# Renal physiology

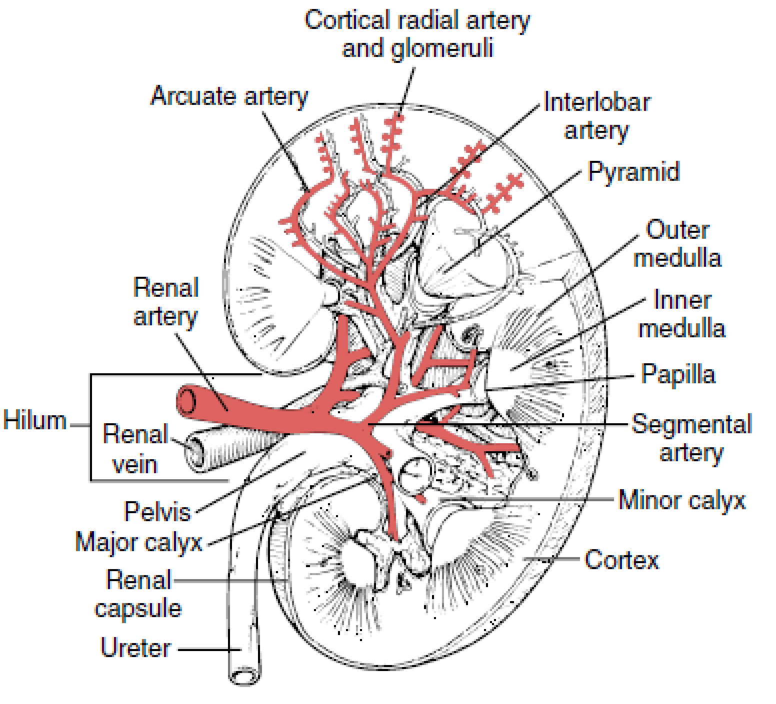
Jana Radošinská

# Contents of the lectures

1. renal system - kidneys, ureters, urinary bladder, urethra
2. water and electrolyte homeostasis
3. acid-base balance

# FUNCTIONAL RENAL ANATOMY

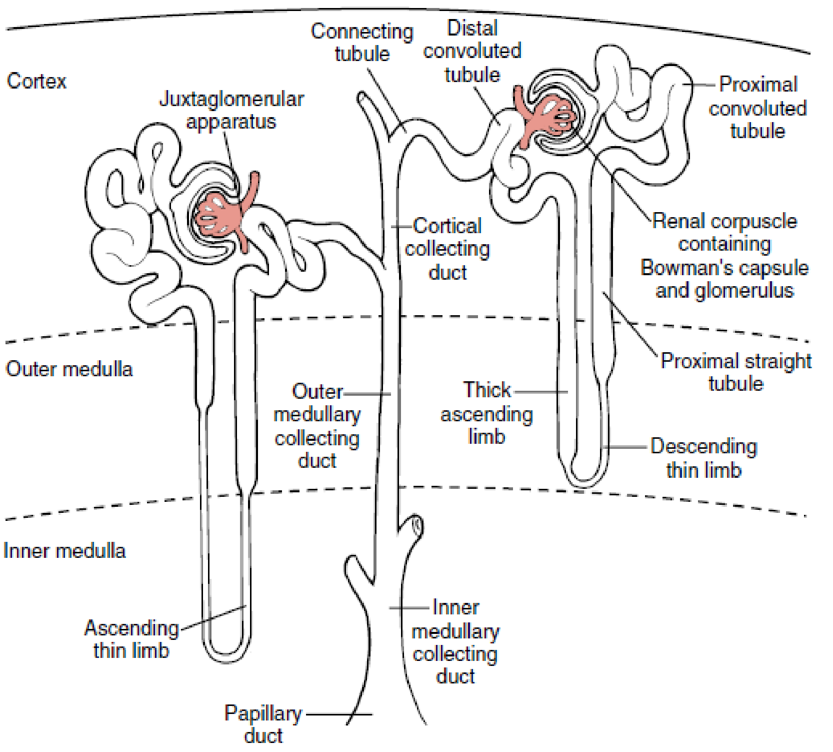
1. cortex – renal corpuscles, convoluted tubules, cortical parts of collecting ducts
   - **isotonic tissue**
2. medulla – loops of Henle, medullar parts of collecting ducts
   - **hypertonic tissue**
   - outer, inner medulla




from: Medical physiology, Part VI: Renal physiology and body fluids

# Nephrons

- superficial
- juxtamedullary – 1/8 of nephrons
  - longer loop of Henle
  - longer both thin limbs
  - larger glomerulus
  - different type of postglomerular blood supply

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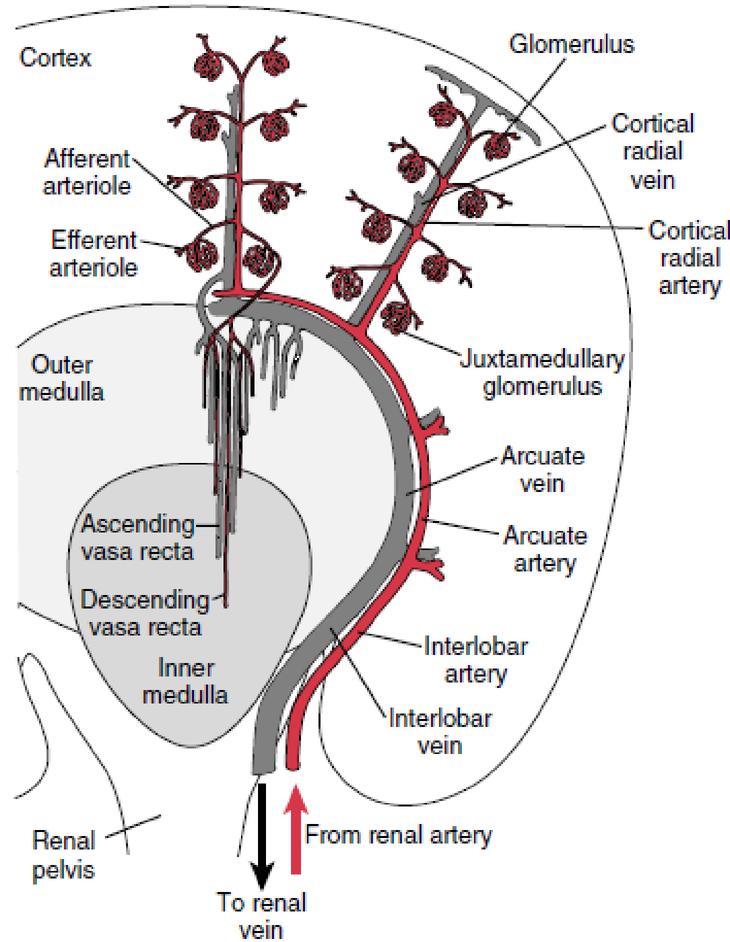
# Kidneys – blood supply

- renal artery – anterior + posterior divisions
- segmental arteries
- interlobar arteries – toward the cortex
- arcuate arteries – between the cortex and medulla
- cortical radial arteries – toward the surface
- afferent arterioles, glomerulus, efferent arterioles
- peritubular capillaries

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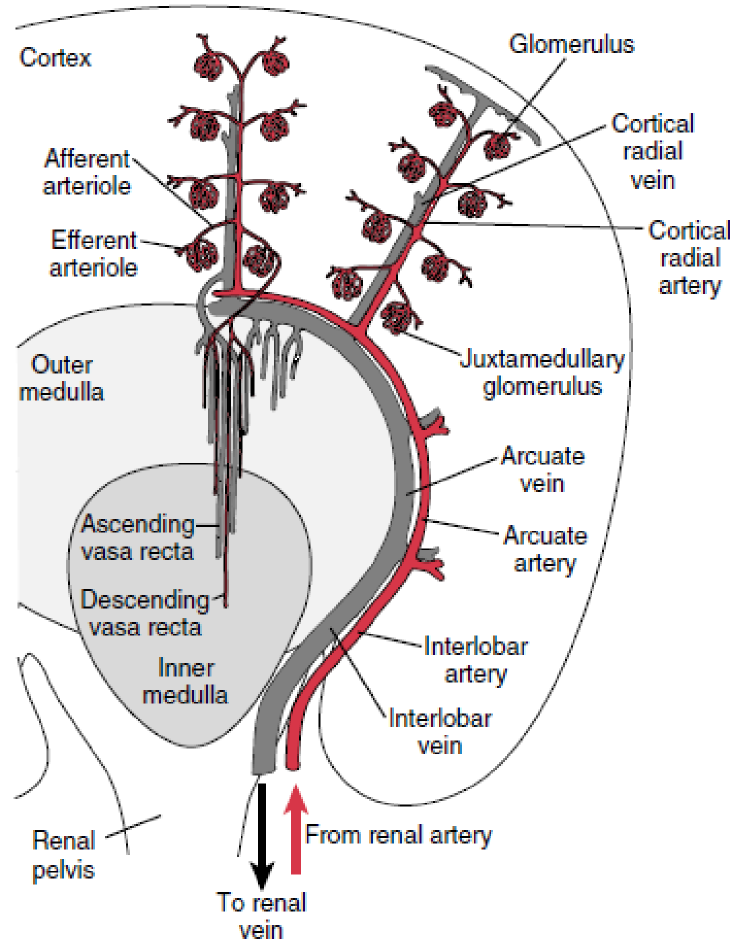


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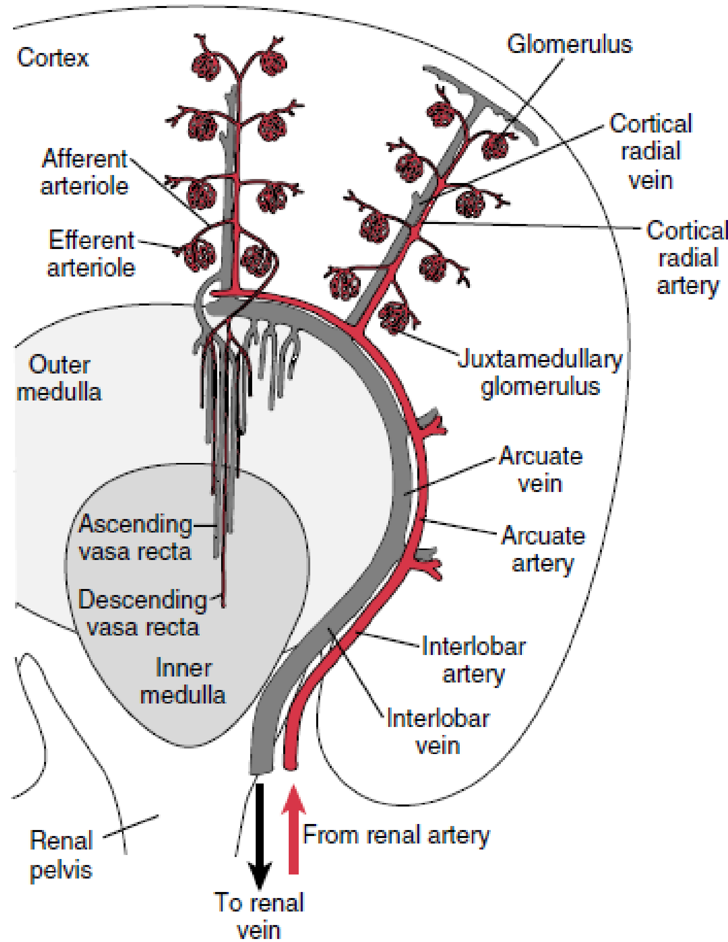
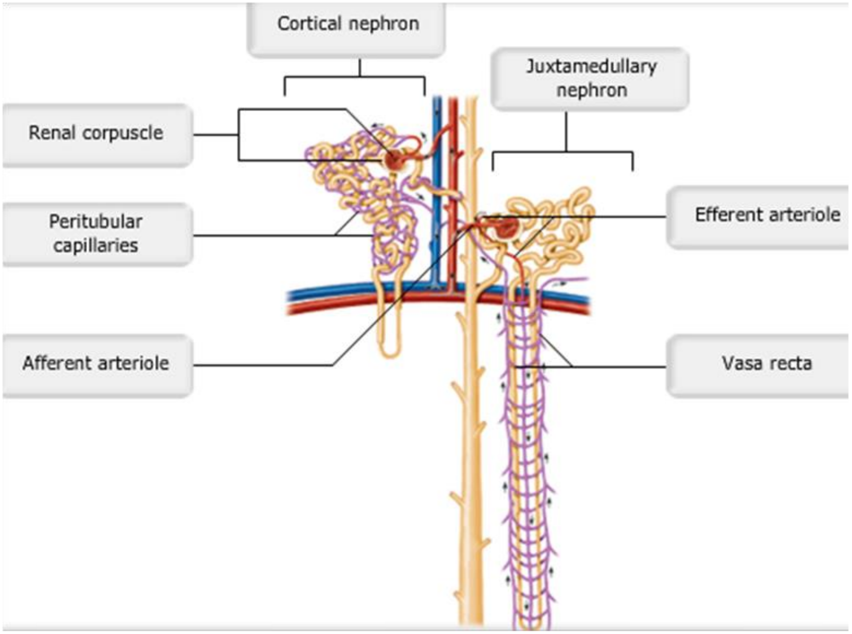



from: Medical physiology, Part VI: Renal physiology and body fluids

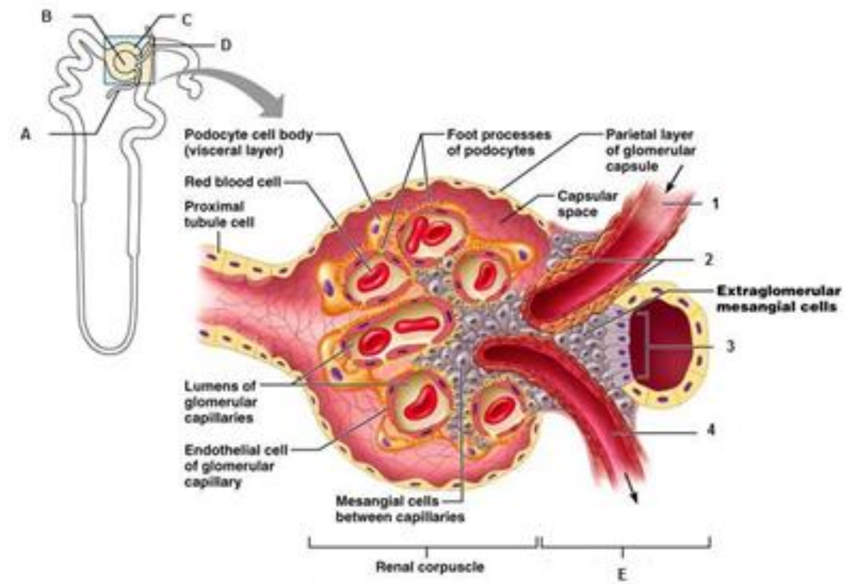
- blood supply to the medulla – derived from efferent arterioles of juxtamedullary glomeruli – vasa recta = long straight capillaries




http://www.easynotecards.com/notecard_set/14394

# Juxtaglomerular apparatus

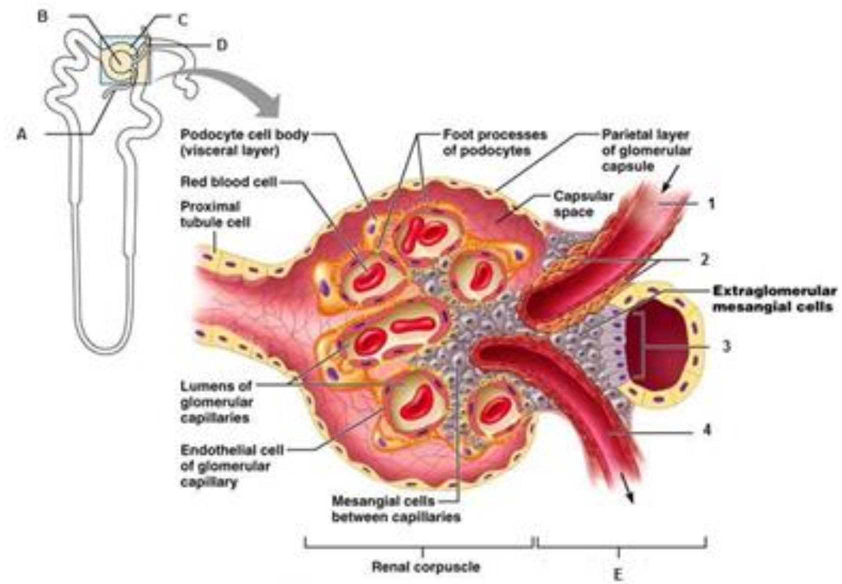
- located near the vascular pole of the glomerulus → thick ascending limb of distal tubule touches the vascular pole of glomerulus
- its main function - regulation of the BP and the filtration rate of the glomerulus




2 - granular cells
3 - macula densa

# Juxtaglomerular apparatus

1. **macula densa** – modified epithelial cells in the distal tubule – monitor the composition of the tubular fluid
2. **extraglomerular mesangial cells** – continuous with glomerular mesangial cells – transmit information from 1 to 3
3. **granular cells** – modified vascular smooth muscle (myoepithelial) cells in the afferent arterioles – synthetize and release renin




2 - granular cells
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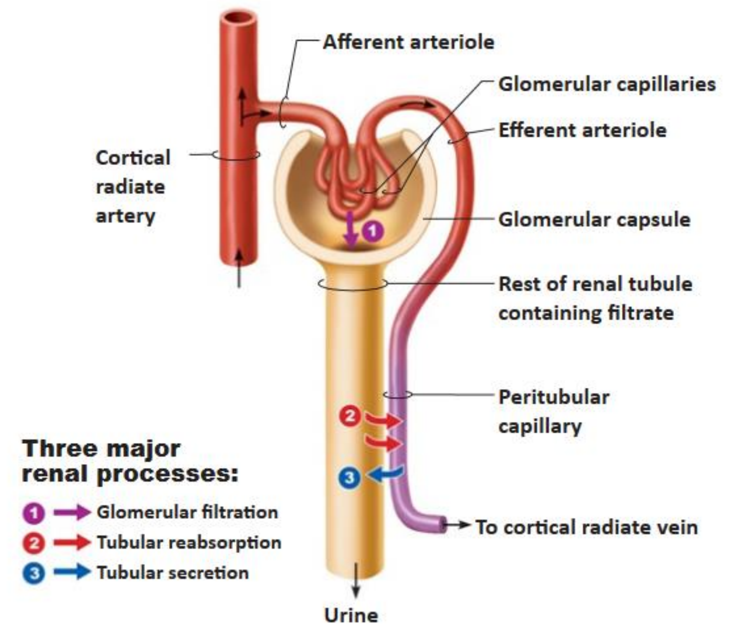
# Renal blood flow

- in resting - 20% of CO
- 4 ml/min/g of tissue (higher perfusion rate - neurohypophysis, carotid bodies)
- blood flow - the highest in cortex, the lowest in inner medulla
- low extraction of oxygen ↔ the lowest AV $O_2$ content difference

# Renal blood flow

2 capillary beds:

1. glomerular
   - high hydrostatic pressure - about 50 mmHg
2. peritubular
   - low hydrostatic pressure - about 10 mmHg



# Renal blood flow - regulation

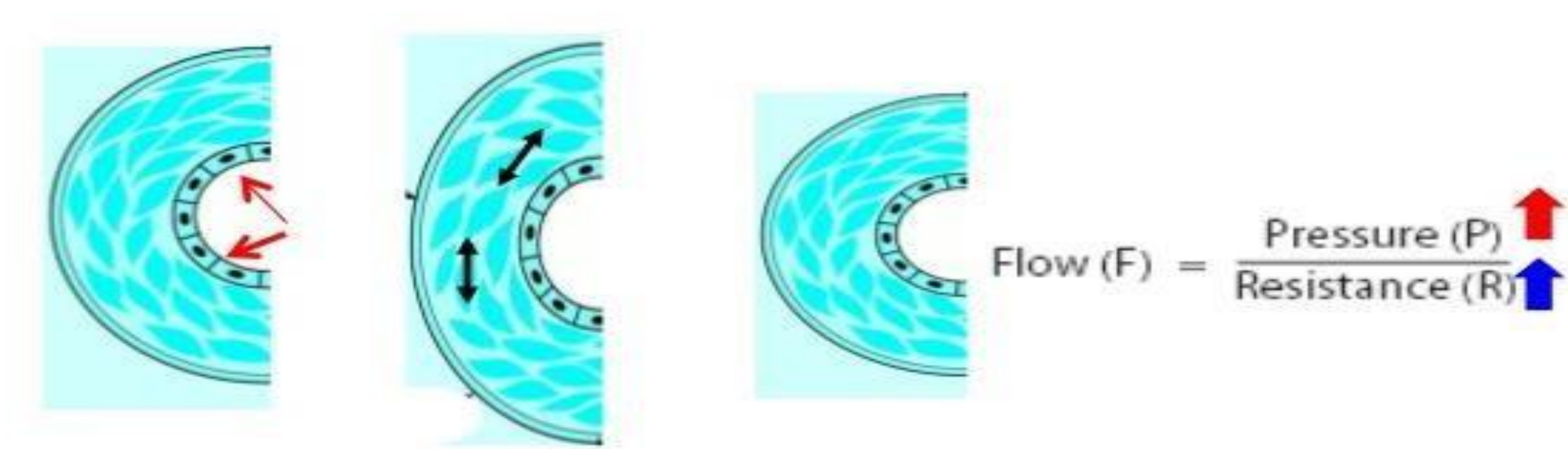
1. Autoregulation
   - present also in denervated kidney
   - constant blood flow in wide range of systemic arterial BP values (80-180 mmHg)
   - 2 mechanisms:
     - myogenic autoregulation
     - tubuloglomerular feedback

2. Nervous

3. Hormonal

# Myogenic autoregulation

- vascular tone - continuous partially contracted state of vascular smooth muscle in the wall of the vessels
- ↑BP → ↑stretch → vasoconstriction → ↑resistance → stable blood flow

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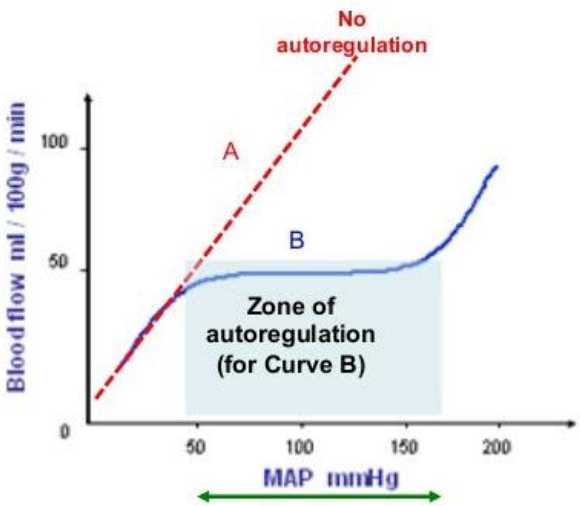
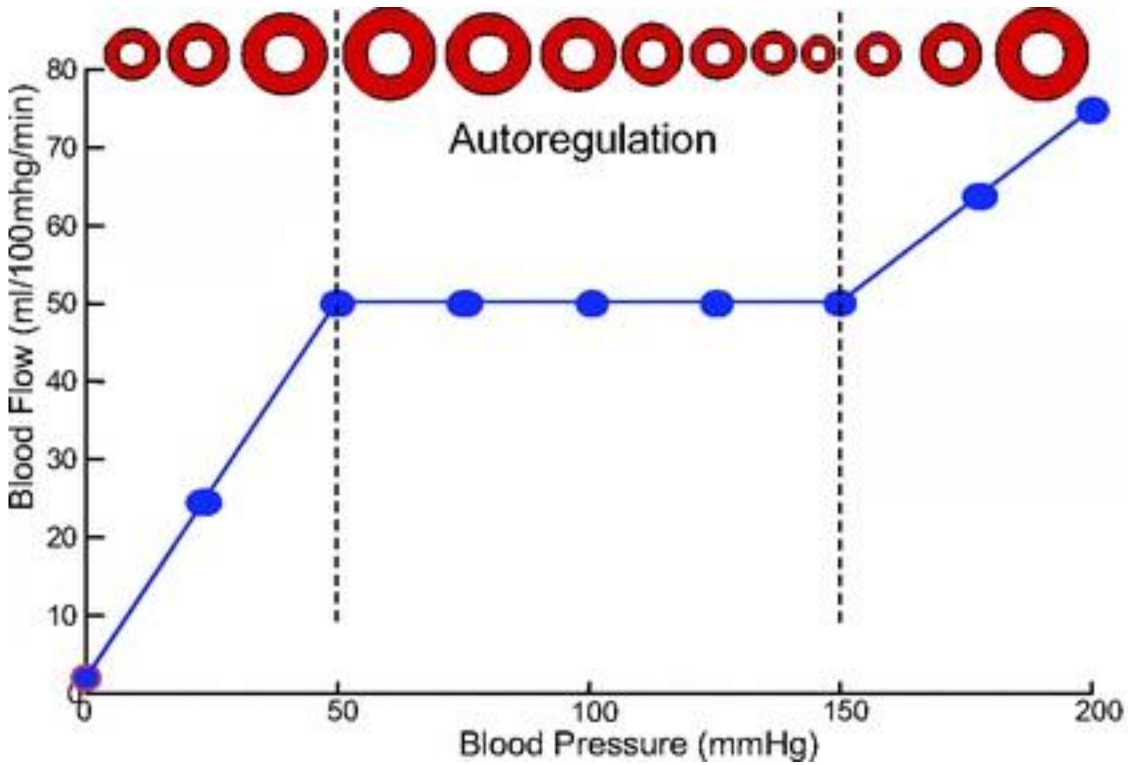
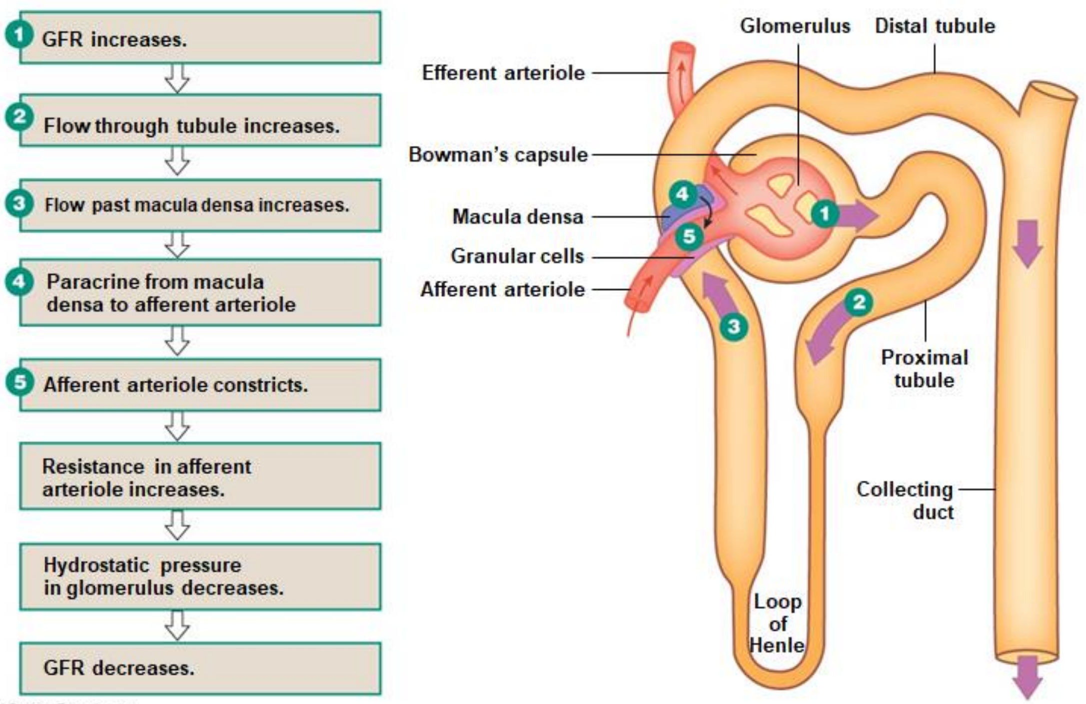



http://www.slideshare.net/VNyuntWai/vtone-t-pfsnnw2012
http://ajpheart.physiology.org/content/304/12/H1598

# Tubuloglomerular feedback

- tubular flow sensing mechanism = macula densa – chemoreceptor - sensitive to NaCl concentration



# Nervous regulation

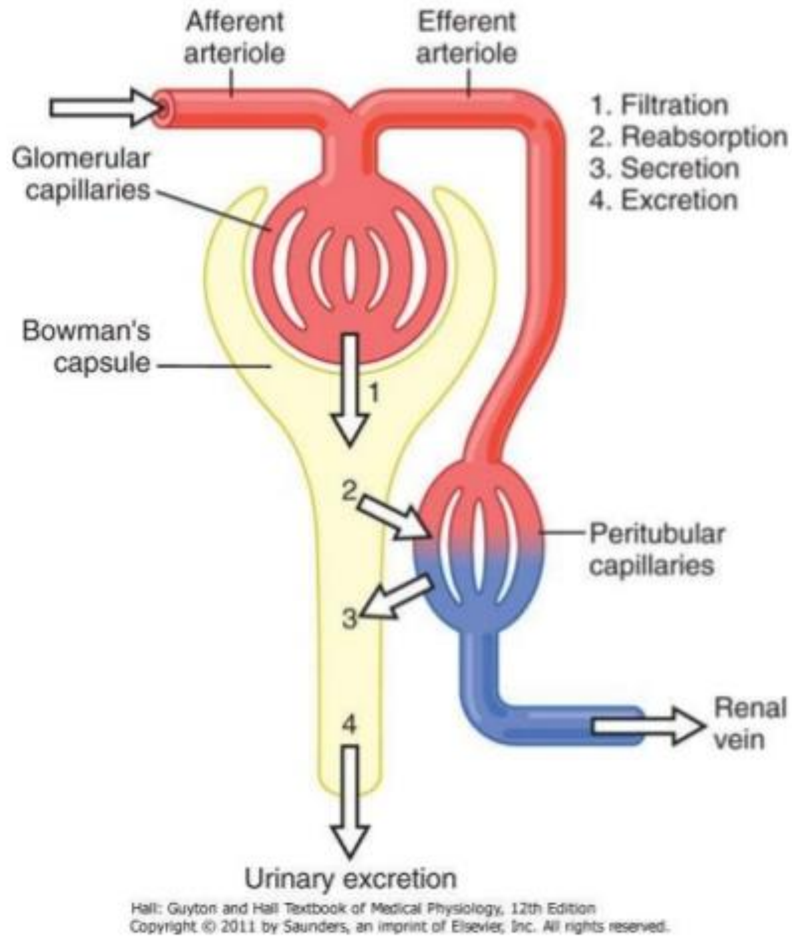
- sympathetic nerve fibers (T10 – L1)
  - stimulation → vasoconstriction → ↓renal blood flow
  - in tubular cells - ↑$Na^+$ reabsorption
  - release of renin
- afferent sensory nerves
  - mechanical stretch
  - chemical

# Hormonal regulation

- angiotensin II - vasoconstrictor of both arterioles
  - efferent arteriole - more sensitive
    - low angiotensin II - ↑ blood flow in glomerulus
    - high levels - ↓ blood flow in glomerulus
- prostaglandins - vasodilation of both arterioles - compensatory mechanism

# Processes in forming urine:

1. glomerular filtration
   - ultrafiltration of plasma → primary urine
2. tubular reabsorption
   - transport out of the tubular fluid
3. tubular secretion, (excretion)
   - secretion - transport into the tubular fluid
   - (excretion = elimination from collecting duct)

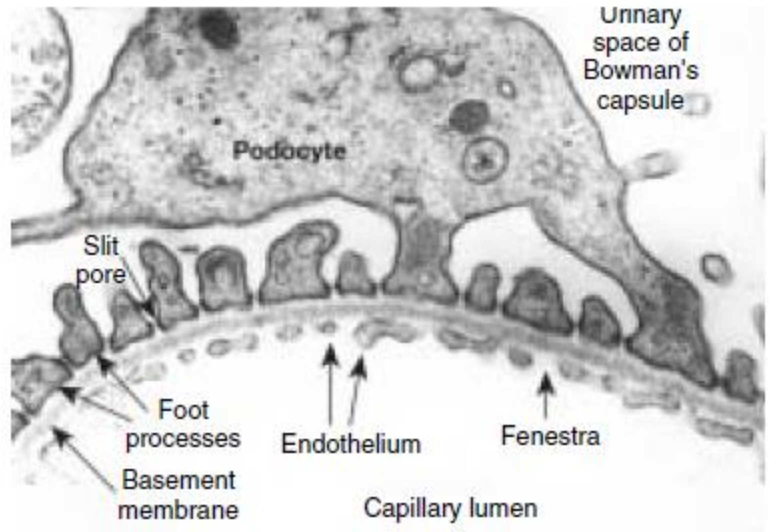



http://www.slideshare.net/dipkari/glomerular-filtration

# Glomerular filtration

Glomerular filtration barrier:

1. capillary endothelium
2. basement membrane
3. podocytes




http://m-learning.zju.edu.cn/G2S/Template/View.aspx?courseId=27252&topMenuId=118135&action=view&type=&name=&menuType=1&curfolid=118697

## Endothelium

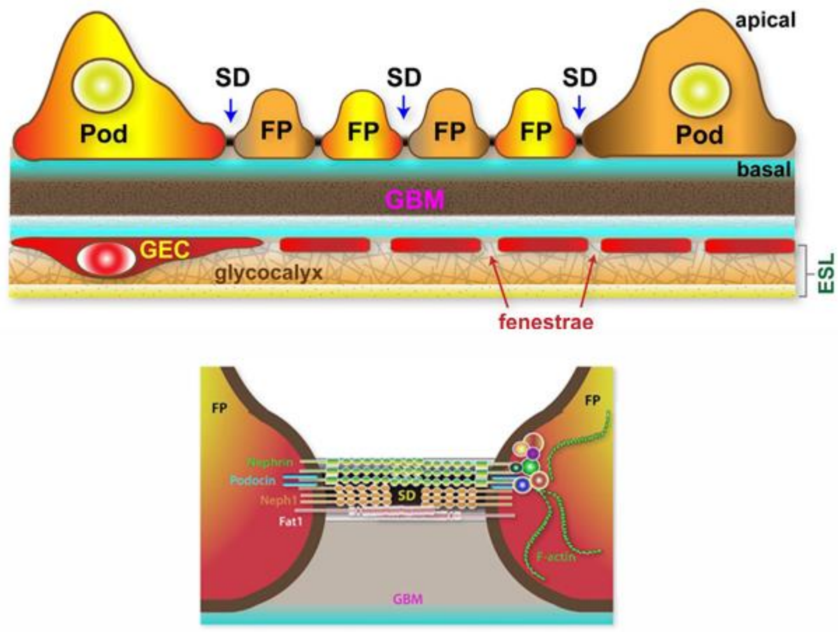
- pores are about 50-100 nm in diameter (~20% of surface area) - barrier for blood elements
- endothelial cells - negatively charged surface (glycocalyx)

## Basement membrane

- contains negatively charged molecules (sialic acid, sialoproteins, heparan sulfate)

## Podocytes

- epithelial cells with extensions - support the glomerular capillary loop
- between the cells - slits with podocyte slit diaphragm → including cell surface proteins → slit pore - 4-14 nm
- negatively charged surface (glycocalyx)

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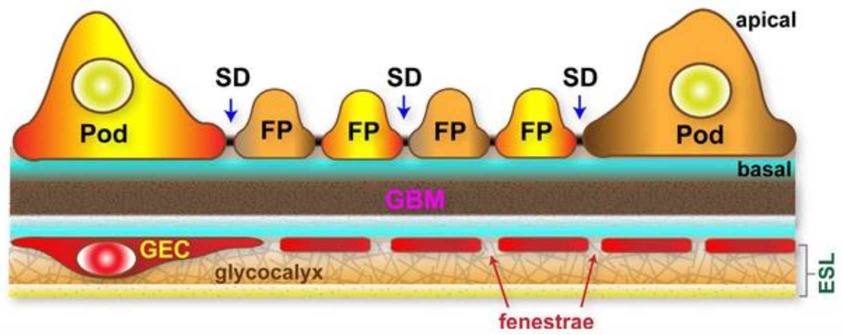


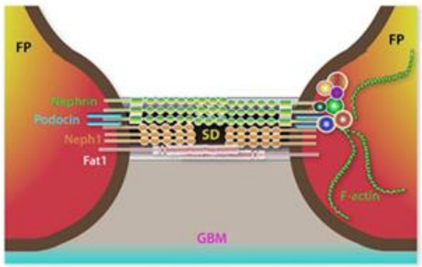


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# Filterability:

Size and charge:

- small molecules – can freely pass
- large molecules - cannot pass
- in between - positively charged pass only

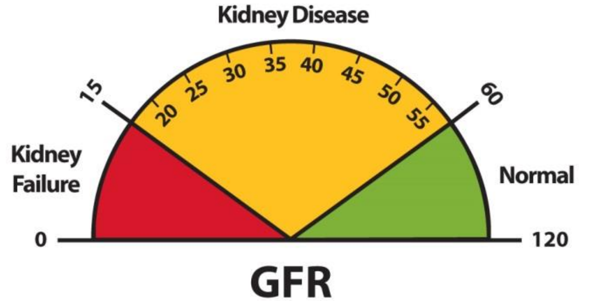
Shape:

- narrow and flexible vs. spherical and non-deformable

# Glomerular filtration rate

GFR

- amount of blood (plasma) filtered by the glomerulus per unit of time
  - volume/time … mL/min
- one way to evaluate kidney function
- normal value ranges may vary among different laboratories



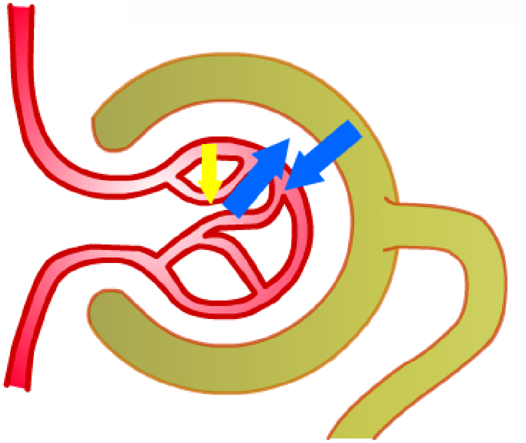

- plasma volume in 70-kg young man - about 3L → the kidneys filter the plasma almost 60 times/day (GFR 120 mL/min = 172,8 L/day)

http://www.niddk.nih.gov/health-information/health-communication-programs/nkdep/learn/causes-kidney-disease/testing/understand-gfr/Pages/understand-gfr.aspx

# Glomerular filtration rate

Like the Starling's forces in every capillary in the body

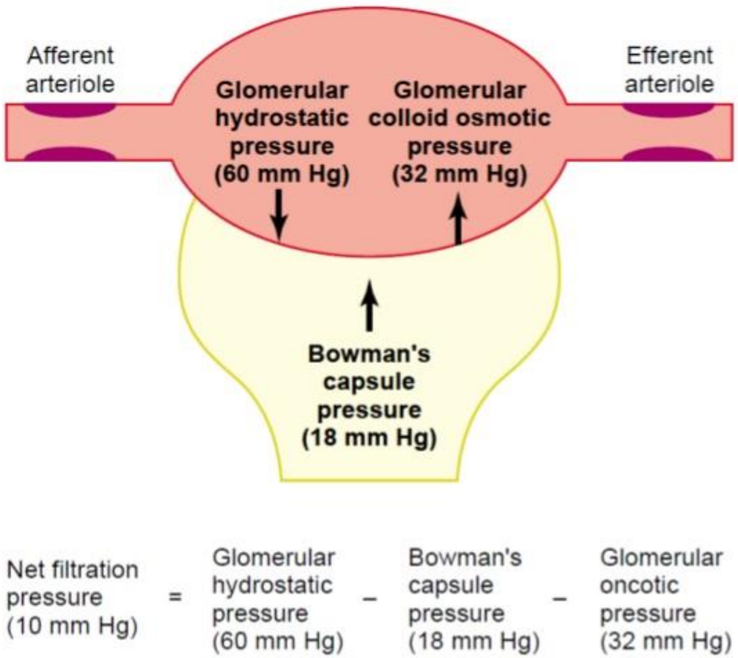
- depends on hydrostatic and oncotic pressures across the GFB
  - hydrostatic pressure in glomerular capillary - pro-filtration
  - hydrostatic pressure in the Bowman's capsule - against
  - oncotic pressure in glomerular capillary - against
  - oncotic pressure in the Bowman's capsule - can be ignored (physiological conditions - no proteins should be filtered by the glomerulus)



http://www.nottingham.ac.uk/nursing/sonet/rlos/bioproc/gfr/6.html

# Effective filtration pressure

effective filtration pressure = glomerular hydrostatic pressure - [glomerular oncotic pressure + Bowman's capsule hydrostatic pressure]

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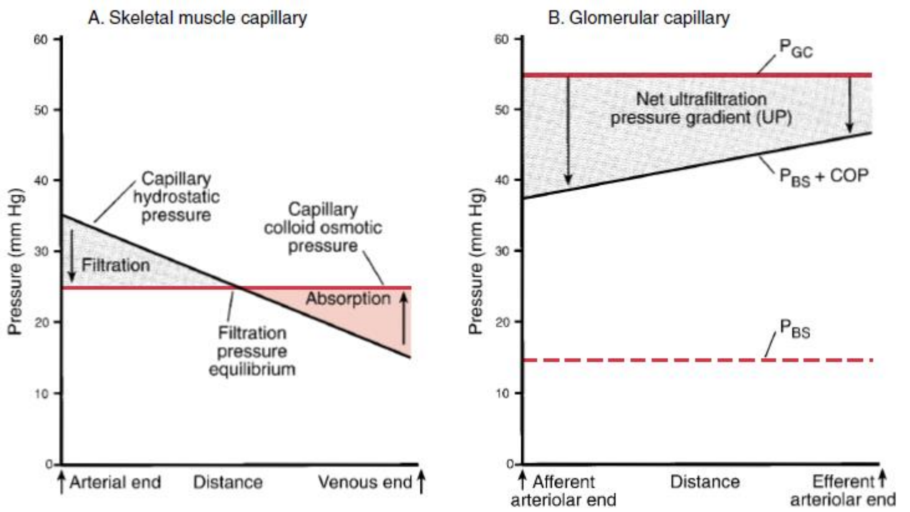
# Ultrafiltration in glomerulus

- high filtration coefficient (high permeability + large surface area)
- the hydrostatic pressure in the capillaries is high (+ does not decrease much along the length of the capillary)
- the large loss of fluid + the impermeability to proteins → the oncotic pressure in the glomerular capillary increases along its length → important in the reabsorption from the proximal tubule into the peritubular capillaries
- a **<u>net outward filtration pressure</u>** along the whole length of the capillary



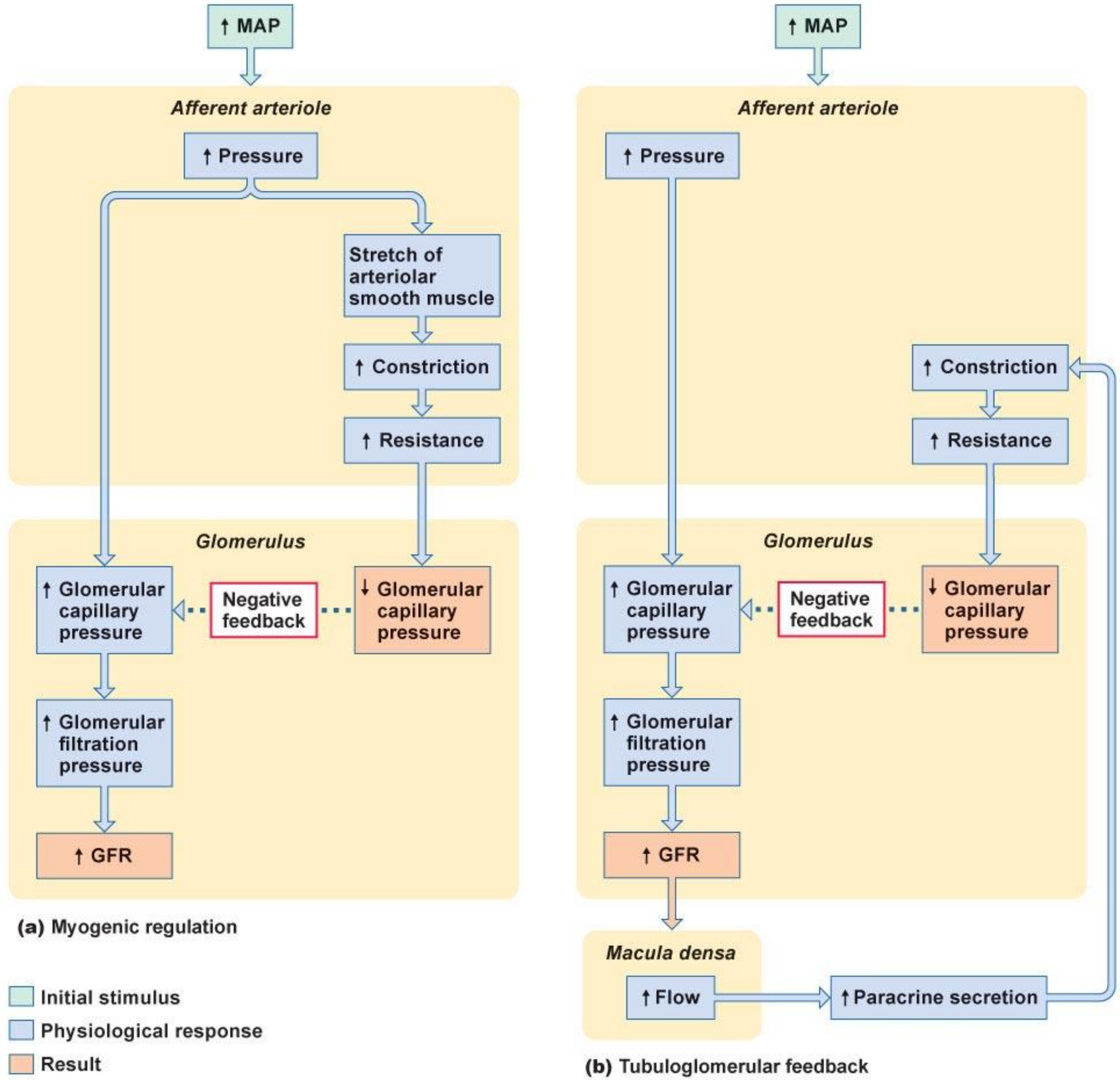

from: Medical physiology, Part VI: Renal physiology and body fluids

# Factors affecting GFR

- glomerular filtration coefficient
  - fluid permeability, surface area, structure and charge of glomerular filter
- BP
  - below 50 mmHg → ↓GF - absence of urine
- nervous and hormonal regulation - afferent and efferent arterioles
- hydrostatic pressure in Bowman's capsule
  - opposes filtration + driving force for fluid movement to the tubular system
- glomerular oncotic pressure

# Regulation of glomerular filtration

- intrinsic = autoregulation of blood flow in the kidney
  - pressure-sensitive mechanism
  - tubulo-glomerular feedback
- extrinsic = regulation of systemic BP
  - neural
  - hormonal


↑ MAP
Afferent arteriole
↑ Pressure
Stretch of arteriolar smooth muscle
↑ Constriction
↑ Resistance
Glomerulus
↑ Glomerular capillary pressure
Negative feedback
↓ Glomerular capillary pressure
↑ Glomerular filtration pressure
↑ GFR
(a) Myogenic regulation
Initial stimulus
Physiological response
Result
↑ MAP
Afferent arteriole
↑ Pressure
↑ Constriction
↑ Resistance
Glomerulus
↑ Glomerular capillary pressure
Negative feedback
↓ Glomerular capillary pressure
↑ Glomerular filtration pressure
↑ GFR
Macula densa
↑ Flow
↑ Paracrine secretion
(b) Tubuloglomerular feedback

# Function of proximal tubule

- fluid entering = primary urine (composition similar to plasma, but without the proteins)

Main functions:

- reabsorption of
  - water
  - glucose
  - aminoacids
  - ions – sodium, bicarbonates, chloride, potassium
- secretion of
  - hydrogen cations

→ modulates volume and composition of urine

# Reabsorption of water in proximal tubule

3 characteristics:

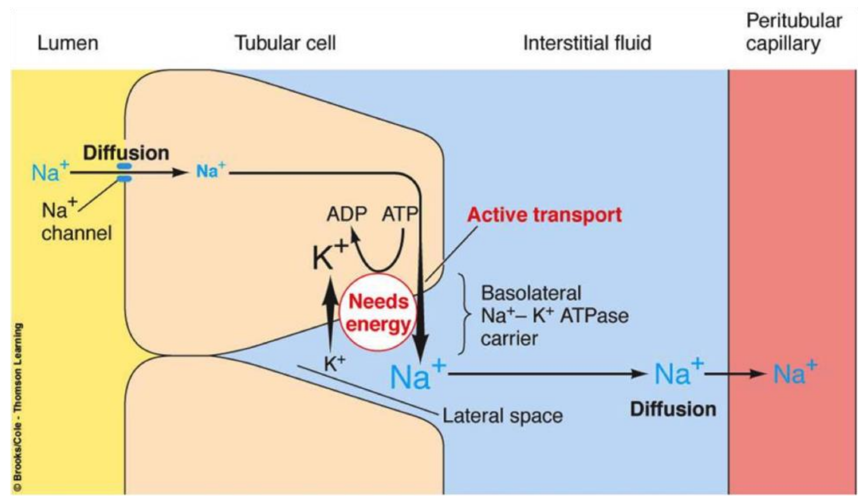
- high – 70-80%
- isosmotic – adequate to reabsorption of solutes
- obligatory – not influenced by hydration of the organism

Driving force:

- sodium concentration gradient

# Absorption of sodium

- inside the cell - passive transport
- outside the cells - active transport = against concentration gradient
- Na,K-ATPase in the basolateral cell membrane – low sodium in tubular cell → <u>maintenance of sodium concentration gradient</u>
- crucial for reabsorption of water, glucose, aminoacids and other solutes

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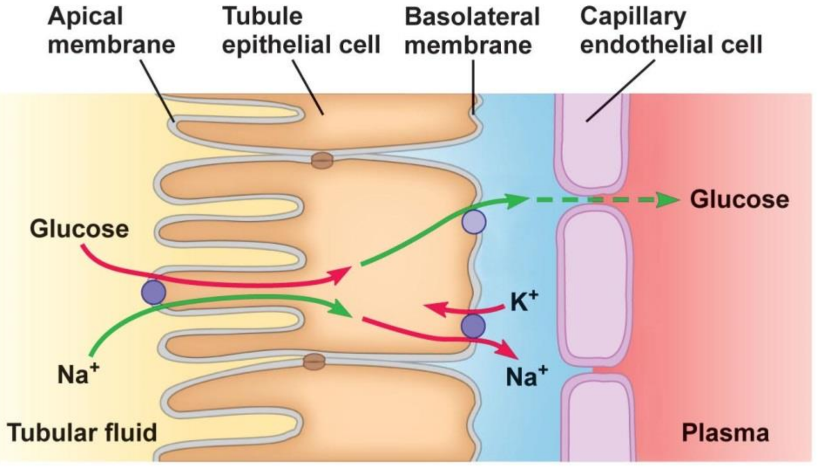
# Reabsorption of glucose

- co-transport mechanism
  - uses energy of sodium concentration gradient

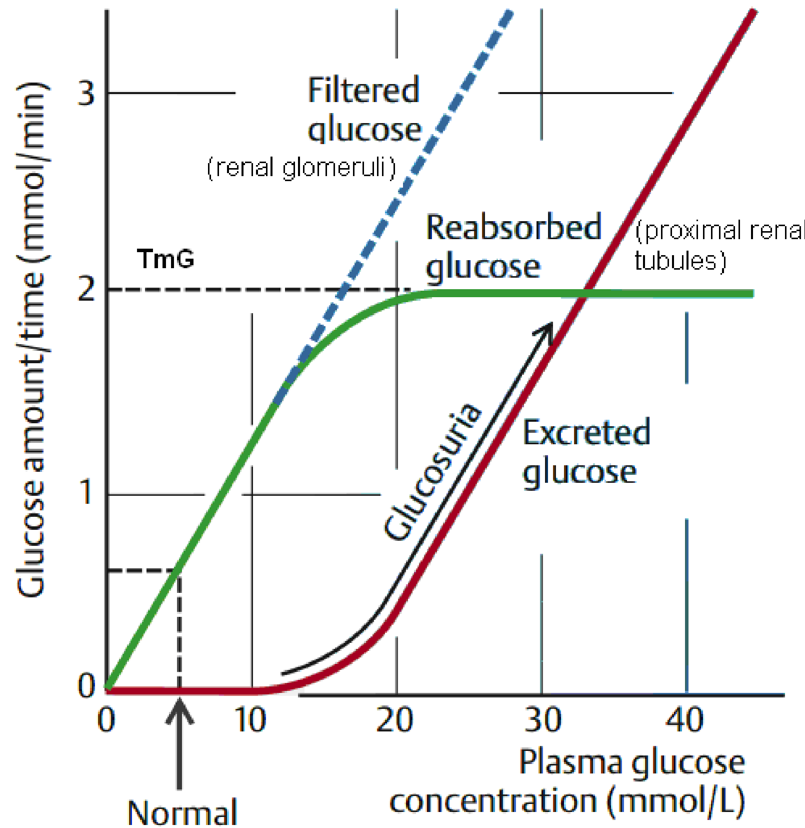




https://droualb.faculty.mjc.edu/Course%20Materials/Physiology%20101/Chapter%20Notes/Fall%202011/chapter_18%20Fall%202011.htm

# Reabsorption of glucose

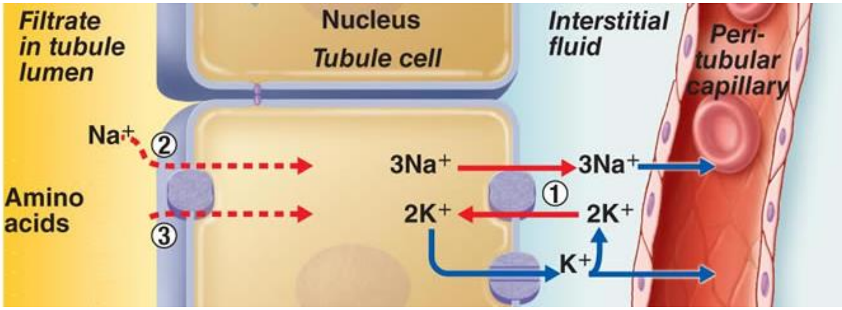
- count of transporters – limited → transport maximum
  - plasma glucose higher than 10 - 15 mmol/L → all transporters saturated → presence of glucose in the final urine
- renal threshold for glucose (…and other substances)




http://www.intechopen.com/books/treatment-of-type-2-diabetes/the-role-of-the-kidney-in-glucose-homeostasis

# Reabsorption of aminoacids

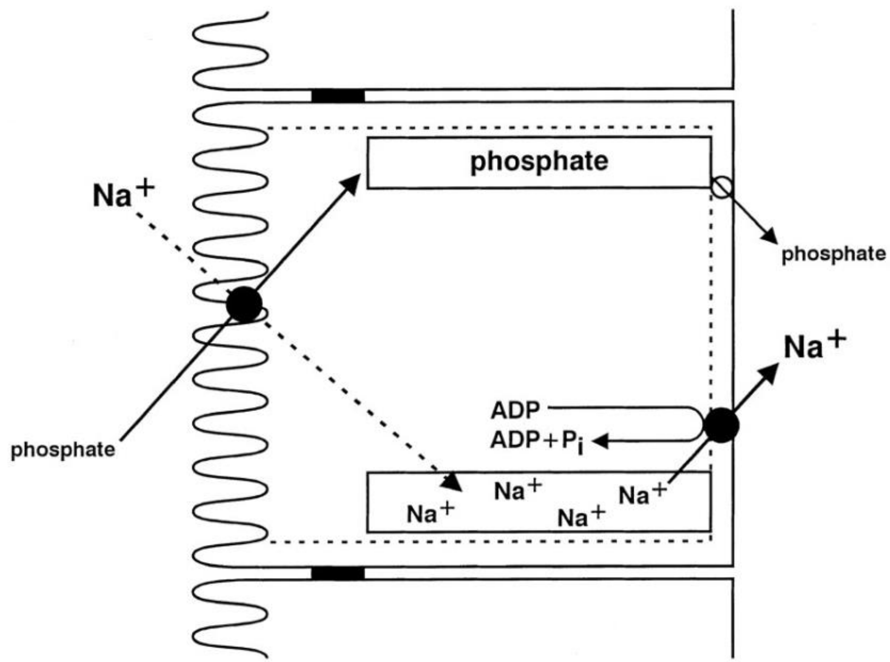
- co-transport mechanism
  - uses energy of sodium concentration gradient
- 7 different transporters:
  - acidic amino acids (Glu, Asp)
  - basic amino acids (Arg, Lys, Orn)
  - five other systems for neutral amino acids




http://classes.midlandstech.edu/carterp/Courses/bio211/chap25/chap25.htm

# Reabsorption of phosphate

- co-transport mechanism
  - uses energy of sodium concentration gradient



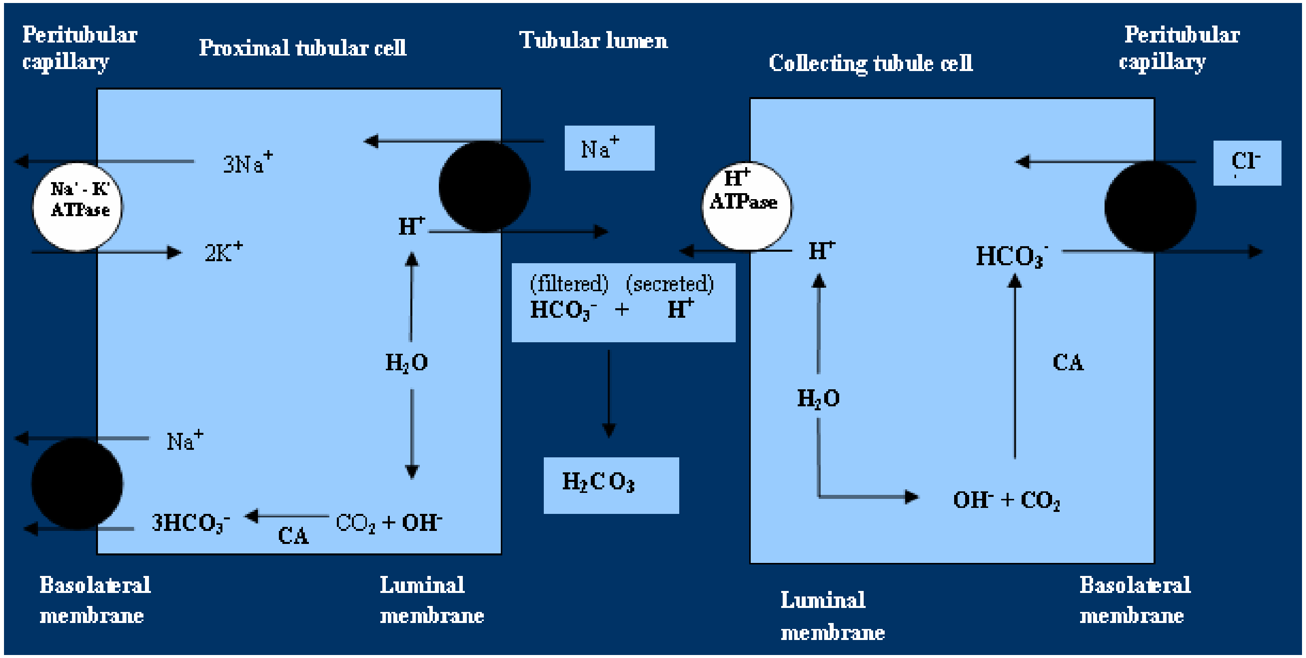

http://physrev.physiology.org/content/80/4/1373

# Secretion of hydrogen ions

2 main mechanisms:

- Na/H-antiporter (exchanger)
- proton pump (H-ATPase)

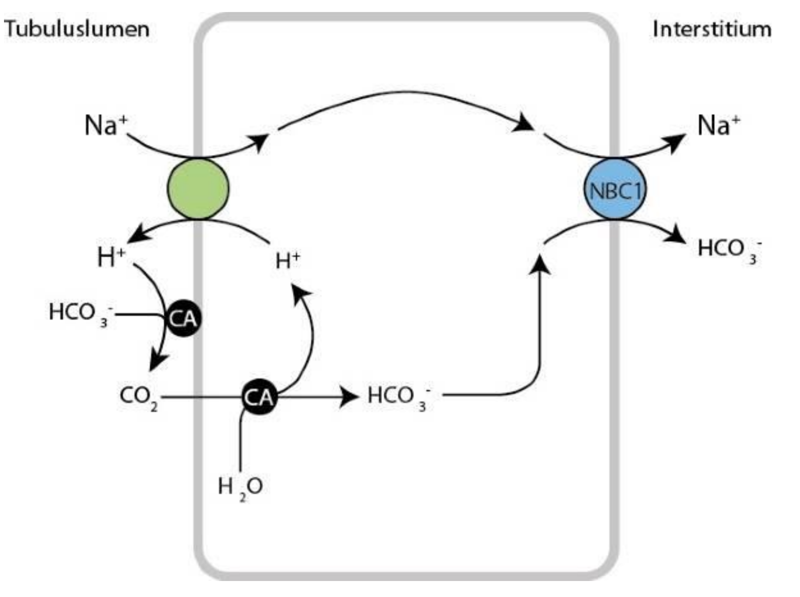
→ result = acidification of urine




http://fitsweb.uchc.edu/student/selectives/TimurGraham/Bicarbonate_reabsorption.html

# Reabsorption of bicarbonates

- absorption of $CO_2$ from tubular fluid
- CA - carbonic anhydrase
- transport of $3HCO_3^-$ and $1Na^+$ in to the interstitium




$$CO_2 + H_2O \xrightarrow{\text{Carbonic anhydrase}} H_2CO_3$$

$$HCO_3^- + H^+ \rightarrow H_2CO_3 \rightarrow CO_2 + H_2O$$

http://pictures.doccheck.com/com/photo/23511-bicarbonate-resorption-in-the-proximal-tubule
https://en.wikipedia.org/wiki/Carbonic_anhydrase

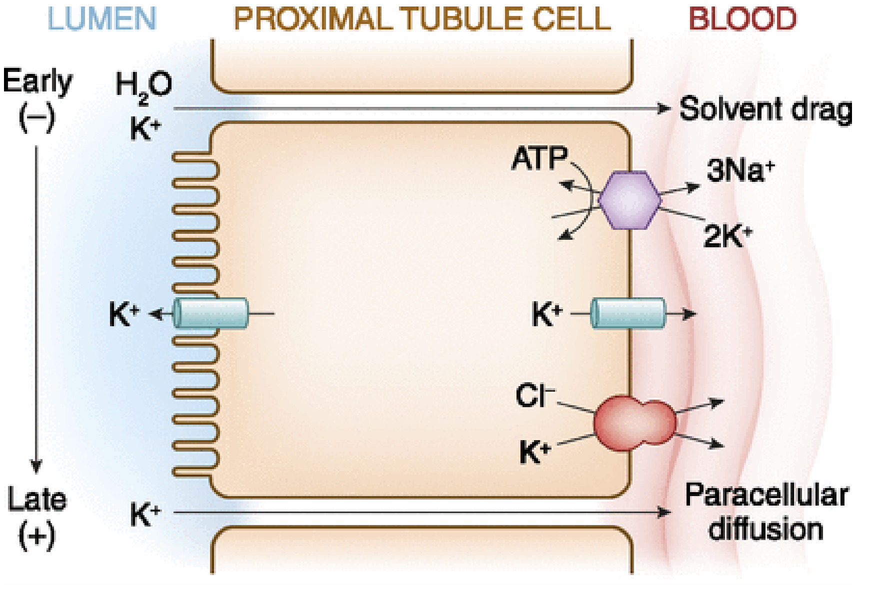
# Reabsorption of chloride anions

- enter the cell via:
  - Na/Cl co-transport
  - Cl/base antiporter (Cl/formate, Cl/oxalate)

- leave the cell via:
  - K/Cl co-transport
  - Cl channels

# Reabsorption of potassium

- paracellular pathway - more important
- transcellular pathway




http://cjasn.asnjournals.org/content/early/2014/04/30/CJN.08580813.full.html

# Secretion

2 mechanisms:

1. transcellular – crossing the cells – urate, glucuronides, penicillin, diuretics
2. cellular – synthesis in tubular cells and then leaving the cells - ammonia

# Functions of the loop of Henle

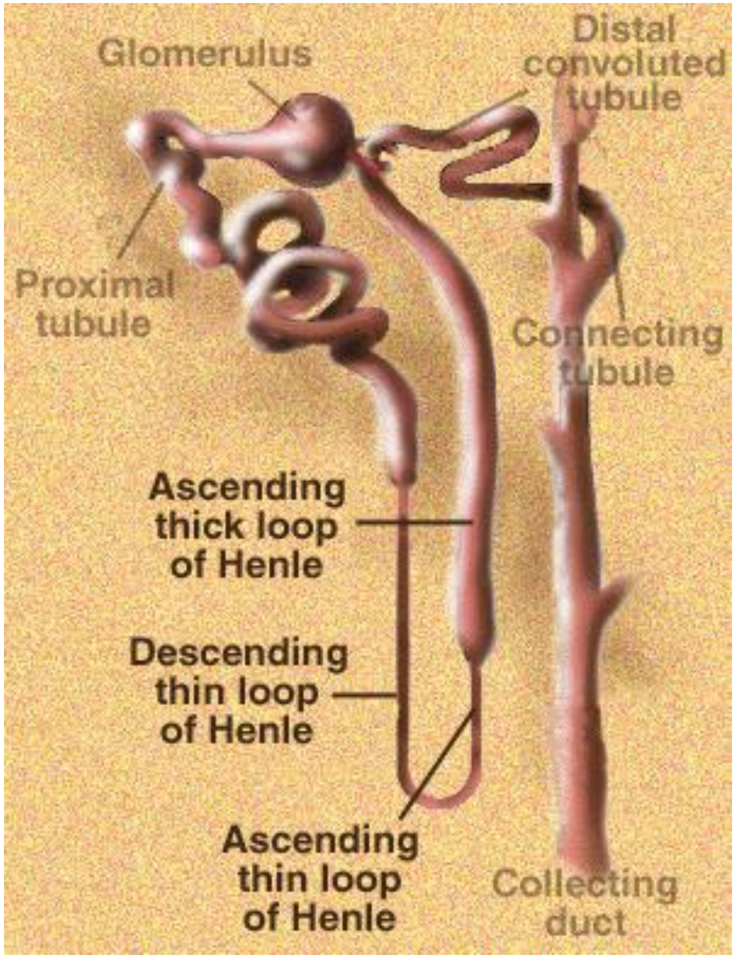
- in the medulla

Functions:

1. reabsoption of water and solutes
2. maintenance of hyperosmotic interstitium
3. production of hypoosmotic urine

3 functional units:

1. thin descending segment
2. thin ascending segment
3. thick ascending segment



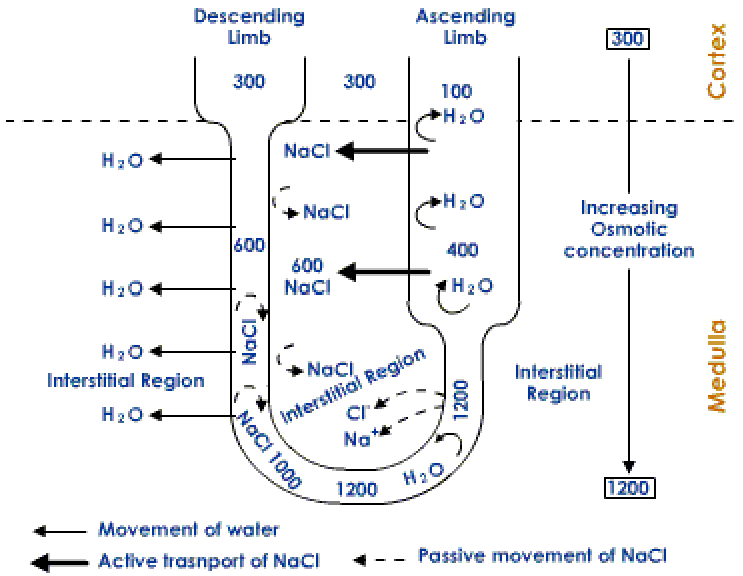

http://humanphysiology.tuars.com/program/section7/7ch03/7ch03p16.htm

# Reabsorption of water and solutes

- 25% of filtered Na, Cl, K
- 10% of filtered water
- Ca, Mg, bicarbonates

Water – in the descending limb only

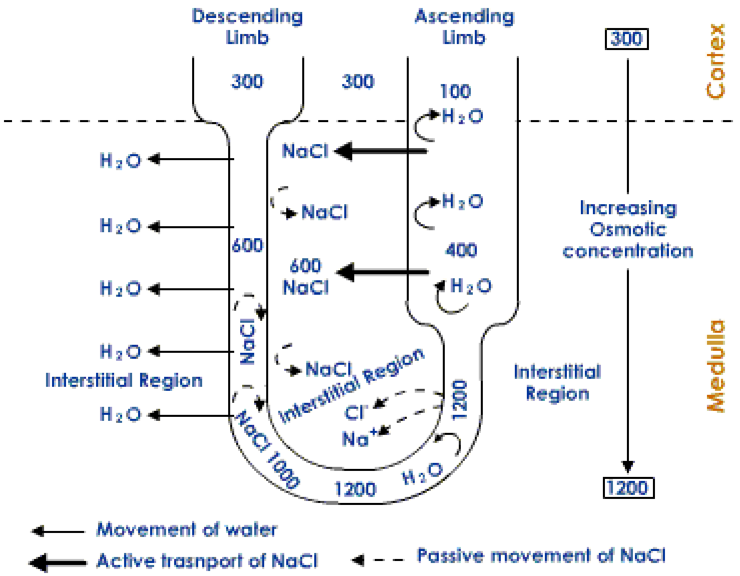
- isoosmotic fluid → hypertonic
- hypertonicity increases with the increasing depth of descending segment (maximum at the bend of the loop)



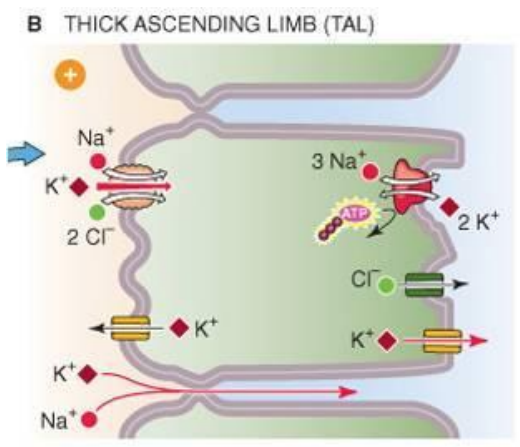

http://www.tutorvista.com/content/biology/biology-iv/excretion/counter-current-mechanism.php

Ascending limb

- impermeable for water
- permeable for solutes (especially thick segment)



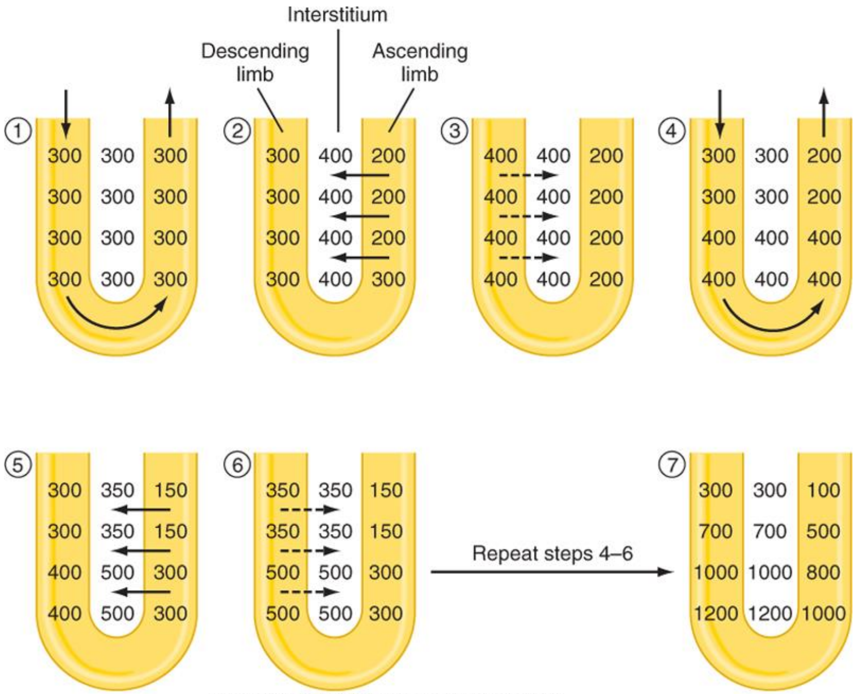

- transporters:
  - basolateral membrane: Na,K-ATPase
  - luminal membrane: Na,Cl,K-cotransporter (all the ions in the cell)
- hypotonic tubular fluid at the end




http://www.tutorvista.com/content/biology/biology-iv/excretion/counter-current-mechanism.php
https://www.studyblue.com/notes/note/n/final-vocab/deck/14869302

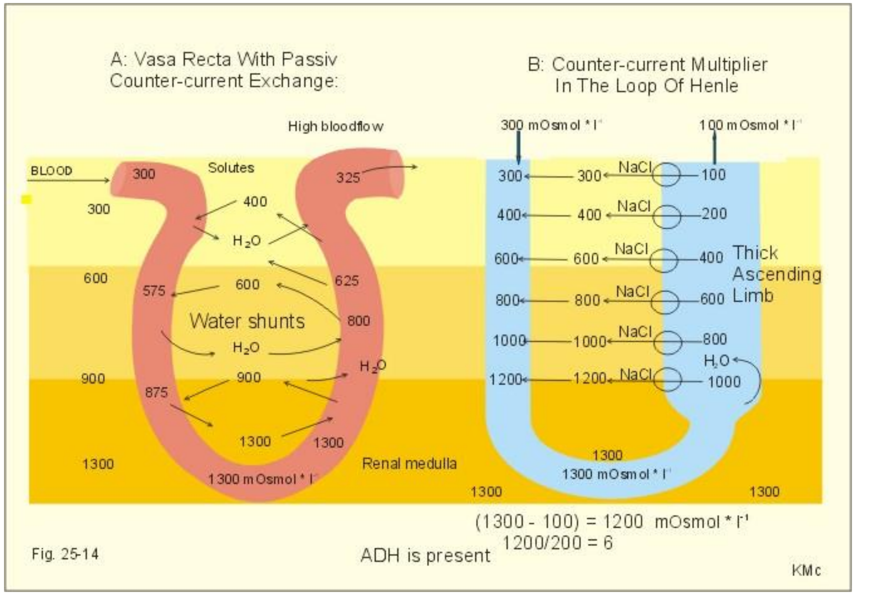
# Countercurrent multiplication

- maintenance of hyperosmotic medullar interstitium
- osmotic stratification – progressive increase of interstitial osmotic pressure toward the depth of medulla
- loop of Henle = countercurrent multiplier



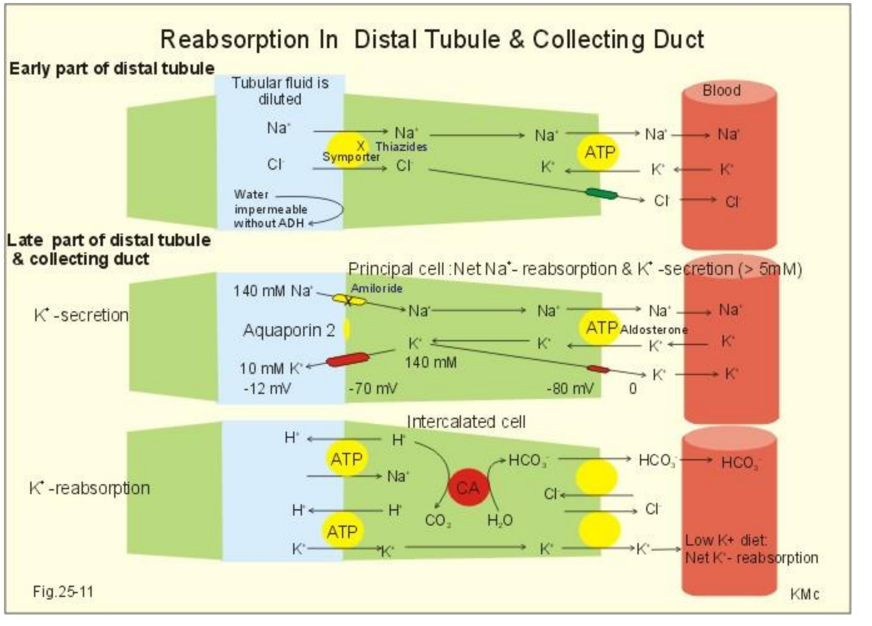
# Vasa recta

- countercurrent exchangers
- blood entering the renal medulla in the descending limb - close to the outgoing blood in the ascending limb
- descending limb - $Na^+$ and $Cl^-$ into the blood, water out
- ascending limb - $Na^+$ and $Cl^-$ into the interstitial fluid
- the hypertonicity of the medulla is maintained



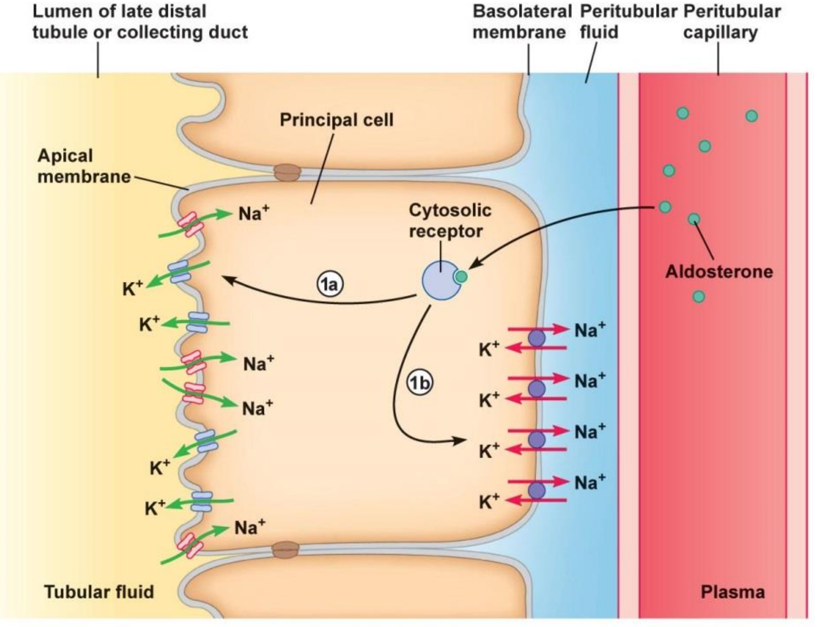
# Functions of the distal tubule

- first part – as thick ascending segment of the Henle's loop
- second part
  - principal cells – reabsorption of sodium and water, secretion of potassium
  - intercalated cells – secretion of $H^+$, reabsorption of bicarbonate, reabsorption of potassium



# Principal cells

- Na,K-ATPase in the basolateral membrane sensitive to aldosterone
- water – aquaporins sensitive to ADH





https://droualb.faculty.mjc.edu/Course%20Materials/Physiology%20101/Chapter%20Notes/Fall%202007/chapter_19%20Fall%202007%20Phy%20101.htm

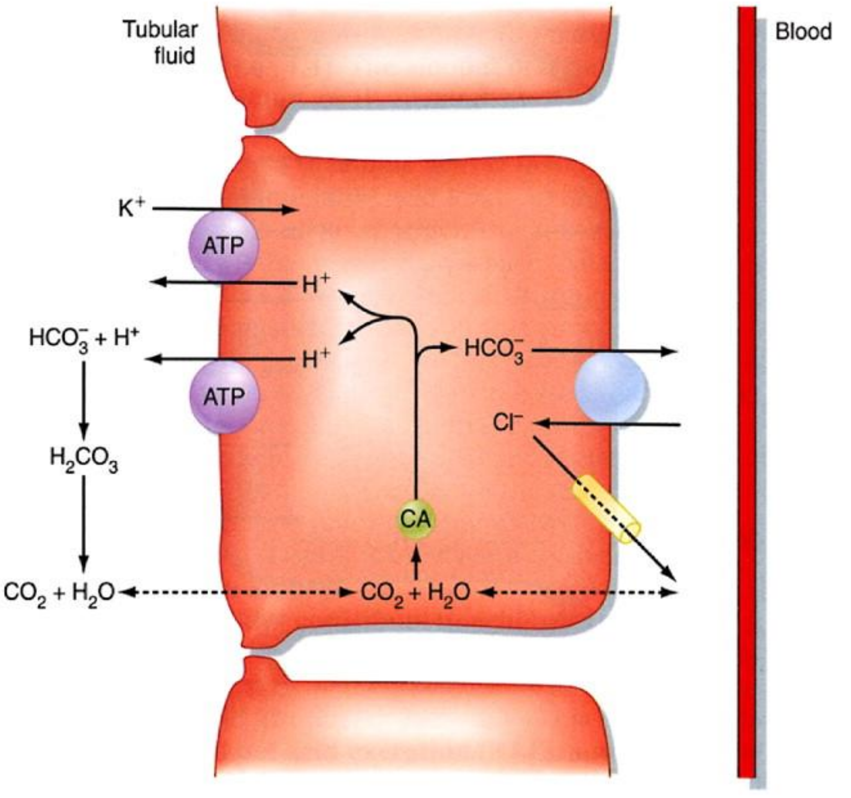
# Intercalated cells

Regulation of ABB (2 types of cells - in opposed mode)

- reaction in the cell

$CO_2 + H_2O \rightarrow H_2CO_3 \rightarrow H^+ + HCO_3^-$

- secretion of $H^+$ out to tubular fluid - $H^+$-ATPase, $H^+/K^+$-ATPase
- bicarbonate out to interstitial fluid and blood
- carbonic anhydrase
- + reabsorption of potassium



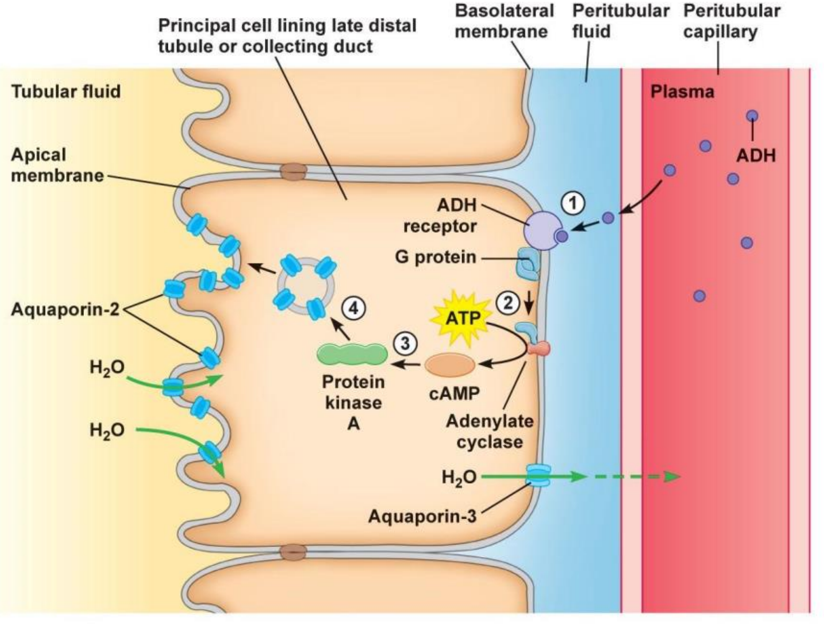

http://advan.physiology.org/content/33/4/275

# Comparison distal vs. proximal tubule

1. lower reabsorption of salt (9%) and water (19%)
   - proximal – 70-80%
2. less leaky epithelium – can establish big gradient for $Na^+$ and water
   - proximal – reabsorption of large quantities of salt and water along small gradients
3. water and $Na^+$ reabsorption can be independent

# Function of collecting duct

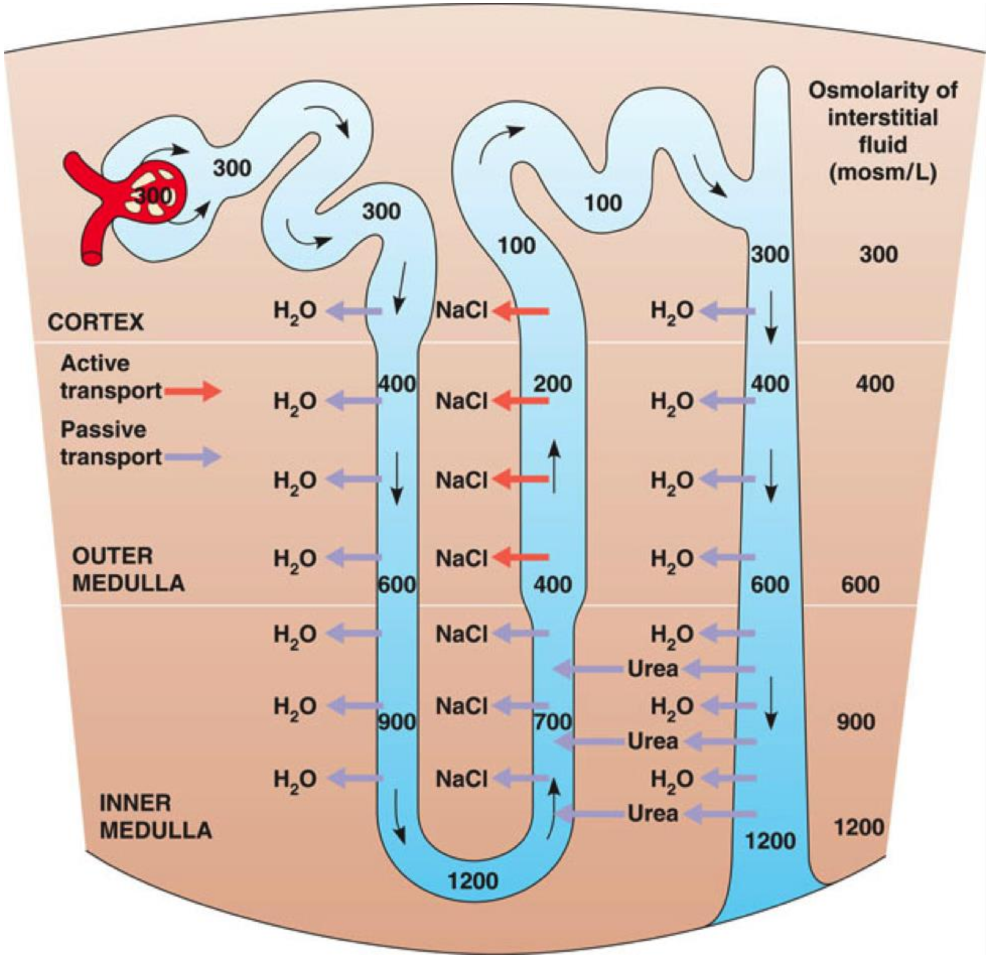
- regulation of osmolarity of final urine
- reabsorption of water according the body needs = facultative
- channels = aquaporins sensitive to ADH
- movement of water (all !) – passive - in osmotic gradient



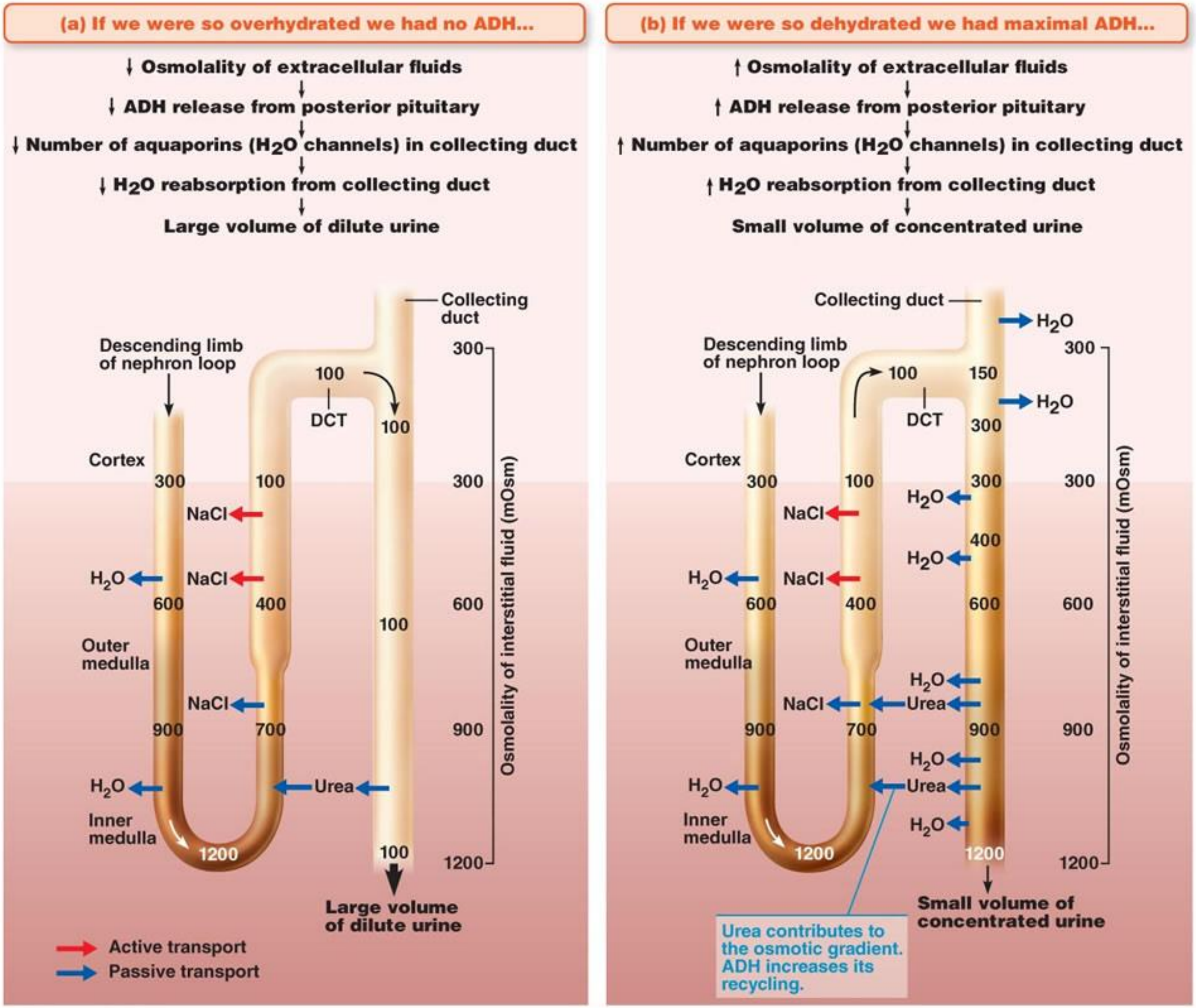


https://classconnection.s3.amazonaws.com/471/flashcards/4757471/jpg/figure_19_10_labeled-147E9D87D283EB8A76C.jpg

# Summary of osmolarities of tubular fluid in renal tubular system




http://socratic.org/questions/how-does-osmolarity-of-the-blood-maintain-homeostasis

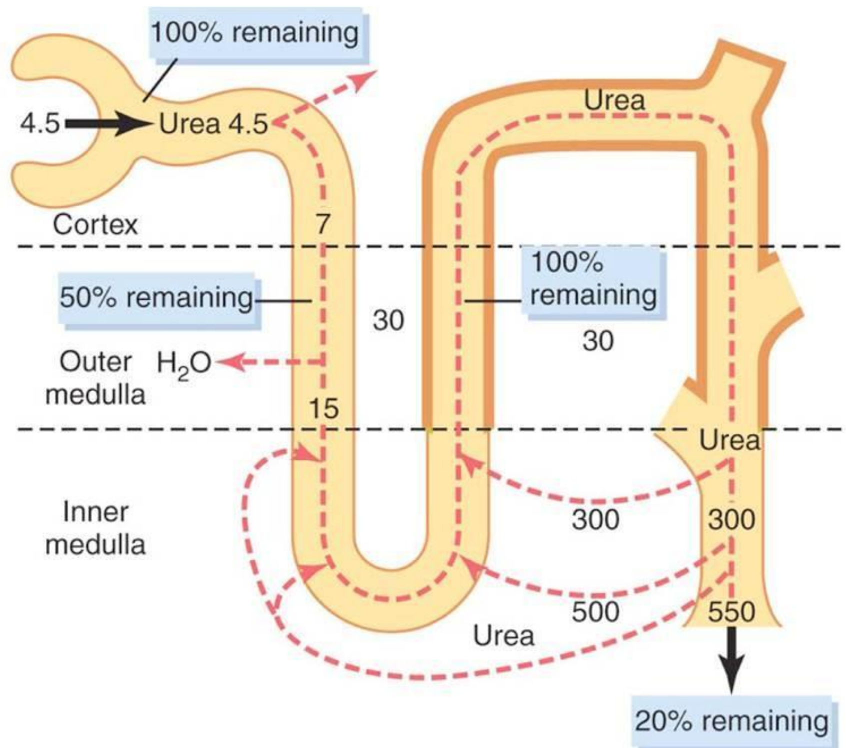





http://classes.midlandstech.edu/carterp/Courses/bio211/chap25/chap25.htm

# Urea

- osmotically active waste product of protein metabolism
- **contributes about 40% to medullary hyperosmolarity**
- reabsorption and secretion of urea - important role in the concentration of urine
- the amount of urea resorption in medullary collecting duct - regulated by ADH
- thick ascending limb, distal tubule, cortical collecting duct – impermeable for urea




Hall: Guyton and Hall Textbook of Medical Physiology, 12th Edition

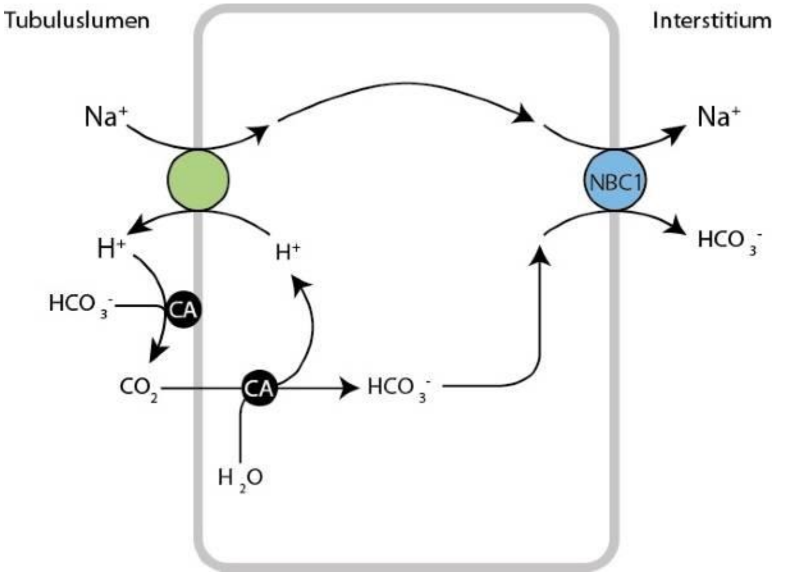

https://classconnection.s3.amazonaws.com/33/flashcards/602033/jpg/counter_current_multiplier1316766518015.jpg

# The role of kidneys in ABB

1. secretion of $H^+$
2. reabsorption of bicarbonates
    - reverse mode - secretion of bicarbonates
3. generation of new bicarbonates

# $H^+$ ions – secretion Reabsorption of bicarbonates

- in glomerulus – all $H^+$-ions filtrated
- in tubular system (proximal and distal tubule, cortical collecting duct) – secretion via 2 mechanisms
- removal of $H^+$ - important for reabsorption of bicarbonate from tubular fluid




http://pictures.doccheck.com/com/photo/23511-bicarbonate-resorption-in-the-proximal-tubule

# Generation of new bicarbonates

- via excretion of buffered $H^+$ = when $H^+$ is being secreted - new bicarbonate is added to the blood → mechanism dependent on the urinary buffer systems

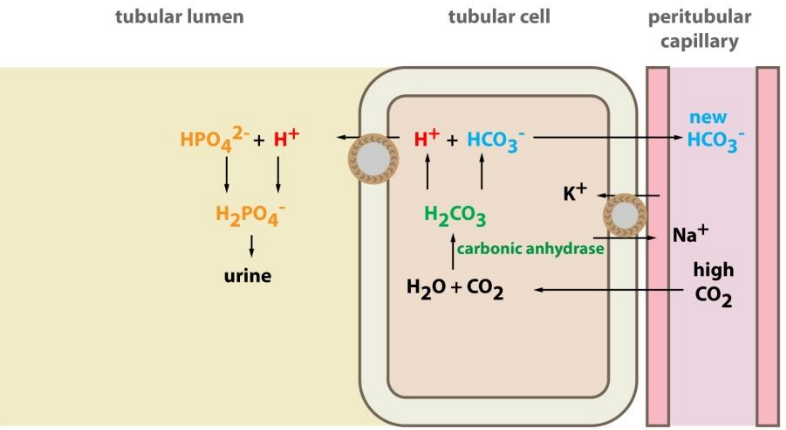
Urinary buffers:

- excretion of acids - allow higher amount of $H^+$ to be excreted
- regeneration of bicarbonate lost in ECF buffering
- 2 main: ammonia and phosphate

# Phosphate buffer

Limitation:

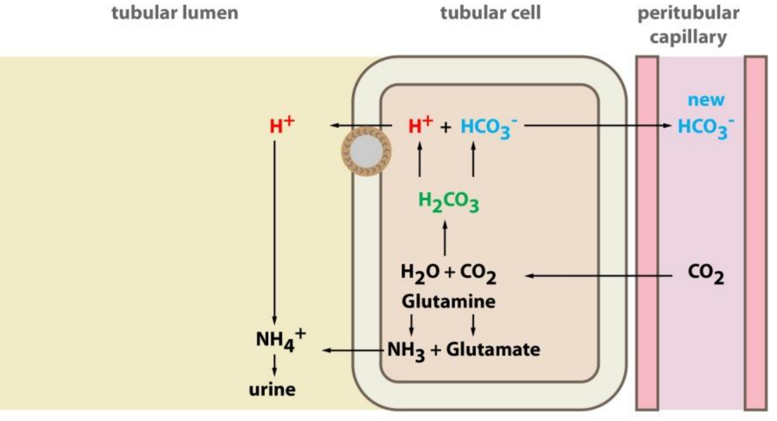
- no production of phosphates in the kidney
- phosphates are derived from diet only, filtration and following reabsorption of phosphate - ↓ availability of phosphates




http://fblt.cz/en/skripta/vii-vylucovaci-soustava-a-acidobazicka-rovnovaha/7-acidobazicka-rovnovaha/

# Ammonia buffer

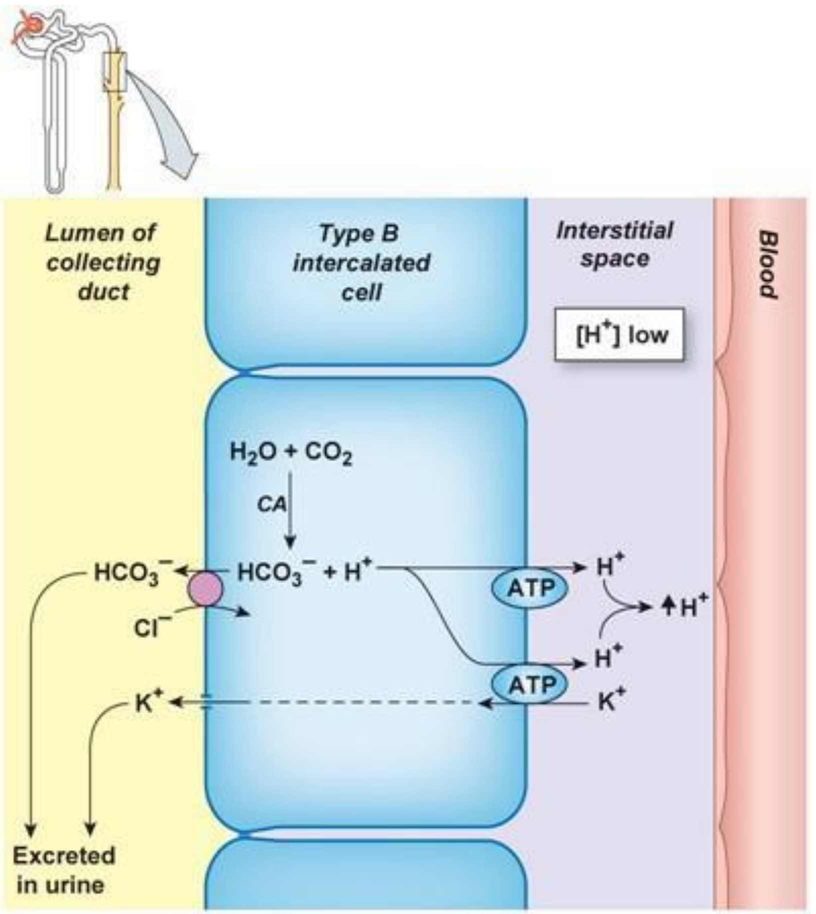
- ammonia – can be produced from glutamine if it is necessary
- 1 glutamine → deamination, oxidation, acidification → $2NH_4^+ + 2HCO_3^-$ in tubular cell
- $HCO_3^-$ → blood
  - $HCO_3^-/Cl^-$ - antiporter
- $NH_4^+$ → tubular fluid
  - $Na/NH_4$-antiporter (proximal tubule)
  - as diffusion of $NH_3$ (collecting duct)




http://fblt.cz/en/skripta/vii-vylucovaci-soustava-a-acidobazicka-rovnovaha/7-acidobazicka-rovnovaha/

# Bicarbonate secretion

- in alkalosis
- type B intercalated cells
  - secrete bicarbonate
  - gain $H^+$




(b) Type B intercalated cell function in alkalosis.

http://slideplayer.com/slide/2780389/

# REGULATION OF THE VOLUME AND OSMOLARITY OF URINE

# Extracellular fluid volume

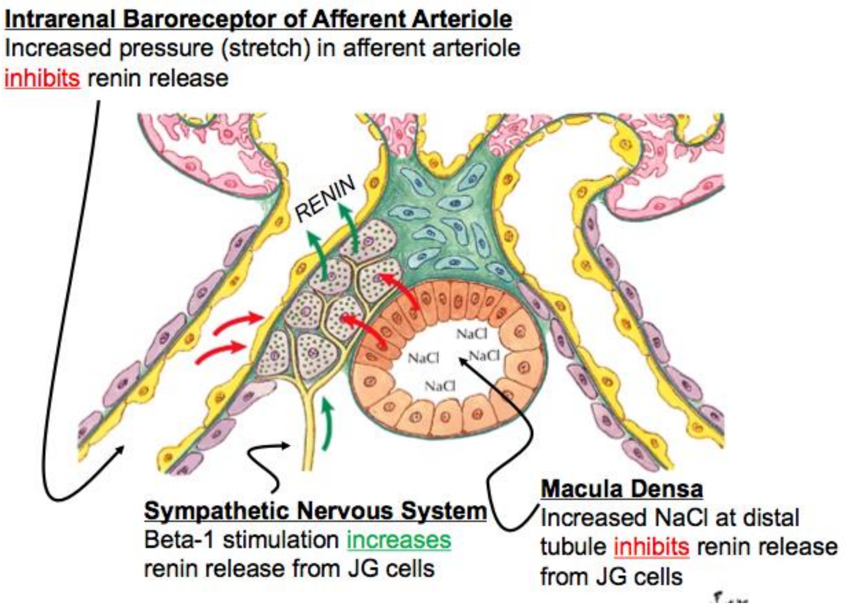
- regulation of ECF volume ↔ regulation of $Na^+$ ↔ regulation of BP
- receptors:
  - baroreceptors, volumoreceptors
- effectors:
  - RAAS
  - renal sympathetic nerve
  - hormones - natriuretic peptides (ANP, BNP), ADH
- response:
  - changes in renal $Na^+$ excretion, water reabsorption

# Renin-angiotensin-aldosterone system

Renin - myoendocrine (myoepithelial, granular) cells of vas afferens

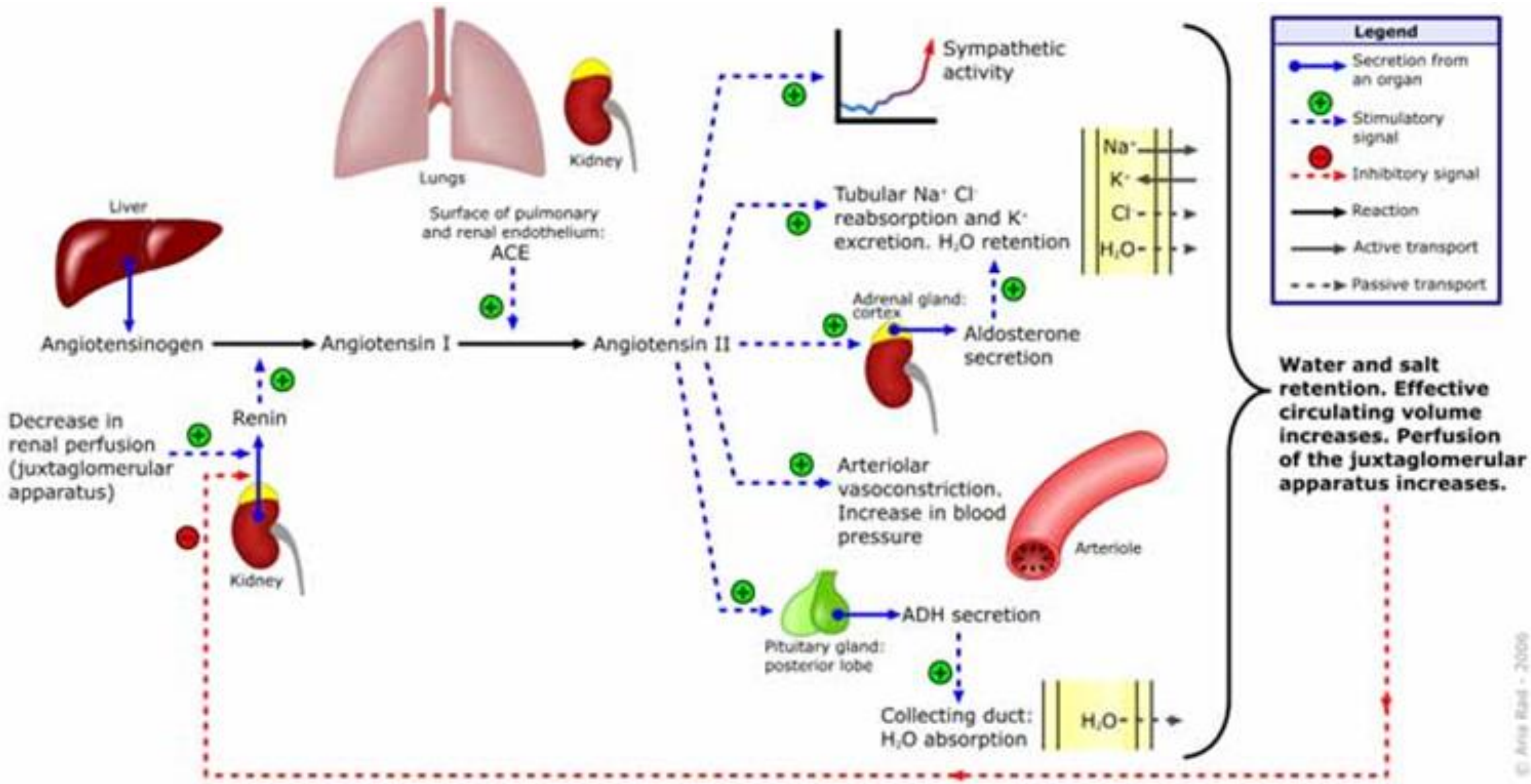
Stimuli for renin release:

- macula densa mechanism - reduced NaCl in the distal tubule
- sympathetic stimulation - β-adreneroceptor stimulation mediated via the formation of cAMP
- hormones, neurotransmitters that can increase cAMP level
- lower BP in the afferent arterioles




https://classconnection.s3.amazonaws.com/686/flashcards/4143686/png/picture_13-147D760DE3C38116714.png

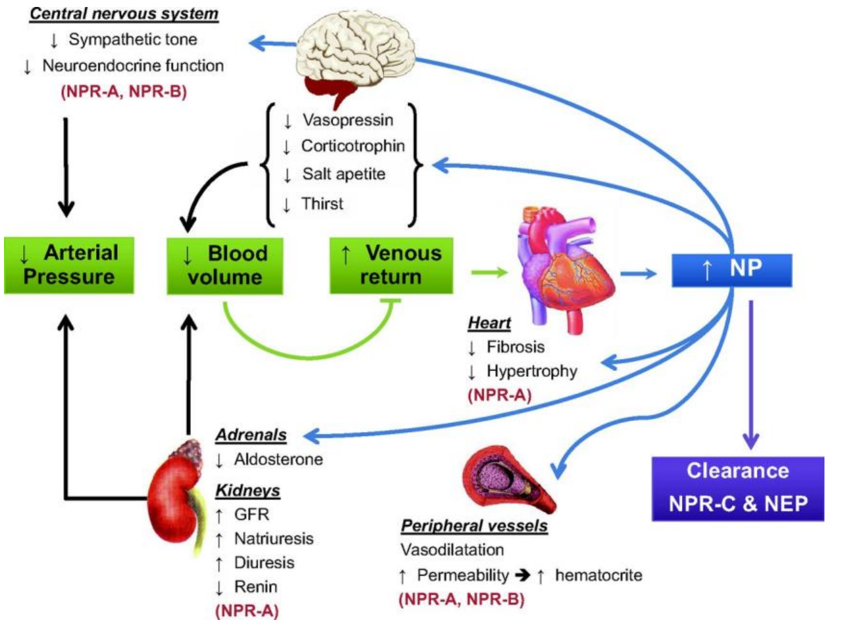
# RAAS




http://www.wikipremed.com/image.php?img=040709_68zzzz386400_Renin-angiotensin-aldosterone_system_68.jpg&image_id=386400

# Natriuretic peptides

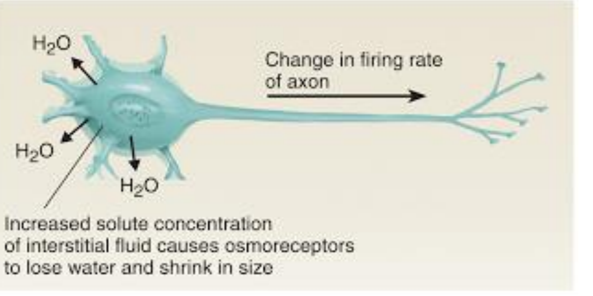
- ANP, BNP, …
- inhibit $Na^+$ reabsorption
- ↑vascular permeability
- vasodilation of arterioles and venules
- inhibition of renin and aldosterone secretion

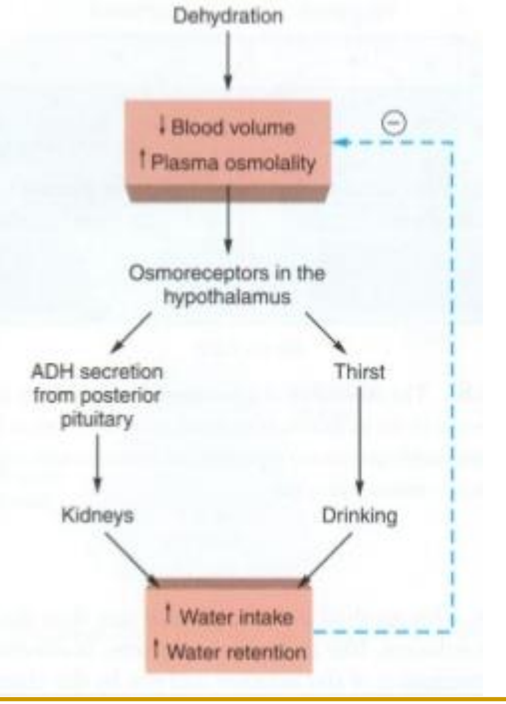



http://ajpheart.physiology.org/content/304/3/H358

# Renal regulation of blood osmolarity

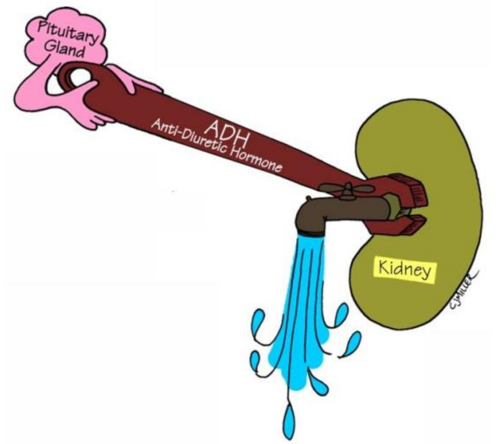
- receptors:
  - osmoreceptors in hypothalamus - respond to 1 to 2% changes in tonicity
- centre - hypothalamus
- responses:
  - ADH → water output
  - thirst → voluntary activity → water input
- response:
  - urine osmolarity
  - water intake




http://lifeafterbeingaleedsstudent.blogspot.sk/2012/06/internal-regulation.html
http://www.slideshare.net/AHS_Physio/1st-lecture-drhameed

# Antidiuretic hormone




Stimuli:

- increase of ADH release
  - ↑osmolarity, ↓blood volume, ↓blood pressure (osmoreceptors, volumoreceptors, baroreceptors)
- decrease of ADH
  - ↓osmolarity, ↑blood volume, ↑blood pressure

Responses:

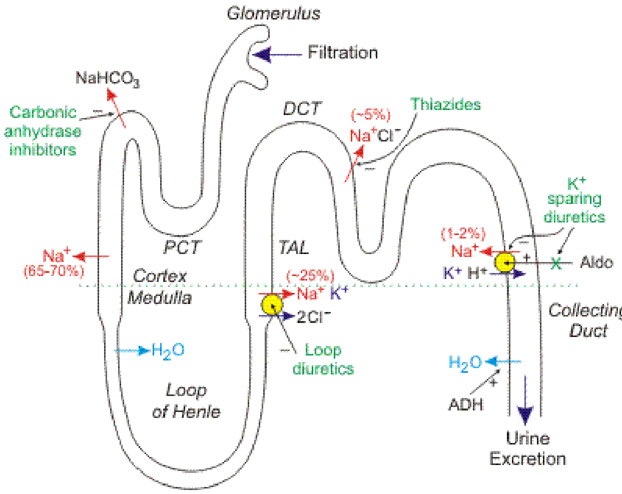
- absence of ADH → large volumes of hypotonic urine = up to 20 liters/day (diabetes insipidus)
- presence of ADH
- vessels

http://28.media.tumblr.com/tumblr_lyq19oEgTF1qkqueuo1_1280.jpg

- primary urine – 180 L
- almost 90% - obligatory reabsorption = 162 L
- about 10% = 18 L – facultative – requires ADH
- obligatory final urine volume – about 0.5 L

- necessary excretion - 600 mOsm of solutes/day
- isotonic urine – excretion of 2L $H_2O$/day
- ability to concentrate urine 4x

# Sodium handling




reabsorption - 99% of filtered sodium

Apical membranes:

1. proximal tubule:
   - sodium co-transporters - glucose, phosphate, aminoacids
   - sodium antiporter - hydrogen ion
2. ascending limb of Henle's loop
   - Na, 2 Cl, K – co-transporter

- distal tubule:
  - Na, Cl – co-transporter
  - reabsorption of Na in exchange for H and K (aldosterone sensitive)

Basolateral membranes: Na,K-ATPases

http://www.cvpharmacology.com/diuretic/diuretics

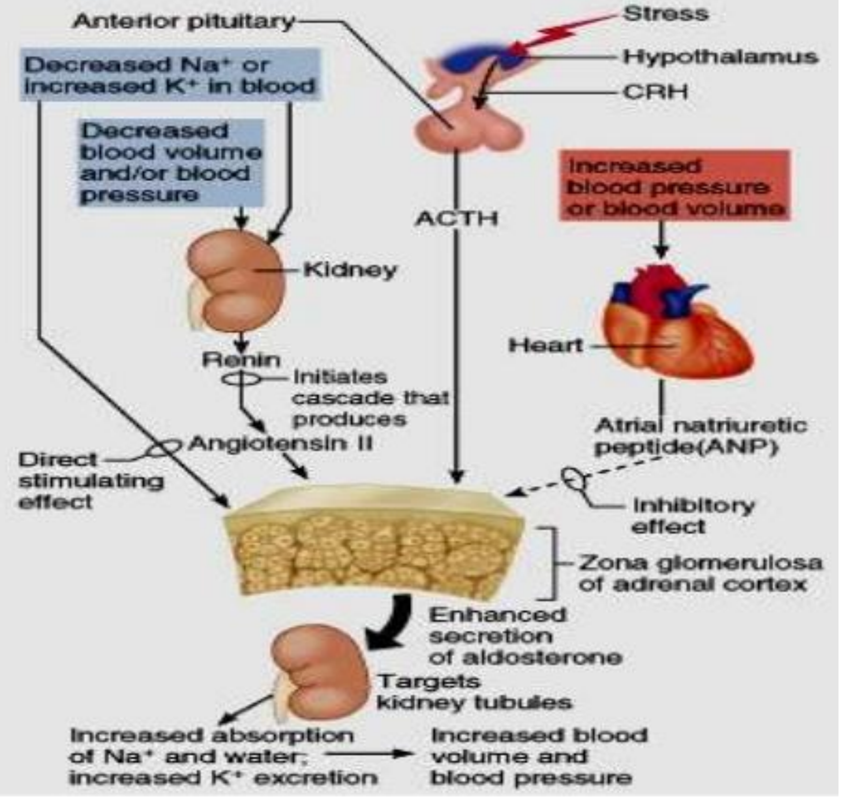
# Aldosterone

secretion stimulated by:

- angiotensin II, adrenocorticotropic hormone, high potassium, sodium deficiency

inhibited by:

- ANP, high sodium concentration, potassium deficiency



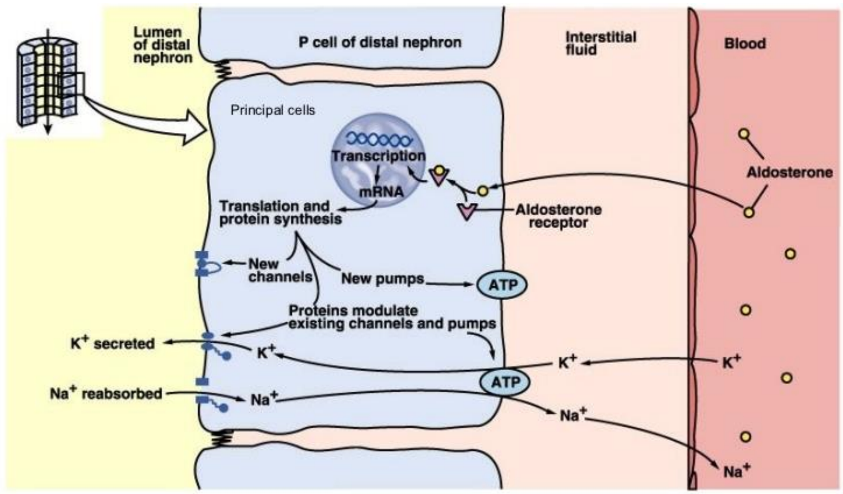

http://www.slideshare.net/rosesrred90/anaesthesia-and-disorders-of-adrenal-cortex

# Aldosterone

Effects:

1. increase the luminal plasma membrane Na and K permeability
2. increase the number and activity of basolateral plasma membrane Na/K-ATPase pumps
3. increase cell metabolism

all of these changes → increased K secretion




http://www.slideshare.net/mvraveendrambbs/body-fluid-and-electrolyte-balance

# Potassium handling

Proximal tubule:

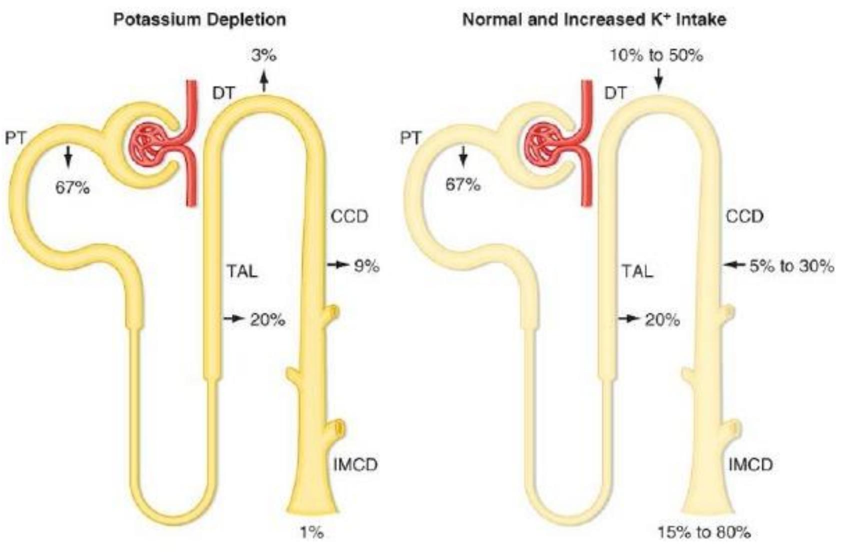
- passive paracelllular (and transcellular)

Thick ascending limb of Henle

- $Na^+$-$K^+$-$2Cl^-$ co-transporter
- $K^+$ exit through a conductive pathway or in cotransport with $Cl^-$

Distal tubule + cortical collecting duct

- aldosterone → changes in $K^+$ secretion
- α-intercalated cell - $H^+$-$K^+$-ATPase - reabsorption of $K^+$




http://www.slideshare.net/fitiwi/potassium-homeostasis-and-its-renal-handling

# Calcium handling

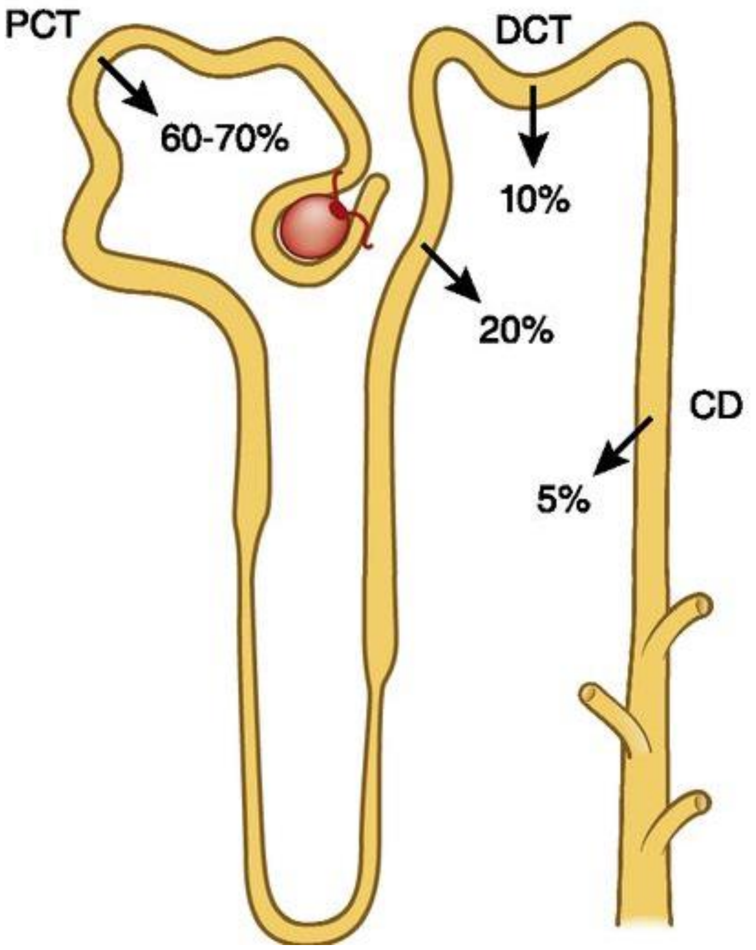
- ultrafiltrate - ionized and complexed Ca (phosphates, citrates)
- 98-99% - reabsorption

Proximal tubule + thick ascending limb of the loop of Henle

- passive paracellular transport in concentration gradient
- active - small amounts

Distal tubule + cortical collecting duct

- transcellular
- parathyroid hormone dependent calcium resorption




http://cjasn.asnjournals.org/content/early/2014/11/30/CJN.09750913.full

# The final urine

- final waste product secreted by the kidneys
- composition:
  - water: 91 - 96%
  - urea: 2%
  - creatinine
  - uric acid
  - inorganic salts - chloride, sodium, potassium,…ions
  - ammonia
  - other substances (urochrome,…)

# The final urine

- transparent liquid
- sterile
- pH about 6 (4.5 - 8)
- volume 1 - 2 L/day
  - polyuria: > 2.5 L/day
  - oliguria: < 400 mL/day
  - anuria: < 100 mL/day
- specific gravity 1001 - 1035 $kg/m^3$

https://www.boundless.com/physiology/textbooks/boundless-anatomy-and-physiology-textbook/the-urinary-system-25/urine-241/chemical-composition-of-urine-1177-2149/

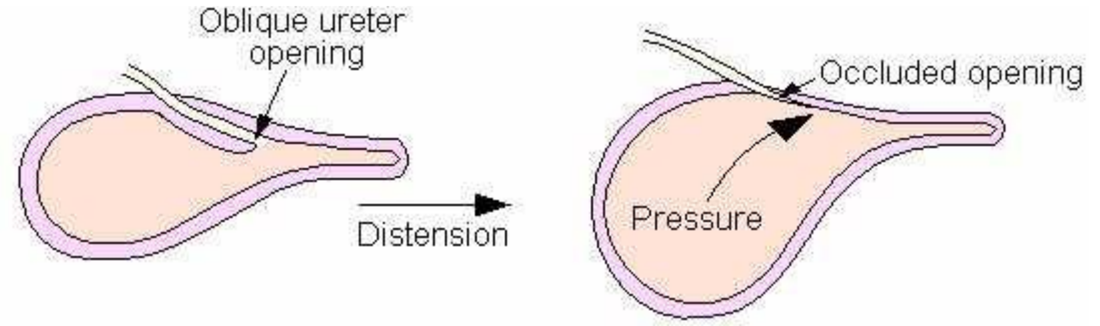
# Ureters

- unidirectional transport of urine from the renal pelvis toward the bladder
- protection of the renal parenchyma from distally generated backflow and back pressure
- 20 - 25 cm long
- smooth muscle in the walls

# Peristalsis in ureters

- initiation by spontaneous activity of renal pelvis pacemaker cells → conduction of electrical and mechanical activities to inactive distal regions
- contraction wave propelling urine distally in boluses = urinary spindles → small amount of urine are transported into the bladder every 1 – 5 times per minute
- regulated by the myogenic mechanisms + neurogenic factors
  - increase of cytoplasmic free calcium concentration = the principal mechanism in smooth muscle contraction
  - efferent and afferent innervation - cholinergic, adrenergic and non-adrenergic non-cholinergic components – especially in the lower ureter

- oblique passage through the urinary bladder wall = prevention of the urine backflow into the ureter when the bladder contracts
- anti-reflux mechanism
- the intravesical portion length
  - at birth - 0.5 cm
  - in adulthood - 1.5 to 2.6 cm




http://137.222.110.150/Calnet/vetURT4/page2.htm

# Urinary bladder

2 main functions:

1. reservoir for urine
2. emptying - removal of urine

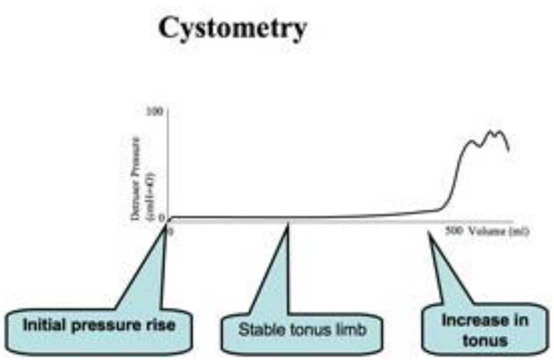
- in adult - 300-500 ml
  - expected capacity = [30 + (age in years x 30)] ml

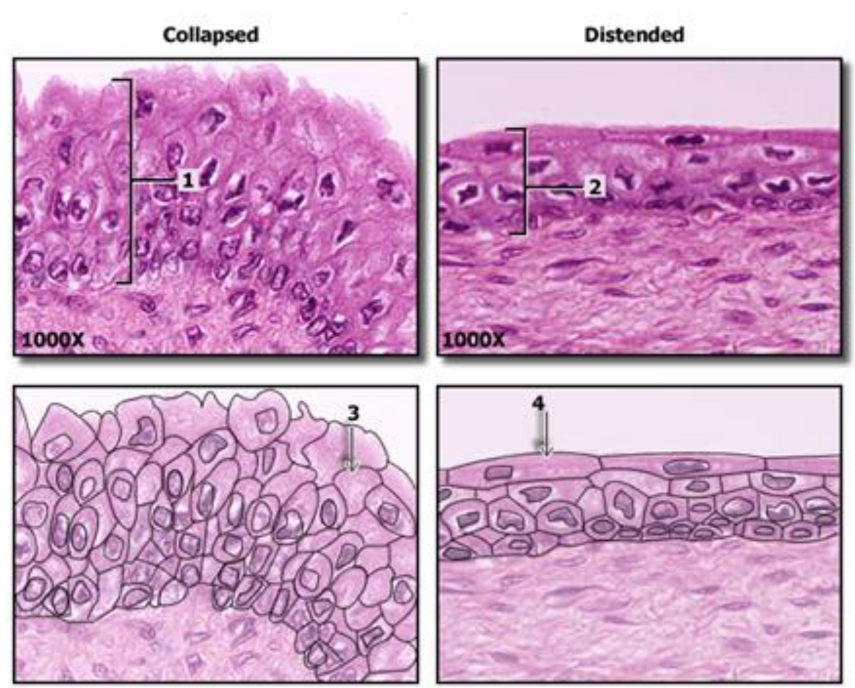
Muscles:

- smooth - in the walls – m.detrusor + involuntary internal sphincter
  - innervation by parasympathetic pelvic nerves + sympathetic hypogastric nerves
- skeletal – voluntary external sphincter
  - innervation by somatic nerves via pudendal nerves

# Filling of the urinary bladder

- tone is adjusted to its capacity (transitional epithelium = urothelium)

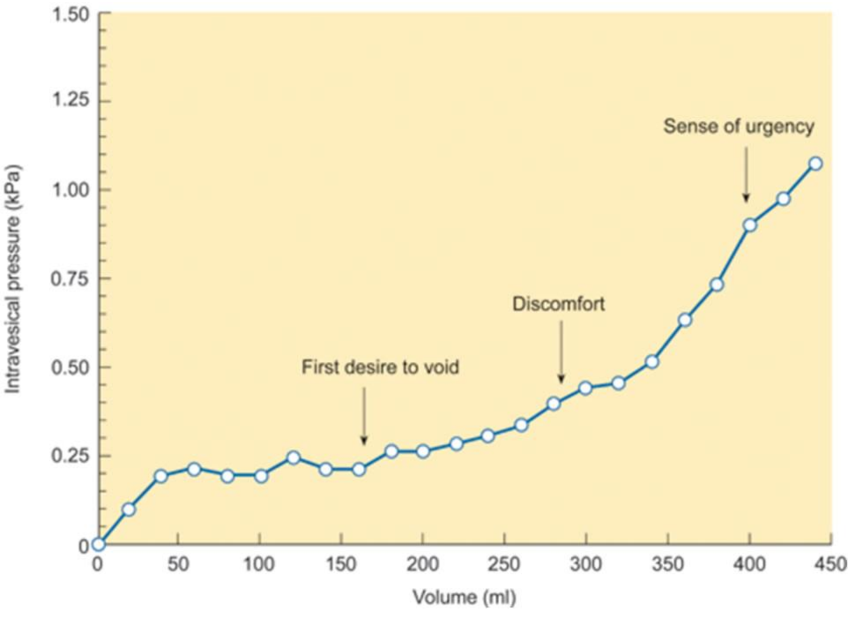



http://ctle.hccs.edu/biologylabs/AP1/03Tissues/003EpithelialIndex.html
http://ngbladder.org/diagnoses/3.asp

# Filling of the urinary bladder

- sensation at about 100 - 150 mL
- desire to void – 150 - 250 mL
- sensation of full bladder – 350 - 400 mL – corresponds to 10 cm $H_2O$
- further increase of volume – steep increase of pressure (reflex contraction of detrusor)
- 600 - 700 mL – pain + loss of control

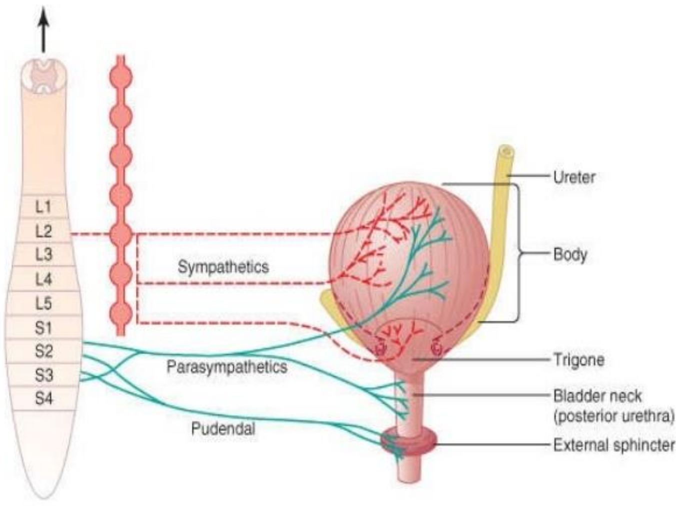



http://humanphysiology.academy/Neurosciences%202015/Chapter%202/P.2.4p%20ANS%20and%20Bladder.html

# Urination (micturition)

- periodic emptying of the urinary bladder
- cooperation of autonomic and somatic nerve pathways + higher centers
- basic reflex
  - receptors – mechano = stretch receptors in the wall
  - centre – sacral spinal cord (in infants) + modification by centres in the pons and cortex (in adults - facilitation, inhibition)
  - response – contraction of detrusor + relaxation of sphincters

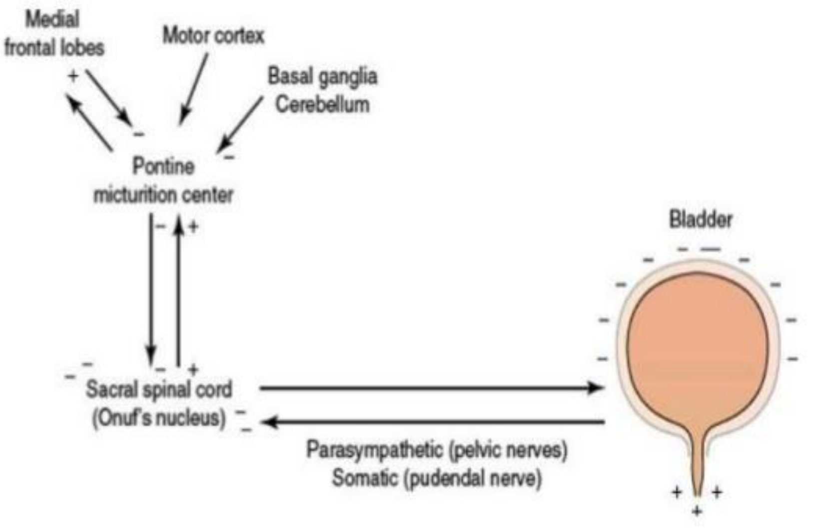
**Bladder Innervation**




http://www.slideshare.net/SMS_2015/micturation-reflex-by-dr-irum

# Higher centres

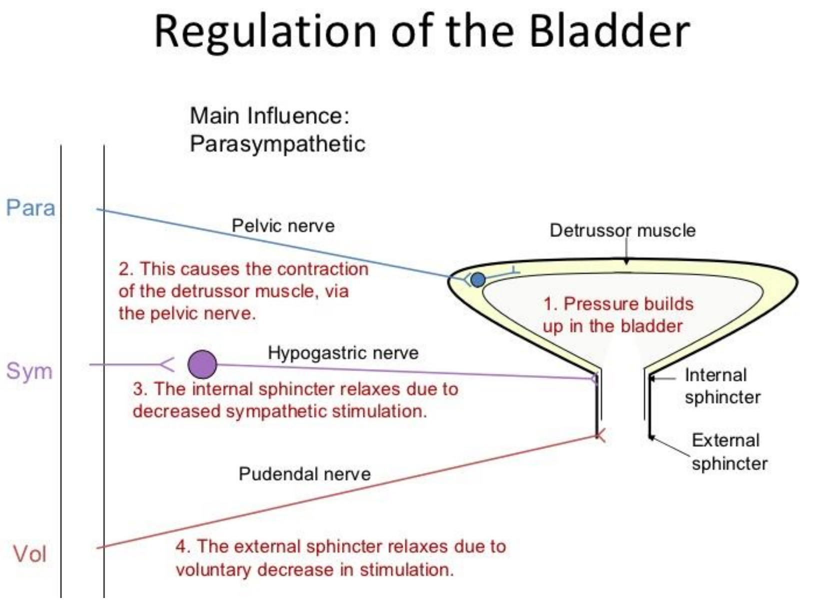
- cortical (medial frontal lobe, motor cortex) – sends inhibitory signals to the pons
- pontine – coordinates the urethral sphincter relaxation and detrusor contraction




Neural pathway for storage of urine (+ = excitatory; − = inhibitory).

# Urination (micturition)

- other mechanisms
  - urine flow through the urethra – further contraction of detrusor
  - increased parasympathetic activity – stimulation of muscle responses
  - sympathetic activity – not essential (prevent reflux of semen into the bladder during ejaculation)
  - relaxation of perineal and levator ani muscles
  - inspiration + contraction of abdominal muscles → increase of intraabdominal pressure




http://www.slideshare.net/SMS_2015/micturation-reflex-by-dr-irum

# Urethra

- tube conveying urine from the urinary bladder to the outside of the body
- in males – passageway for cells and secretions from reproductive organs

# Regulation of acid-base balance

- acid-base balance = inputs and outputs of acids and bases are equal → isohydria

- alkalemia, acidemia – about $H^+$ concentration
- acidosis, alkalosis – about pH value

- commonly – ECF (arterial blood): pH = 7.36-7.44
- IC pH – about 7 (2.5 fold higher $H^+$ concentration in the cells + concentration gradient directed out of the cells → lower venous and interstitial pH – about 7.35)

- acid-base balance parameters are calculated for plasma which pH is alkaline (alkaline pH - 7.2 = acidosis)

- sources of $H^+$ ions – food (diet generates an excess of protons), metabolism
  - acids – 2 groups:
    - carbonic acid – $H_2CO_3$ – in equilibrium with volatile gas $CO_2$ – concentration set by respiratory activity
    - non-carbonic (nonvolatile, fixed) acids – buffered + excreted by the kidneys
  - metabolism
    - source of $CO_2$
    - incomplete (C, F) – produces nonvolatile acids (lactic, acetoacetic, β-hydroxybutyric acids
    - protein metabolism – $H_2SO_4$, HCl, and $H_3PO_4$

# Diet – acid gain

- overall effect – depends on metabolism
- meat – protein oxidation – production of acids
- basic anions – citrate, lactate, acetate – oxidized to $CO_2$ and $H_2O$
  - orange juice (pH = 3-4) – final alkalinizing effect
  - cranberry juice – contains benzoic acid - acidifying effect

# Buffering mechanisms

1. chemical buffers – blood, kidneys – minimize change in pH without removal acid or base from the body

2. respiratory response – begins in min, maximum about 12 – 24 hours
   - expiration of $CO_2$
   - powerful – adjusting ventilation
   - BUT – works only with volatile acids

3. renal response – slower: full renal compensation may take 1 – 3 days

# Chemical buffers

- bind or release $H^+$ (pairs of weak acid and its salt)
- rapid in ECF – in minutes, in cells or bones – in hours

- $HCO_3^-/H_2CO_3$ – main in ECF (ratio 20:1)
- $H_2PO_4^-/HPO_4^{2-}$ – important in ICF and bones (phosphates – low in ECF, lower pH in the cells – closer to $pK_a$ of phosphate)
- proteins – amphoteric (blood – albumins and globulins, intracellular proteins, hemoglobin)
  - amino group accepts $H^+$, carboxyl group gives $H^+$

# Renal regulation of pH

- the most effective regulator

- excess acid – remove $H^+$ (more common)
- excess base – remove $HCO_3^-$
- the lowest pH of urine – 4.5
- daily urine output – 1-2 L → most of $H^+$ ions combine with urinary buffers

- ammonia $NH_3/NH_4^+$ (high $pK_A$ – mainly $NH_4^+$ form)
- titratable bases – phosphate, creatinine and other bases
  - measured by amount of strong base needed to get urine pH to 7.4

# Urinary acidification

- glomerular ultrafiltrate – same pH as plasma

Proximal tubule

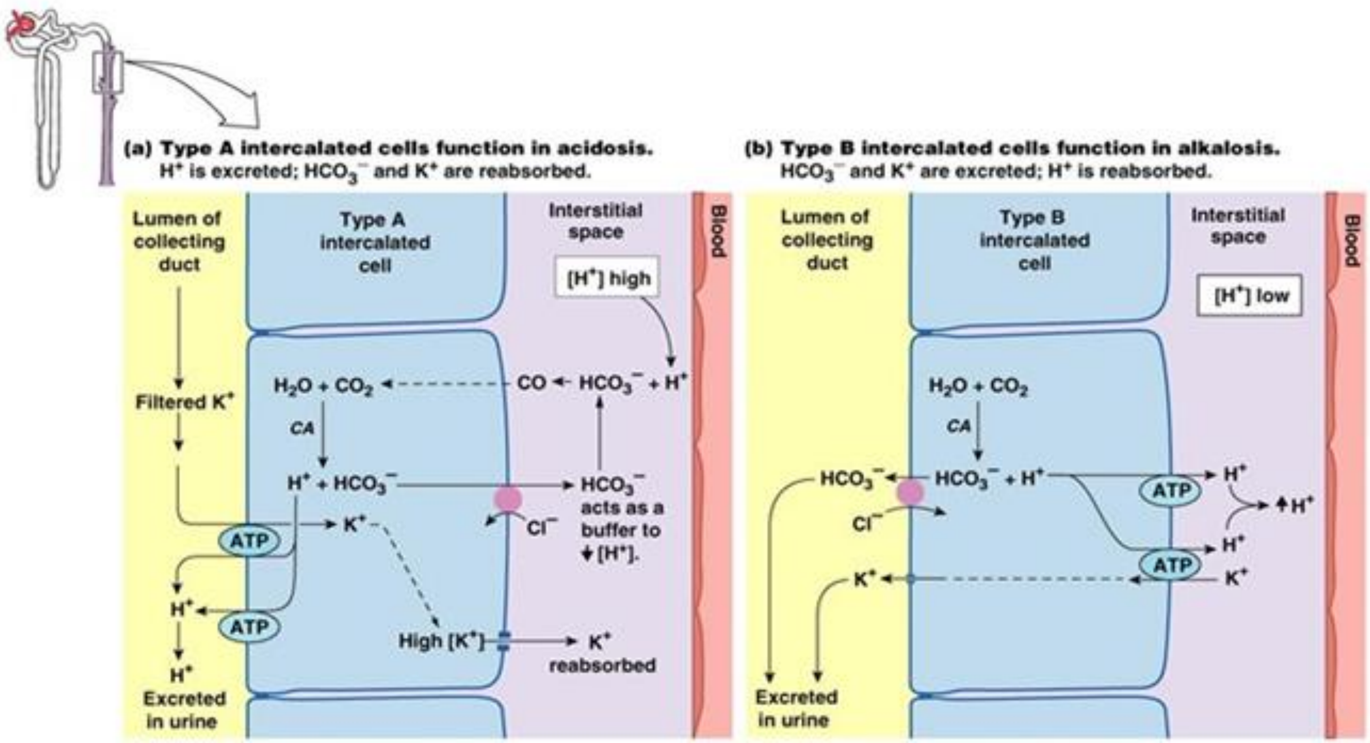
- 2/3 – $Na^+/H^+$ antiporter
- 1/3 – $H^+$-ATPase
- at the end pH about 6.7 – $H^+$ buffering + ↑permeability of the epithelium
- reabsorption of bicarbonates

Distal tubule – less extensive secretion

- electrogenic - $H^+$-ATPase
- electroneutral - $H^+/K^+$- ATPase
- tight epithelium – steeper urine-to-blood $H^+$ gradient
- reabsorption of small amounts of bicarbonates

Cortical parts of collecting ducts

- acid-secreting α-intercalated cells (type A)
  - luminal – $H^+$-ATPase, $H^+/K^+$- ATPase
  - basolateral – $Cl^-/HCO_3^-$ exchanger
- bicarbonate-secreting β-intercalated cells (type B) – has opposite polarity




http://slideplayer.com/slide/2776246/

# Factors influencing urine acidification

1. intracellular pH - tubular cells
   - ↓pH → ↑$H^+$ secretion
2. arterial $pCO_2$
   - increased → ↑$H^+$ formation → ↑$H^+$ secretion
   - decreased → ↓$H^+$ secretion → ↓reabsorption of filtered bicarbonates
3. carbonic anhydrase activity
   - CA – responsible for hydration of $CO_2$ in the cells and dehydration of $H_2CO_3$ in proximal tubule lumen
   - inhibition of activity – loss of filtered bicarbonates → ↓pH
4. sodium reabsorption
   - higher – more negative intraluminal potential – higher excretion of $H^+$
5. plasma potassium concentration
   - lower – movement of $K^+$ out the cells followed by inflow of $H^+$ → ↓pH in tubular cell → ↑$H^+$ secretion
   - ↓ K in the tubular cell → ↑ammonia synthesis → ↑reabsorption of bicarbonates → ↑generation of new bicarbonates → metabolic alkalosis

6. aldosterone – stimulation of $H^+$ secretion
   - direct stimulation of proton pump in cells
   - via increasing of $Na^+$ reabsorption → more negative intraluminal potential →↑$H^+$ secretion by electrogenic $H^+$-ATPase
   - via promotion of K+ secretion → hypokalemia →↑$H^+$ secretion
   - hyperaldosteronism → alkalosis
7. pH gradient
   - $H^+$ secretion – gradient limited (plasma pH=7.4 – urine pH=4.5)

# Regulation of intracellular pH

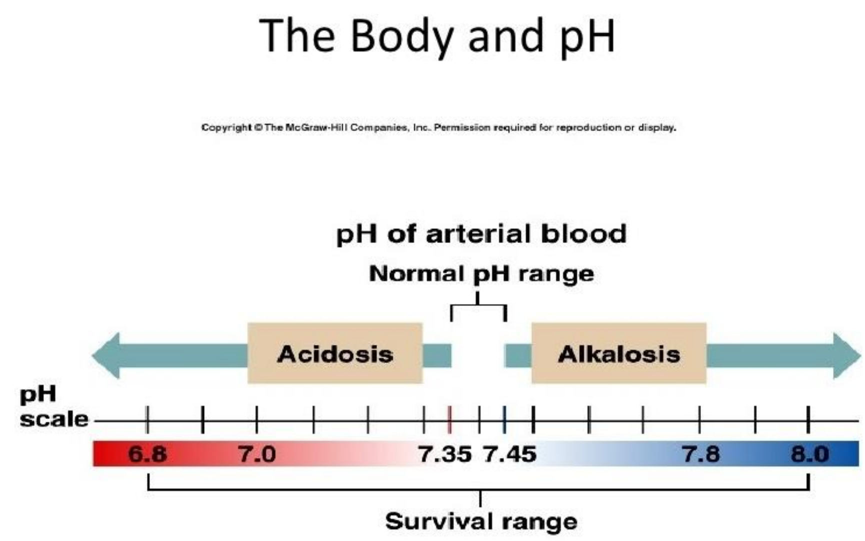
- via maintenance of ECF pH
- almost all the cells - $Na^+/H^+$ antiporter (several isoforms – tissue dependent)
- in some cells – bicarbonate transport systems
- protein and phosphate buffers

# Disturbances of acid-base balance

Normal pH – 7.4 ± 0.4 (0.5)

- lower – acidosis, higher – alkalosis
- too much or too little bicarbonates – metabolic
- too much or too little $CO_2$ – respiratory

- pH range for survival – 6.8-8



# Respiratory acidosis

- abnormal $CO_2$ accumulation
- hypoventilation, breathing of $CO_2$-enriched air

Compensation:

- bicarbonate level do not fall
- chemical buffering – intracellular buffers
- renal responses
  - acute respiratory acidosis - excess $CO_2$ – CA reaction toward $HCO_3^-$ production
  - chronic respiratory acidosis - increase of $HCO_3^-$ reabsorption
    - proximal - ↑ apical $Na^+/H^+$ exchange + basolateral $Na^+/3HCO_3^-$ co-transport
    - distal – more $H^+$-ATPases and $HCO_3^-/Cl^-$ exchangers

# Metabolic acidosis

Cause:

- direct – loos of $HCO_3^-$ (via GIT, kidneys)
- indirect - accumulation of acid (lactic, ketones)

Respiratory response – increase of ventilation

Renal response:

- low concentration of bicarbonates in plasma → in ultrafiltrate
- direct stimulation of glutamine metabolism in proximal tubule
  - $NH_4$ for urinary secretion
  - bicarbonate generation
- increase of $H^+$ secretion and $HCO_3^-$ reabsorption
  - proximal - ↑ apical $Na^+/H^+$ exchange + basolateral $Na^+/3HCO_3^-$ co-transport
  - distal – more $H^+$-ATPases and $HCO_3^-/Cl^-$ exchangers
- direct stimulation of renin release → angiotensin II → aldosterone → increase of $H^+$-ATPase activity in type A intercalated cells

# Respiratory alkalosis

Cause:

- increase of ventilation (fever, hypoxemia, brain disease, side drug effects, high altitudes…)

Compensation:

- buffering - intracellular
- renal – decreased acid secretion + decreased bicarbonate reabsorption

# Metabolic alkalosis

Cause:

- loss of acid (via GIT, kidney)
- addition of bicarbonates (lactate, citrate, acetate)

Consequence: high bicarbonate → inhibition of ammoniagenesis

Renal response:

- depend on chloride ions: low chlorides → promotion of metabolic alkalosis
  - collecting duct – active $H^+$ secretion is associated with passive co-transport of $Cl^-$
  - type B intercalated cell – secretion of bicarbonate in exchange for chloride
- chloride responsive vs. chloride resistant

Respiratory response

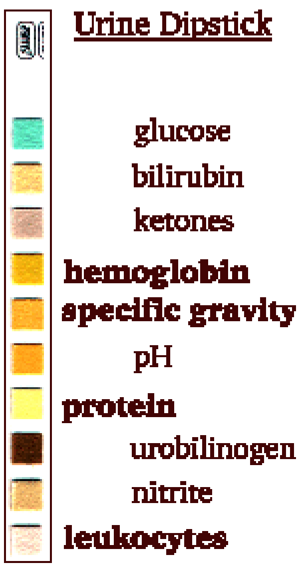
  - limited by hypoxia

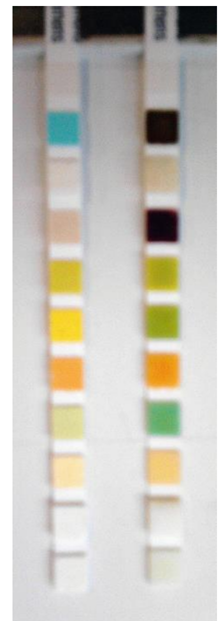
# Tests of renal function

1. urinalysis
   - 24-hour urine sample
   - concentration, dilution tests
2. blood, serum - creatinine, blood urea nitrogen
3. GFR - creatinine clearance
4. imaging techniques
5. biopsy

# Urinalysis

- semiquantitative - using dipsticks (diagnostic strips)



glucose (+++)
bilirubin (+)
ketones (++++)
hemoglobin (+)
specific gravity (1.025)
pH (5)
proteins (+)
urobilinogen (-)
nitrites (-)
leukocytes (-)

http://pro2services.com/lectures/Spring/RenalTests/renaltests.htm
https://en.wikipedia.org/wiki/Urine_test_strip

# Urinalysis

- appearance (blood, leucocytes)
- volume - normal, oliguria, anuria, polyuria
- determination of specific gravity or osmolality
- microscopic examination of the urine sediment for cells, casts and crystals

| Test | Normal Results |
|---|---|
| appearance | clear and straw colored or yellow |
| volume | 0.8 - 1.8 L/24 hours |
| protein | undetectable (< 150 mg/24 hours) |
| hemoglobin | undetectable |
| microscopic examination | few leukocytes<br>absence of red cells<br>presence of hyaline casts is normal |

| | random | 24 hr. | after 12 hr. fluid fast | after fluid load |
|---|---|---|---|---|
| specific gravity (or osmol-ality) | 1.002 - 1.03 | 1.015 - 1.025 | > 1.025<br>900 - 1250 mOsM | < 1.005<br>< 100 mOsM |

http://pro2services.com/lectures/Spring/RenalTests/renaltests.htm

# Creatinine clearance

- the volume of blood plasma that is cleared of creatinine per unit time (usually 1 min)
- creatinine - only filtered (the same - inulin)
- clinically useful estimation of GFR (amount of plasma filtered by the glomerulus per unit of time)
- is calculated from measurements of serum creatinine concentration (Crs), urine creatinine concentration (Cru), and the urine volume (V) collected over a time period (t, in minutes)

$$\text{Creatinine Clearance} = (Cru \times V/t) / Crs$$