregulation:
  - Myogenic mechanism
  - Tubuloglomerular feedback
- Vascular smooth muscle contracts in response to increased stretch—stretch receptors in the wall of afferent arterioles

Figure 8: Autoregulation

© Elsevier Ltd. Berne et al: Physiology 5E www.studentconsult.com
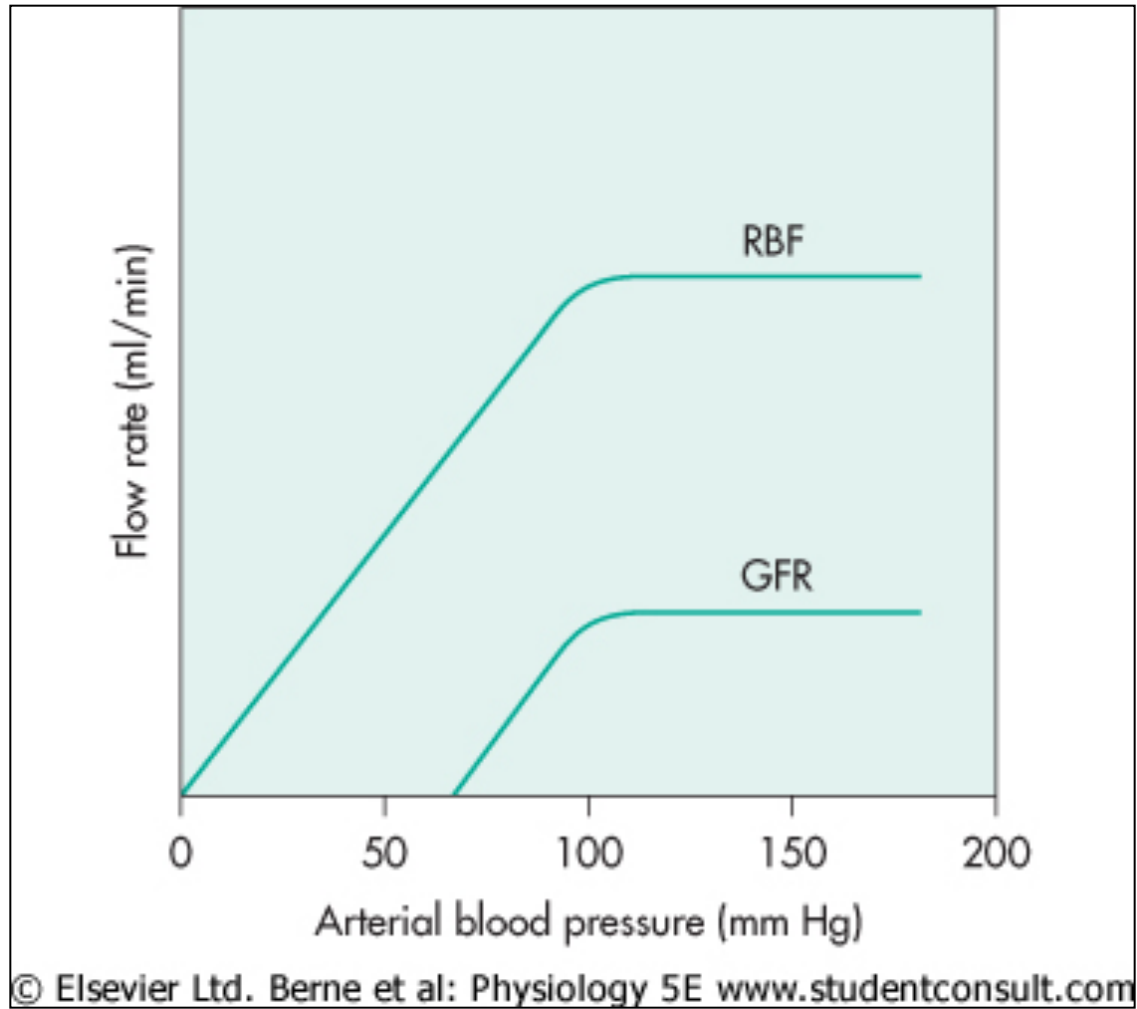
Tubuloglomerular feedback

- Changes in GFR induced by changes in tubular flow rate [Fig 7a and 7b: illustrations from The Renal System, Churchill Livingstone, 2001]

- Mediated by specific cells in macula densa

- Sense changes in the delivery of chloride

- Alterations in the local release of adenosine

- Induce constriction of afferent arteriole

Figure 9

Tubuloglomerular Feedback

Glomerulus

Afferent arteriole constriction

Efferent arteriole

Adenosine ATP others?

GFR ↑

NaCL

TAL/Macula Densa

MM
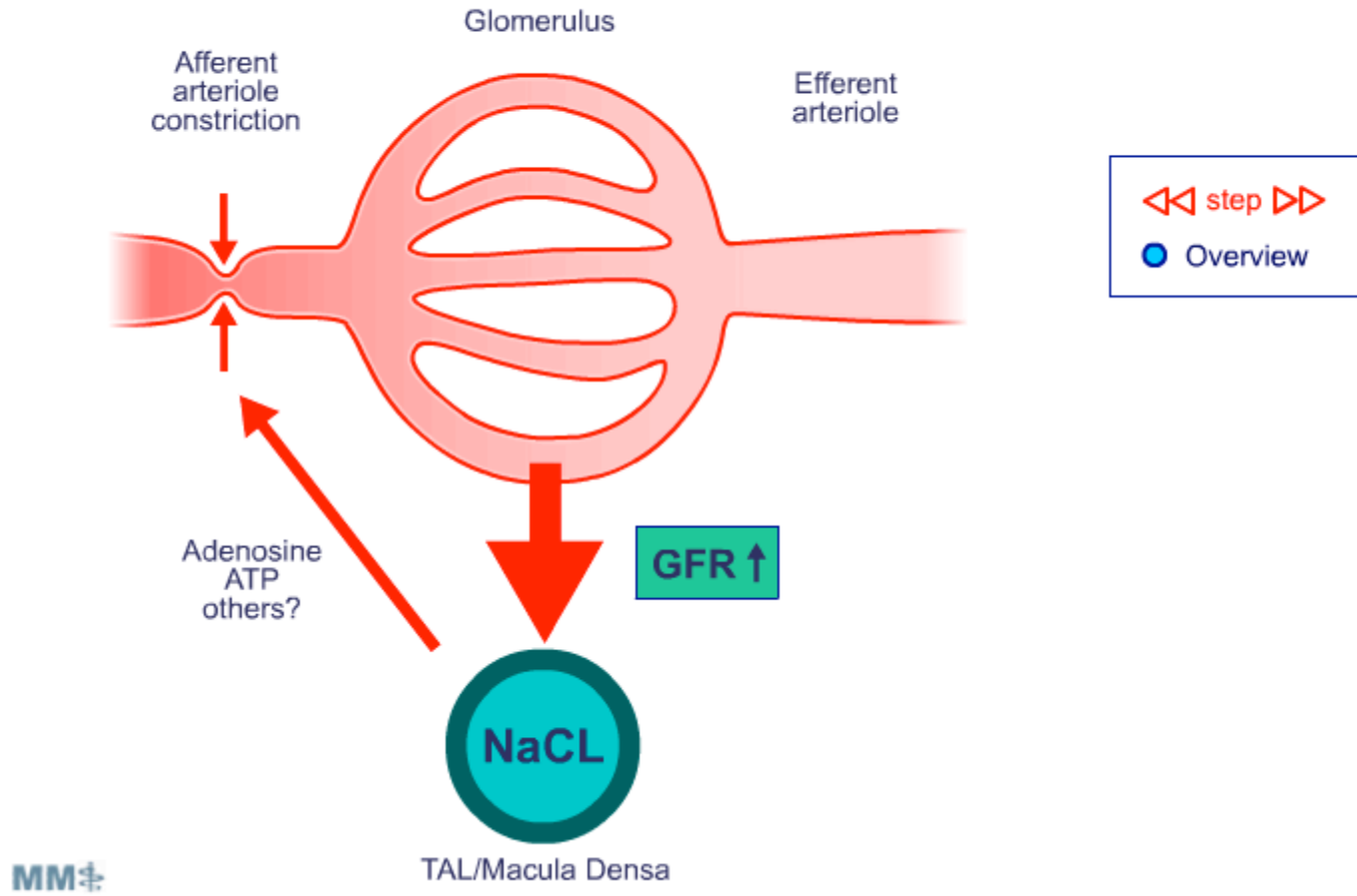
What is Clearance?

- The clearance of a substance is the volume of plasma from which that substance is cleared by the kidneys per unit time. Each substance in the plasma has its own distinct clearance value but it is always in the form of volume of plasma per time.

- To measure GFR
  - Substance able to achieve constant plasma concentration
  - Freely filtered at the glomerulus
  - Not reabsorbed or secreted

- Filtered substance (eg inulin)= excreted substance

  GFR x P_{in} = U_{in} x V

- Use creatinine clearance as estimate of GFR
  - Creatinine clearance=U_{cr} x V/P_{cr}

Fractional excretion

F.E. is defined as the excretion of sodium divided by the filtered load of Na^+

Fractional excretion = mass excreted /mass filtered

$$FE_{Na} = \frac{U_{Na} \times V}{P_{Na} \times GFR} \quad x \quad 100$$

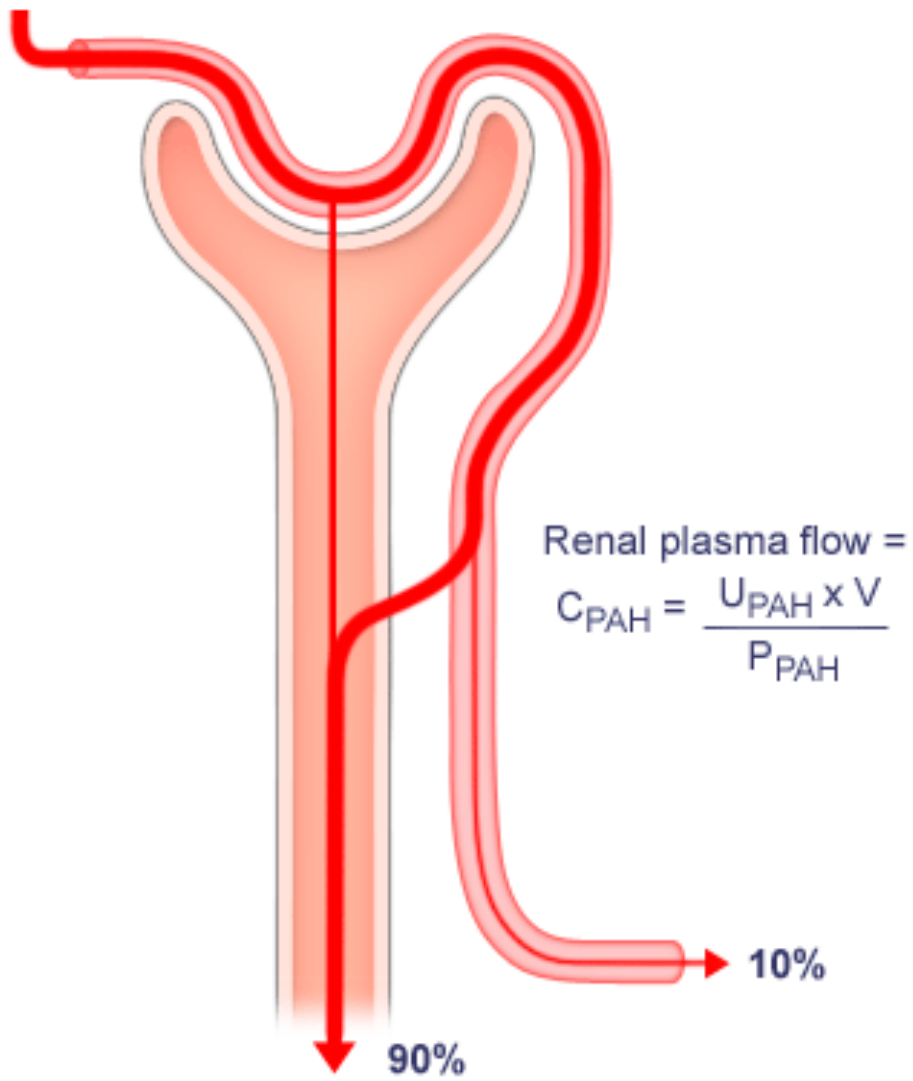Can use creatinine clearance as an estimate for GFR

Renal Plasma Flow

- PAH delivery to kidney=PAH excretion

  $ERPF \times P_{PAH} = U_{PAH} \times V$

Note: PAH only 85-90% is removed by kidney on single pass, thus it will underestimate renal plasma flow (filtered and secreted)

Renal Handling of PAH

Figure 8

Renal plasma flow =

$$C_{PAH} = \frac{U_{PAH} \times V}{P_{PAH}}$$

10%

90%

MM⚕

What regulates RBF?

- Hormonal effects: renin-angiotensin II, aldosterone, sympathetic nervous system and prostaglandins

- Local (constant) effects of autoregulation and tubuloglomerular feedback

Renin-Angiotensin system

- Angiotensinogen produced in the liver (also present in the proximal tubule) and is cleaved by renin released from renal juxtaglomerular cells to generate angiotensin 1.

- Angiotensin 1 is converted by angiotensin-converting enzyme into angiotensin II.

- ACE is found in vascular endothelial cells

Renin: released when there is an increase in sympathetic activity (eg. Hypotension, volume depletion)

– Initiation of steps towards increasing Ang II levels

Ang II:

1. Renal sodium and water retention

Angiotensin II promotes salt and water retention and thus expands the plasma volume.

- stimulates sodium reabsorption of the proximal tubule

- increases secretion of aldosterone from the adrenal cortex, which enhances sodium transfer in the cortical collecting tubule.
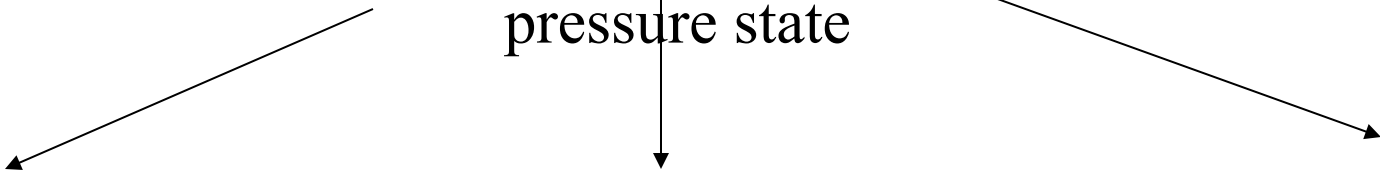
2. *Systemic vasoconstriction*

Angiotensin II produces arteriolar vasoconstriction and elevated systemic vascular resistance and in turn increases systemic blood pressure. The vascular action of angiotensin II involves enhanced sensitivity to release of norepinephrine. This results into release of substances that mediate vasoconstriction whereas vasodilator prostaglandins tend to minimize the increase in vascular resistance.

3. Regulation of GFR

Angiotensin II also regulates GFR and renal blood flow. This will be described later. Angiotensin II can affect renal blood flow and GFR by constricting the efferent and afferent glomerular arterioles. Though angiotensin II affects both afferent and efferent arterioles, the efferent arteriole has a smaller diameter and increase in efferent arteriolar resistance will be as much as 3 times greater than the afferent arteriole.

Angiotensin II increase in
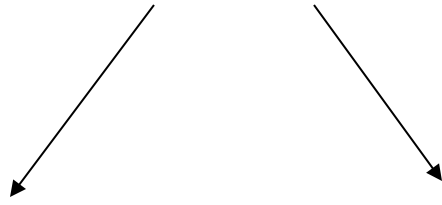levels in eg. Low blood
pressure state

Increase aldosterone
secretion

Increase systemic
vascular resistance

Afferent arteriole
vasoconstriction and
lower GFR

Intrinsic control

Myogenic reflex

Tubuloglomerular feedback

Afferent arteriole smooth muscle tone

Filtrate flow sensed by distal tubule
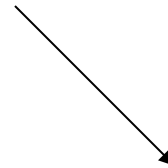
Afferent arteriole

Extrinsic Control

Renin-Ang-Aldosterone

SNS

Ang II

Systemic arteriole vasocontriction

- Systemic arteriole vasocontriction
- Increase aldosterone release
- Promote Na and water absorption in PT

What is the significance of the juxtaglomerular apparatus?

1. **Macula densa, mesangial cells and Renin producing granular cells of the afferent and the efferent arterioles**

2. **Important player in the tubuloglomerular feedback mechanism**

34 year female donates a kidney to her sister. Her serum creatinine before surgery is 88 umol/L and a month after surgery, her serum creatinine is 120 umol/L.

- Why did her serum creatinine go up?
- What has happened to her GFR, urine creatinine and renal plasma flow?

56 yo male is diagnosed with renal disease. His calculated GFR is 40 ml/min (normal 120ml/min).

- What may happen to his fractional excretion of sodium? Usually he takes in 150mEq/day of sodium.

- What will happen to his serum creatinine and urine creatinine?