Physiology of the kidneys and GFR

Outline

- Filtration
- Autoregulation of renal blood flow
- Reabsorption
- Secretion
- Clearance

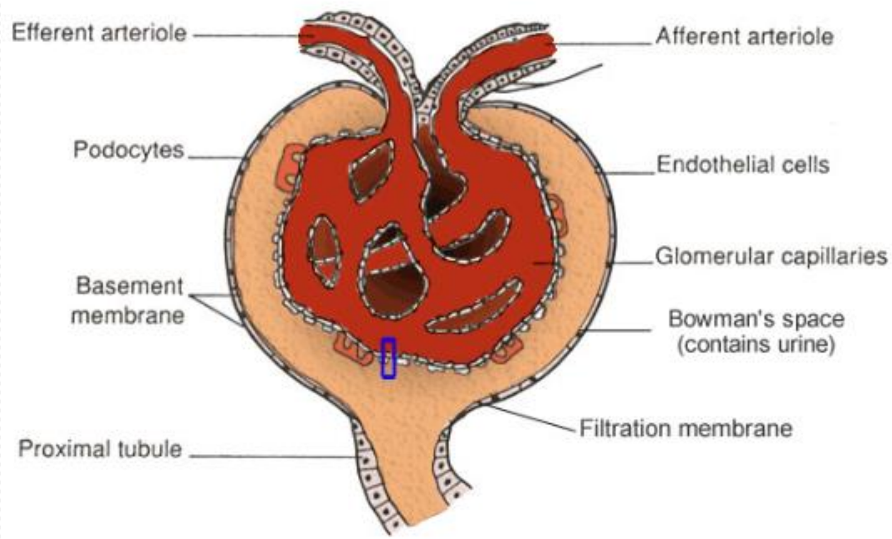
The function of the kidney involves **filtration**, **reabsorption** and **secretion** which take place in the Bowman's capsule, proximal tubule, loop of Henle, distal tubule and collecting duct.

Transepithelial transport= the net movement of solutes and water across the epithelium of the nephron

Glomerular Filtration

- The main filtration barriers are the basement membrane and the podocytes which wrap around the capillaries.
- The membrane allows the filtration of small solutes like ions but prevents large plasma proteins from passing into the Bowman's capsule.

Substance	MW	Ratio filtrate/plasma (=filtrand)
Glucose	180	1
Insulin	5000	0.98
Myoglobin	17,000	0.75
Haemoglobin	68,000	0.03
Serumalbumin	69,000	<0.01



- The filtration membrane is negatively charged which also reduces its permeability to negatively charged proteins, eg. albumin.
- Filtration is dependent on hydrostatic pressure (P) and colloid osmotic pressure (B), in both glomerular capillary (gc) and Bowman's capsule (bc).
- The short afferent arteriole and resistance of the efferent arteriole creates increased hydrostatic pressure. This means that the net outward force for filtration is high and together with the large surface area and permeability, results in a high glomerular filtration rate (GFR).

GFR= k.s. [(Pgc-Pbc)- s (Pgc – Pbc)]

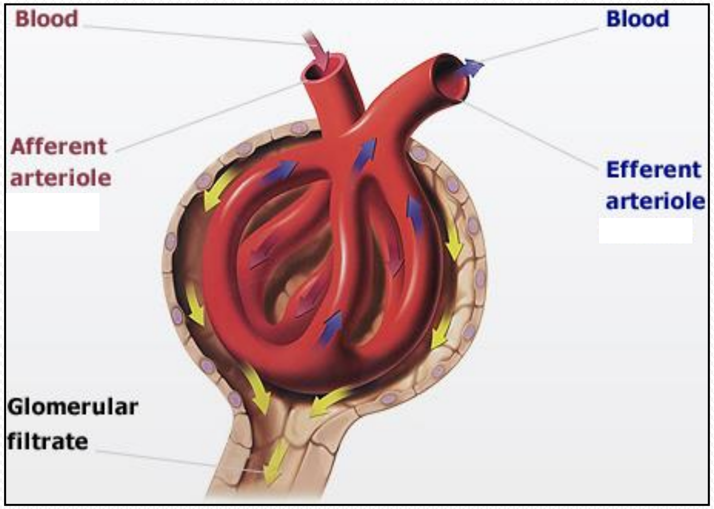
s= area of capillary available for filtration
k= permeability of the filtration membrane

Because considerable net filtration occurs, B gc rises as one moves from afferent to efferent end. The higher B aids reabsorption in the peritubular capillaries later.

Control of filtration rate

Glomerular filtration rate = amount of filtrate removed from blood/minute

GFR varies with sex and age but is approximately 120-130mL/min per 1.73m^2 surface area in adults.
GFR is an important clinical indicator of renal function. Reduced GFR = renal failure.
Constriction of the afferent arteriole (eg. Sympathetic) = reduced GFR. Constriction of efferent arteriole (eg. Angiotensin II) = increased GFR



- Favouring filtration: glomerular capillary pressure (P_{GC})= 60 mmHg
- Opposing filtration: hydrostatic pressure in Bowman's space (P_{BS})= 15 mmHg. Osmotic force of plasma proteins ($\prod_{GC}$)= 29mmHg

- $P_{GC}-P_{BS}-\prod_{GC}$= 16mmHg (net filtration pressure)

Autoregulation of renal blood flow

If arterial pressure changes, a proportional change occurs in renal vascular resistance to maintain a constant RBF.

Mechanisms of autoregulation include:

Myogenic mechanism

The renal afferent arterioles contract in response to stretch. Thus, increased renal arterial pressure stretches the arterioles, which contract and increase resistance to maintain constant blood flow.

Tubuloglomerular feedback

Increased renal arterial pressure leads to increased delivery of fluid to the macula densa (epithelial cells in the distal convoluted tubule of the kidney that lie adjacent to the afferent arteriole just before it enters the glomerulus). The macula densa is sensitive to the sodium chloride concentration of the tubular fluid.

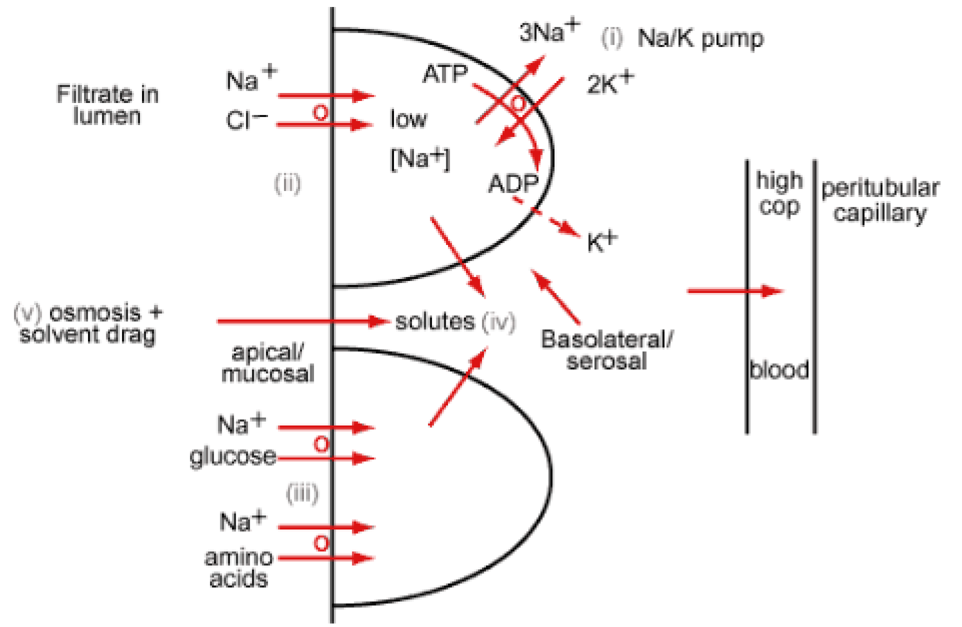
High sodium chloride concentration= elevated GFR. This causes constriction of the nearby afferent arteriole and decrease in renin release which reduces GFR.

Reabsorption

The proximal tubule is largely responsible for reabsorption from the ultrafiltrate. It is made up of two parts; the proximal convoluted tubule (PCT) and the pars recta.

The diagram shows the transport of different ions and solutes in the proximal tubule.

i) Na+/K+ active transport. Helps to maintain low [Na+].
ii) Na+ entry from the lumen down an electrochemical gradient which is coupled to Cl-
iii) Na+ entry from the lumen down an electrochemical gradient which is coupled to: amino acids or glucose (100% reabsorbed usually) and H+ ion secretion; hence HCO3 reabsorption (about 90% complete) with the aid of carbonic anhydrase
iv) Standing gradient draws water (plus solutes= solvent drag) through intercellular junctions.
v) High colloid osmotic pressure in the peritubular capillaries aids removal of reabsorbed material.



Reabsorption and filtration are proportional, linked via changes in colloid osmotic pressure in the peritubular capillaries ie. an increase in filtration leads to an increase in colloid osmotic pressure which results in increased reasorption in the proximal tubule (= ‘glomerulotubular balance’)

The Loop of Henle

The Loop of Henle creates a hypertonic medulla through the **counter-current multiplier** by which concentrated urine is formed. There is increasing osmolality from the cortex to the tip of the loop of Henle. The hyperosmotic gradient is necessary for forming concentrated urine in the collecting duct.

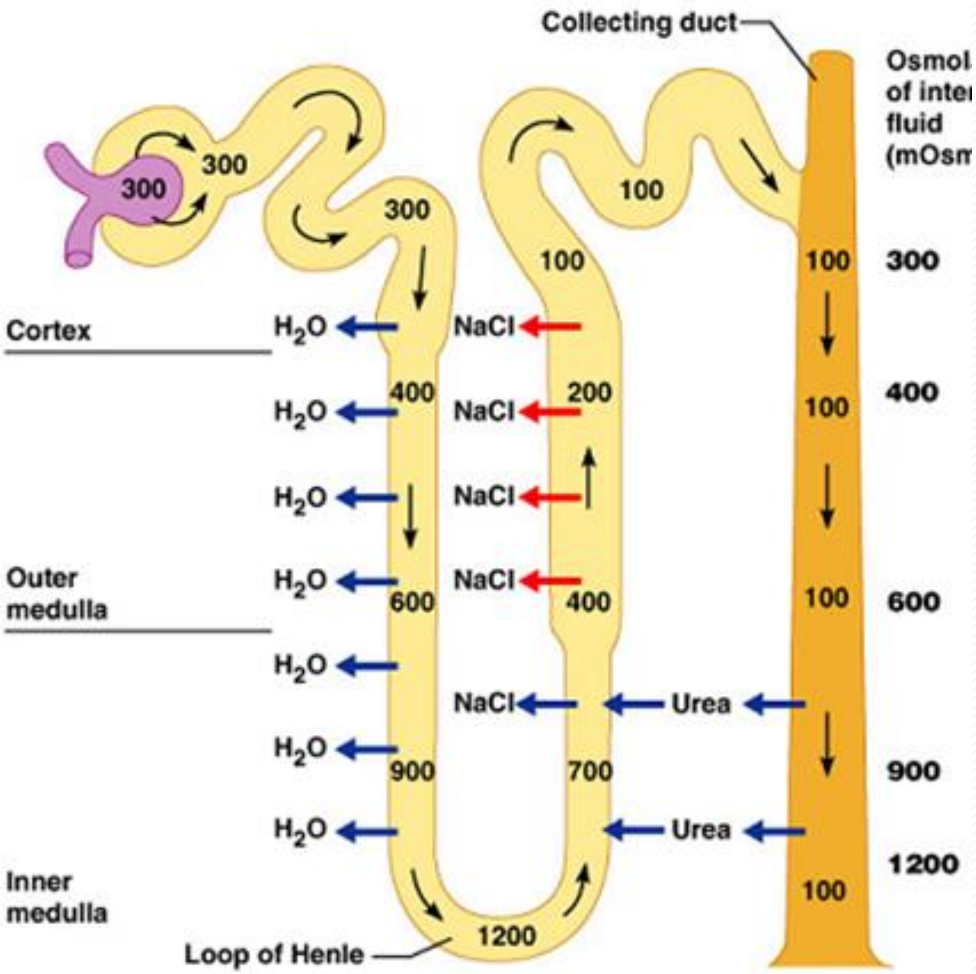
The descending loop of Henle :

- Is permeable to water- water moves into the medulla by osmosis creating a hypertonic solution in the tubule
- Is relatively impermeable to solutes

The ascending loop of Henle:

- Is impermeable to water
- Actively transports sodium, potassium and chloride into the surrounding interstitial fluid through co-transporters creating a hypotonic solution in the tubule.

Countercurrent multiplication is augmented by ADH which stimulates NaCl reabsorption in the thick ascending limb. Vasa recta are the capillaries that supply the loop of Henle. Vasa recta blood equilibrates osmotically with the interstitial fluid of the medulla and papilla, acting as osmotic exchangers to maintian the gradient.



Secretion

The Distal Tubule and Collecting Duct

Fluid and ion reabsorption and secretion are regulated by various hormones. These are important regions for the homeostasis of Na^+, K^+, H^+ and water.

Two important hormones act on the distal tubule and collecting ducts:

- **Aldosterone** - affects Na^+ entry, Na^+ pumping and ATP levels. (Also causes K^+ and H^+ secretion at the same time via apical K channels and proton secretory proteins). Very important for regulation of Na^+ and K^+ excretion.
- **ADH** - inserts preformed water channels into the membrane of the late distal tubule and collecting duct, making them more permeable to water, thus being very important for osmoregulation.

Clearance

Renal clearance of a substance is the volume of plasma that is completely cleared of the substance by the kidney per unit of time

Measurement of clearance has several uses:

- Determination of how kidney handles a substance, eg whether it is reabsorbed or secreted i.e. whether handling is normal
- Measurement of GFR and RPF
- Water balance
- Clinical measurements

Consider a substance, y:
Amount y appearing in urine per min = volume urine / t(time) x [y]urine

Volume of plasma per min required to supply this amount of y, i.e. the volume of plasma "cleared" of y per min = amount y in urine / [y]plasma, which reduces to:

Clearance = (volume urine / t) x ([y]urine / [y]plasma)

Use of clearance to measure GFR

GFR is a very important renal parameter. Low GFR = renal failure.

Take a substance, p, that is freely filtered, neither reabsorbed nor secreted, not metabolised or synthesised by the nephron. Then by definition, amount of p filtered per min = amount of p excreted in urine per min.

But the amount filtered will be the product of GFR (in ml/min) and its plasma concentration, the amount excreted the product of urine flow and urine concentration, so:

GFR x [p]plasma = (volume urine / t) x [p]urine

Rearranging:

GFR = (volume urine / t) x ([p]urine / [p]plasma)

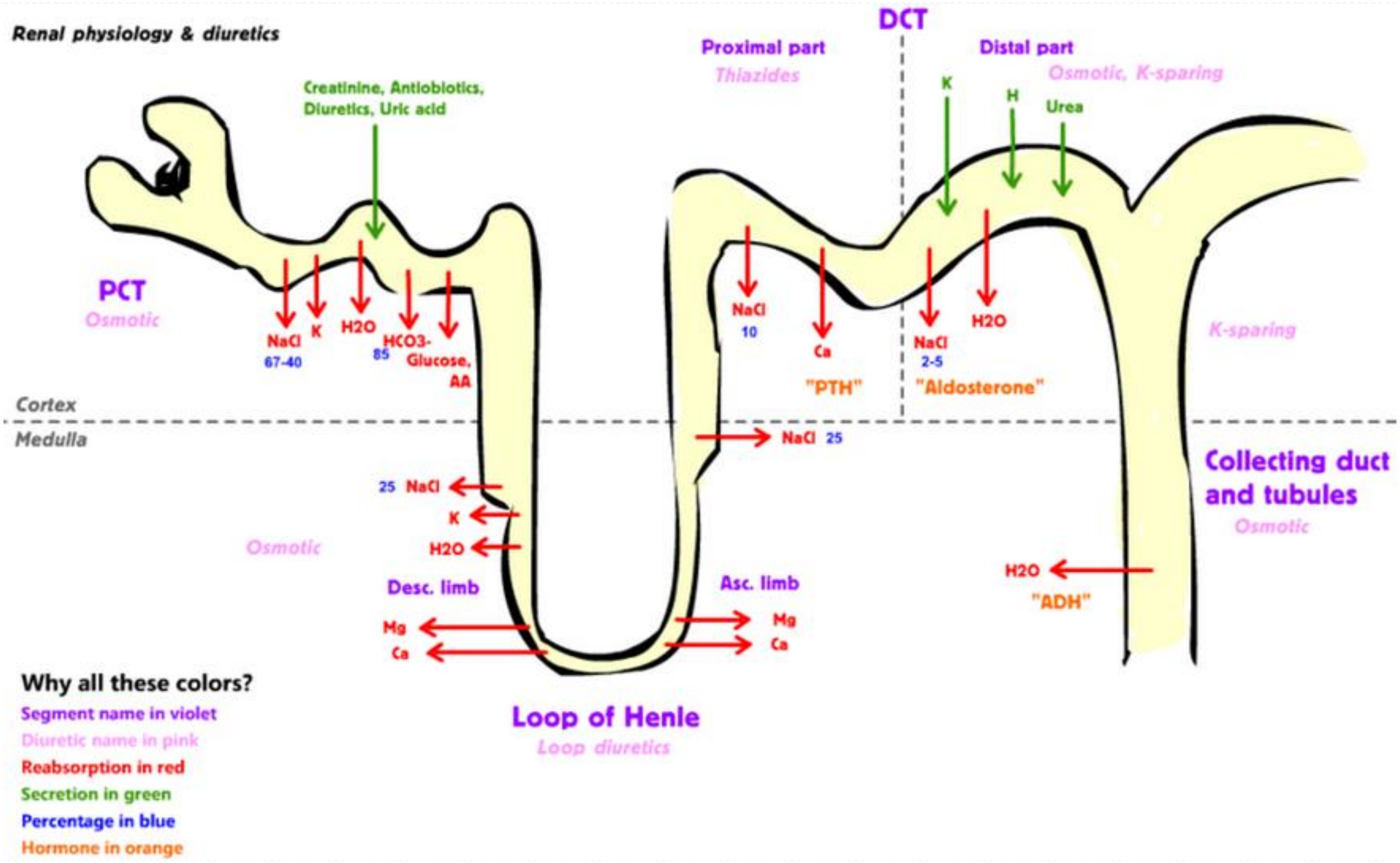
GFR = clearance of p

Substances used to measure clearance include inulin and creatinine.

Hormones that act on the kidney

Hormone	Stimulus for Secretion	Action on kidney
PTH	Decreased plasma [Ca^{2+}]	Decreased phosphate reabsorption (proximal tubule) Increased Ca^{2+} reabsorption (distal tubule) Stimulate 1a-hydroxylase (proximal tubule)
ADH	Increased plasma osmolarity Decreased blood volume	Increased H_2O permeability (late distal tubule and collecting duct)
Aldosterone	Decreased blood volume (via renin-angiotensin II) Increased plasma [K^+]	Increased Na^+ reabsorption (ENaC, distal tubule) Increased K^+ secretion (distal tubule) Increased H^+ secretion (distal tubule)
ANP	Increased atrial pressure	Increased GFR Decreased sodium reabsorption
Angiotensin II	Decreased blood volume (renin)	Increased Na^+-H^+ exchange and HCO_3^- reabsorption (proximal tubule)

In Summary!



Renal physiology & diuretics
DCT
Proximal part
Thiazides
Distal part
Osmotic, K-sparing
Creatinine, Antiobiotics, Diuretics, Uric acid
K
H
Urea
PCT
Osmotic
NaCl
67-40
K
H2O
HCO3-
85
Glucose, AA
NaCl
10
Ca
"PTH"
NaCl
2-5
H2O
"Aldosterone"
K-sparing
Cortex
Medulla
NaCl 25
Collecting duct and tubules
Osmotic
25 NaCl
K
H2O
Osmotic
H2O
"ADH"
Desc. limb
Asc. limb
Mg
Ca
Mg
Ca
Why all these colors?
Segment name in violet
Diuretic name in pink
Reabsorption in red
Secretion in green
Percentage in blue
Hormone in orange
Loop of Henle
Loop diuretics