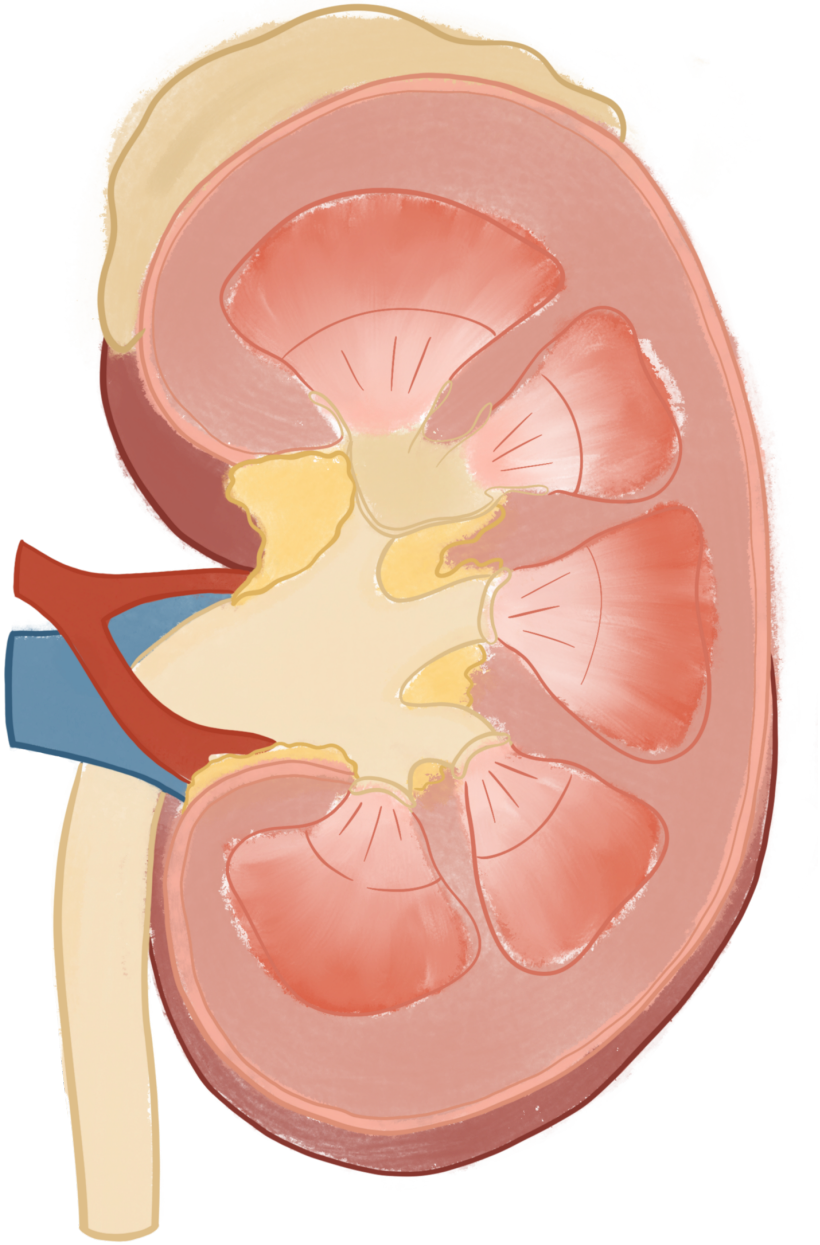

RENAL PHYSIOLOGY

Amalie Misund • Ane Mari Hole • Ida Marie Lisle

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Authors and illustrators
Amalie Misund
Ane Mari Hole
Ida Marie Lisle

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Section 1 – Anatomy of the Kidney

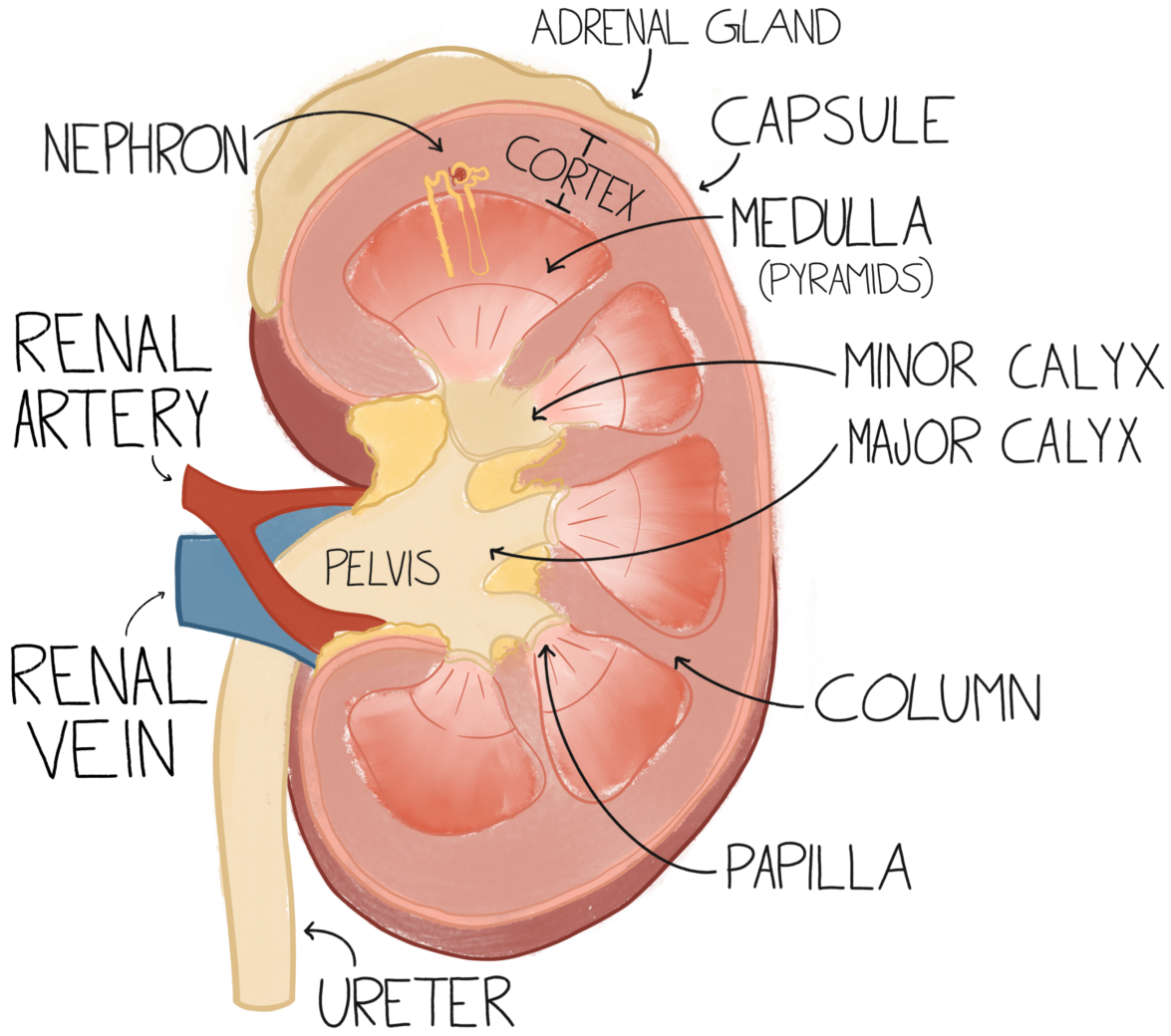
1.0 – The Large Structures of the Kidney

I. The cortex

- Renal corpuscles
- Proximal and distal convoluted tubule
- Cortical collecting duct
- Blood vessels

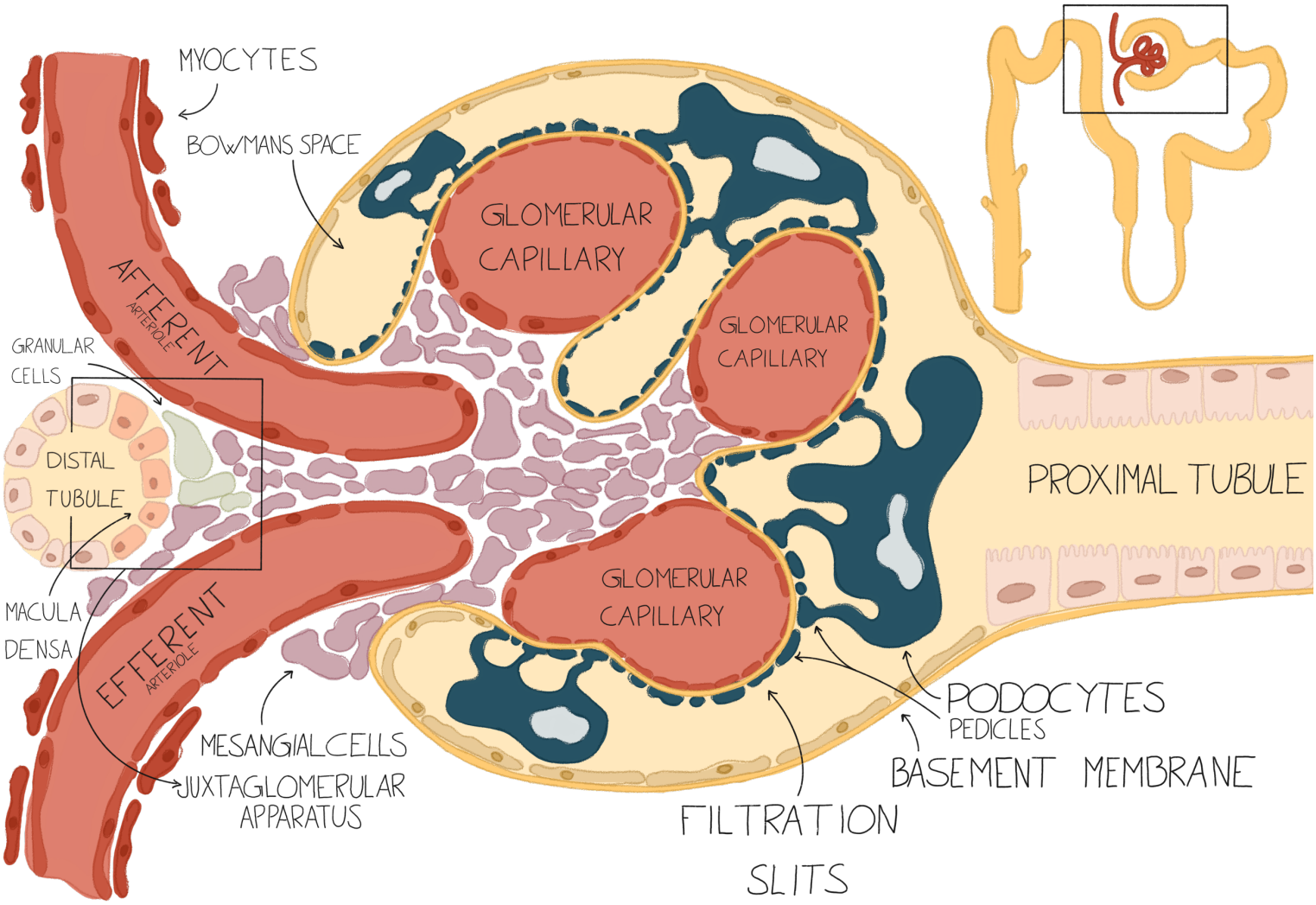
II. The medulla

- Separated into different sections called pyramids
- Contains the loop of Henle with its blood supply, and the collecting ducts



III. The renal corpuscle

- Consists of the glomerulus and the Bowman capsule
- Where filtration of the blood occurs

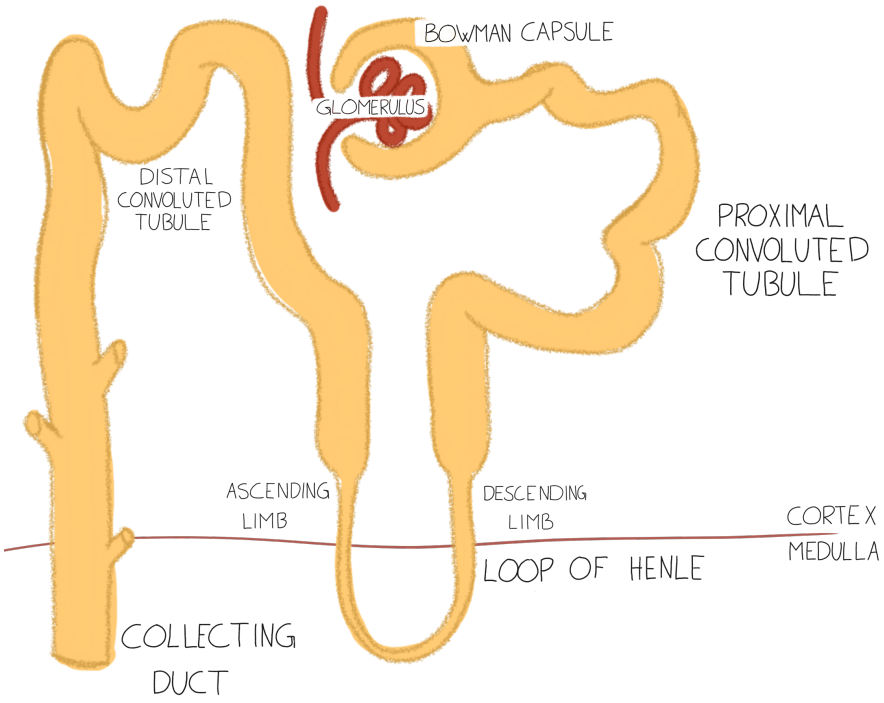


1.1 – The Nephron

Corticomedullary nephrons

Glomeruli located in the outer cortex

Short loops of Henle

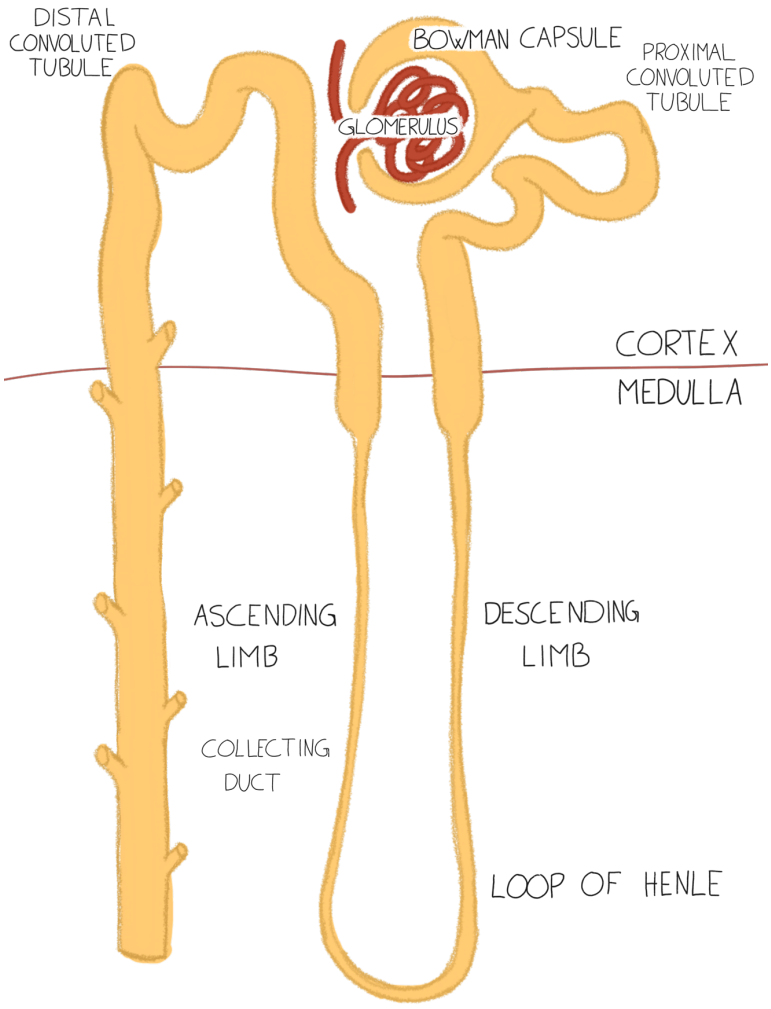


Juxtamedullary nephrons

Glomeruli located close to the corticomedullary border

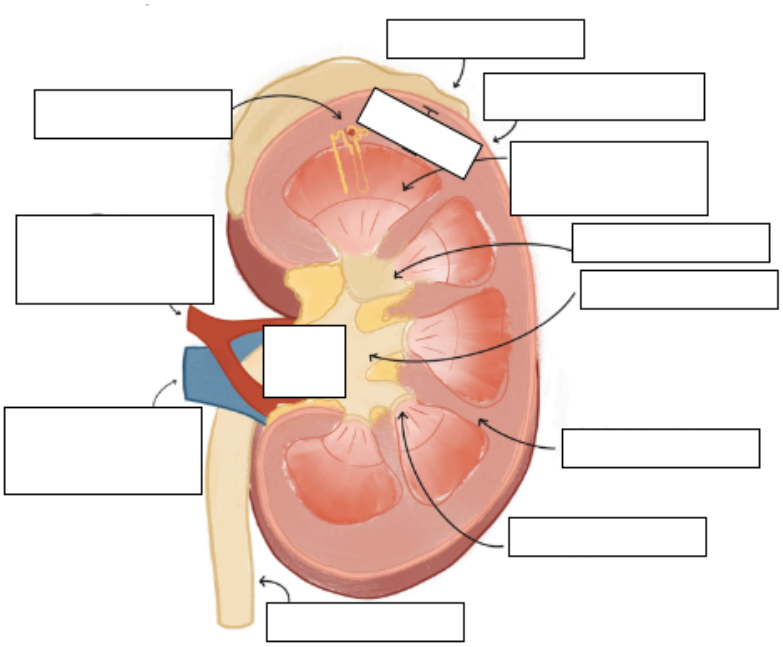
Long loops of Henle

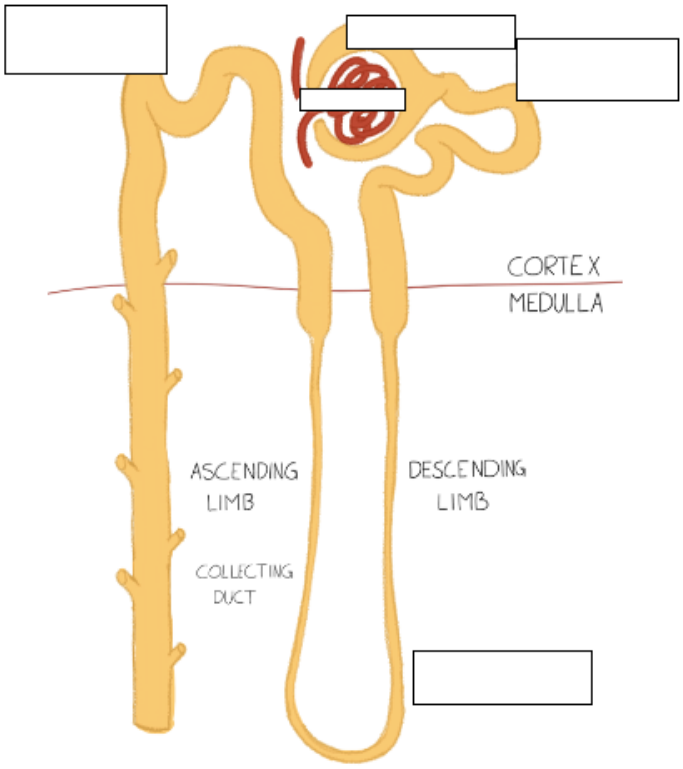
Larger glomeruli and higher GFR compared to the corticomedullary nephrons

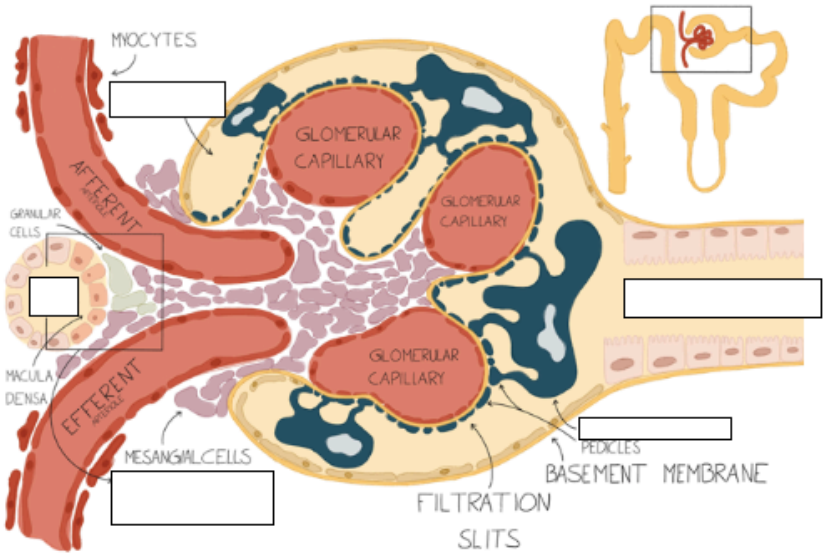


1.2 – Test Yourself

1) Fill in the blank spaces:



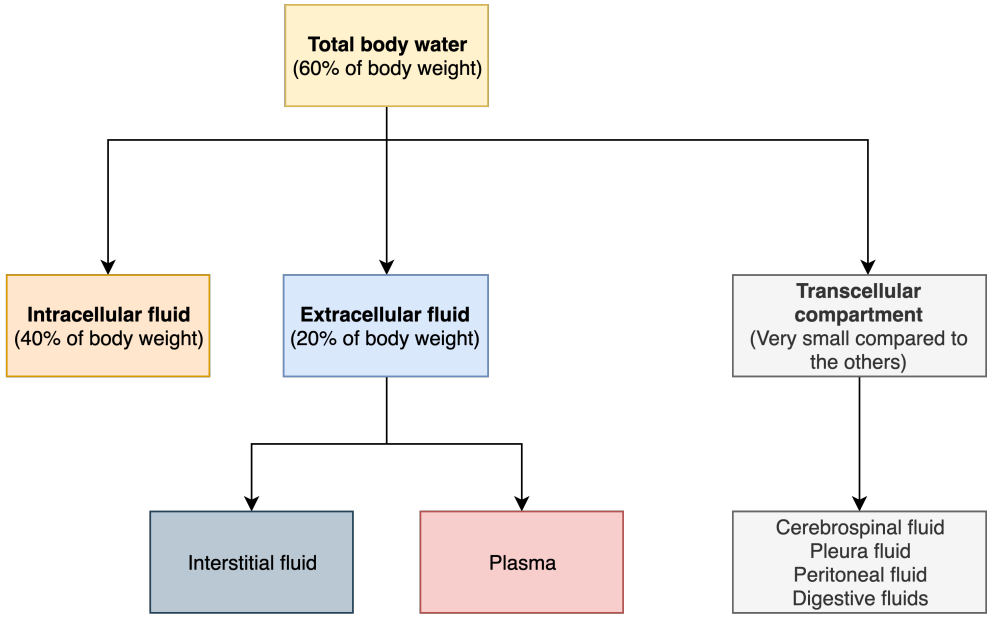


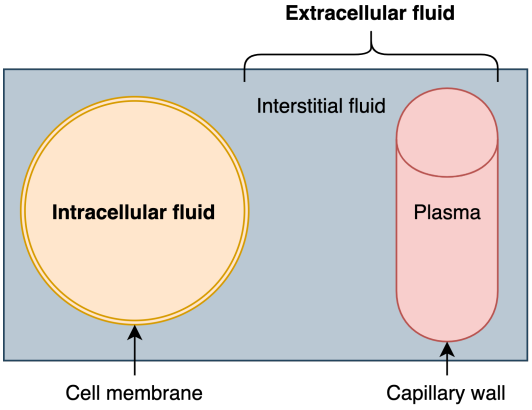


Section 2 – Body Fluids

2.0 – Overview

- Body water content is inversely related to amount of adipose tissue in the body
- ↑ Body fat = ↓ Body water
- Women will have lower levels of total body water than men, because they generally have higher amounts of adipose tissue.
- Obese women will therefore have the lowest amount of total body water, while thin men will have the highest amount of total body water.
- *The 60 – 40 – 20 rule:* With this rule you can remember that 60% of our body weight is water. 40% of that is intracellular fluid, while 20% is extracellular fluid (ECF).





2.1 – Plasma

<table>
<tr><th colspan="3">Blood</th></tr>
<tr><td colspan="2">Plasma
(55% of total blood volume)</td><td rowspan="2">Blood cells
(45% of total blood volume)

The percent of the blood volume occupied by red blood cells is called hematocrit, and can be used to understand the hydration level of your patient.</td></tr>
<tr><td>Plasma proteins
(7% of plasma volume)</td><td>Water
(93% of plasma volume)</td></tr>
</table>

2.2 – Interstitial Fluid

- Formed by filtration across the capillary walls, which is why interstitial fluid is called an "ultrafiltrate" of plasma
- The capillary walls allows fluids and electrolytes to pass, but not plasma proteins or blood cells: Interstitial fluid = Plasma – Plasma proteins and blood cells

2.3 – Electrolytes

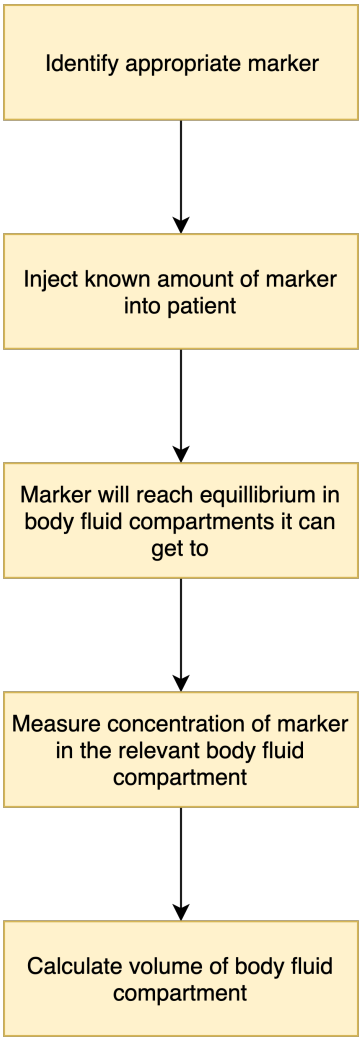
	Intracellular fluid	Extracellular fluid
Major cations	- K^+ - Mg^{2+}	- Na^+
Major anions	- Proteins and organic phosphates[1]	- Cl^- - HCO_3^-

[1] (e.g.: ATP, ADP, AMP)

I. Gibbs-Donnan effect

- Plasma will have a slightly higher concentration of small cations than interstitial fluid, because the plasma proteins are negatively charged and attract the small cations.

2.4 – Measuring the Volume of Body Fluid Compartments



2.4.0 – Identifying the appropriate marker

- To find an appropriate marker to measure the volumes in different body fluid compartments, we use different substances according to their size.
- Intracellular fluid (ICF) and interstitial fluid volume is cannot be directly measured, but they can be calculated:
    1. ICF = Total body volume – ECF volume
    2. Interstitial fluid = ECF volume – plasma volume

Size of marker	Body fluid	Characteristics	Examples
Small	**Total body water**	Small enough to be able to enter all compartments where water is found	- Isotopic water - Antipyrine
Medium	**ECF**	Small enough to be filtrated across the capillaries, but too large to enter cells	- Mannitol - Inulin - Sulfate
Large	**Plasma**	Too large to be filtered across the capillaries	- Radioactive - Albumin - Evans blue[1]

[1]A dye that binds to albumin

2.4.1 – Calculating the volume of the body fluid compartments

- The amount of marker present = marker originally injected – amount excreted in the urine.
- The concentration of the marker can be measured
- When we have the amount of marker present in the body and the concentration, we can calculate the volume: Volume = Amount/concentration

2.5 – Disturbance of Body Fluids

- Many diseases can cause a shift of body fluids between the different compartments (for example diarrhea or high sodium intake)
- To understand what happens in these diseases, there are a few principles to be aware of.

Solute concentration	The volume of any fluid compartment depends on the solute concentration in that compartment.	The ECF volume is determined by the concentration of [1]Na^+ and its accompanying anions. ↑ Na^+ content = ↑ Volume
Osmolarity	The concentration of particles that are osmotically active[2]	Normal osmolarity of body fluids = 290 mOsm/L Plasma osmolarity is estimated from the plasma concentrations of Na^+, glucose and blood urea nitrogen (BUN). These are the main solutes of ECF.
Steady state	When intracellular osmolarity = extracellular osmolarity Maintained by water. As soon as the osmolarity changes in one compartment, water will diffuse and produce equilibrium.	If the intracellular osmolarity decreases, water will move out of the cell, causing the osmolarity to increase again.
Ability to cross membranes	Some solutes, like NaCl, $NaHCO_3$ and mannitol, cannot easily cross cell membranes.	For example, if a person eats a large amount of NaCl, it will only be added to the ECF volume because it cannot easily move into the cells.

[1] The major ECF cation

[2] Osmotically active solutes will attract water

2.5.0 – Types of body fluid disturbances

I. Volume contraction

- Fluid loss

	Example	ECF volume	ICF volume	Osmolarity	Hematocrit	[Plasma protein]
Hyperosmotic	Sweating[1], fever, DI[2]	↓	↓	↑	–	↑
Isosmotic	Diarrhea, burn wounds	↓	–	–	↑	↑
Hyposmotic	Adrenal insufficiency[3]	↓	↑	↓	↑	↑

[1] Sweat contains more water than solutes (hypoosmotic fluid), which means more solutes than water are left in the body.

[2] Diabetes insipidus

[3] ↓ Aldosterone = ↓ NaCl reabsorption ⟶ Excess NaCl excretion in the urine

II. Volume expansion

- Excess fluids

	Example	ECF volume	ICF volume	Osmolarity	Hematocrit	[Plasma protein]
Hyperosmotic	↑ NaCl intake	↑	↓	↑	↓	↓
Isosmotic	Isotonic NaCl infusion	↑	–	–	↓	↓
Hyposmotic	SIADH[1]	↑	↑	↓	–	↓

[1] Syndrome of inappropriate ADH (excess water reabsorption at the collecting duct)

III. How to interpret these tables

- *ECF volume:* Decreased in volume contraction and increased in volume expansion.

- *ICF volume and osmolarity:* Never changes if there is an *isosmotic* contraction/expansion, because the fluid that is lost/in excess contains the same relative amounts of water and solutes as the ICF. When the osmolarity does not change, there is no reason for the ICF to change. If the change is hyper/hypoosmotic, on the other hand, the ICF volume and osmolarity will change like the table indicates to reach equilibrium.

- *Hematocrit:* Remains unchanged in hyperosmotic volume contraction because while the concentration of red blood cells (RBCs) decreases, water also moves out of the RBCs themselves. The decreased RBC volume works against the increased concentration of RBCs, which leaves the hematocrit unchanged.
  The opposite occurs in hypoosmotic volume expansion: The increased ECF volume causes a decreased [RBC], but water will move into the cells, which will increase the RBC volume. This will leave the hematocrit unchanged.

- *[Plasma protein]:* Will change in an opposite manner compared to the ECF volume, because plasma proteins will become more concentrated if ECF volume decreases, or more diluted if the ECF volume increases.

2.6 – Test Yourself

1) What is the 60 – 40 – 20 rule?

a) A rule that tells you that 60% of body water is located inside the cells, 40% is extracellular and 20% is plasma

b) A rule that tells you that 60% of our body weight is water, 40% of that is intracellular, while 20% is extracellular fluid (ECF)

c) A rule that describes the relationship between ions in the ECF: 60% Na^+, 40% Cl^- and 20% HCO_3^-

d) A rule that tells you the relative amounts of plasma components: 60% is water, 40% is red blood cells and 20% is electrolytes

2) Why will women generally have lower total body water than men?

_____

_____

_____

3) Write how many % of the blood volume plasma and red blood cells take up:

a) Plasma _____ %

b) Red blood cells _____ %

4) Which ions are more prominent in the intracellular fluid?

a) K^+, Mg^{2+} and proteins and organic phosphates

b) Mg^{2+}, Cl^- and HCO_3^-

c) Proteins and organic phosphates and Na^+

d) Na^+, Cl^- and HCO_3^-

e) HCO_3^-, proteins and organic phosphates and Cl^-

5) Which electrolytes are more prominent in the extracellular fluid?

a) K^+, Mg^{2+} and proteins and organic phosphates

b) Mg^{2+}, Cl^- and HCO_3^-

c) Proteins and organic phosphates and Na^+

d) Na^+, Cl^- and HCO_3^-

e) HCO_3^-, proteins and organic phosphates and Cl^-

6) Which type of fluid can be considered an ultrafiltrate? (multiple answers can be correct)

a) The blood inside capillaries

b) Intracellular fluid

c) Interstitial fluid

d) Urine

7) What characteristic is mainly considered when identifying the appropriate marker to measure body fluid volume?

a) Charge

b) Size

c) Type of molecule (e.g.: Proteins, ions, sugars etc)

8) What is the normal osmolarity of body fluids?

a) 250 mOsm/L

b) 260 mOsm/L

c) 270 mOsm/L

d) 280 mOsm/L

e) 290 mOsm/L

9) Fill in arrows indicating the correct change in the parameters

a) Volume contraction

	Example	ECF volume	ICF volume	Osmolarity	Hematocrit	[Plasma protein]
Hyperosmotic	Sweating[1], fever, DI[2]	↓			–	↑
Isosmotic	Diarrhea, burn wounds	↓	–	–		↑
Hyposmotic	Adrenal insufficiency[3]	↓				↑

b) Volume expansion

	Example	ECF volume	ICF volume	Osmolarity	Hematocrit	[Plasma protein]
Hyperosmotic	↑ NaCl intake	↑				↓
Isosmotic	Isotonic NaCl infusion	↑	–	–		↓
Hyposmotic	SIADH[1]	↑			–	↓

10) Why does hematocrit stay constant in hyperosmotic volume contraction and hypoosmotic volume expansion?

Section 3 – Renal Clearance

I. Overview

- Renal clearance is the rate at which the kidneys remove a substance from the plasma:

C	Clearance in ml/min
$[U]_x$	Urine concentration of substance x in mg/ml
V	Urine flow rate in ml/min
$[P]_x$	Plasma concentration of substance x in mg/ml

$$C = \frac{[U]_x \times V}{[P]_x}$$

- The renal clearance of different substances depend on the characteristics of the substance and how the kidneys handle it. For example:
    1. *Albumin* is too large to be filtered and is not secreted, which means the renal clearance of albumin is zero.
    2. *Glucose* is filtered but, at normal blood glucose levels, all of it is reabsorbed, which means the renal clearance for glucose is also zero.
    3. *Inulin* is a unique example. It is an exogenous substance that is freely filtered and not reabsorbed or secreted, which means all of it will be cleared. Clearance of inulin is therefore equal to the GFR.

II. Clearance ratio

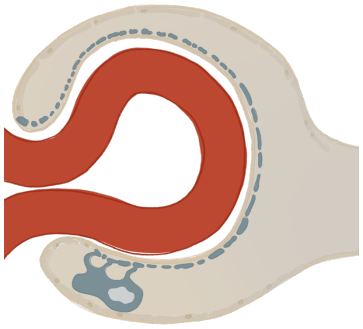
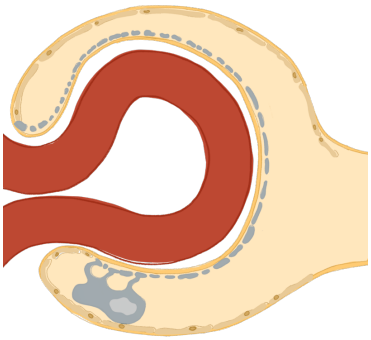
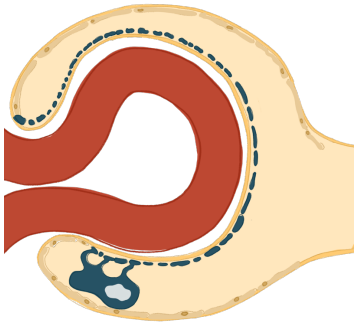
- Used to investigate how a substance is handled by the kidneys
- Because clearance of inulin = GFR, we can use it to compare a clearance of a substance to the GFR: Clearance ratio = C_x / C_{Inulin}

$C_x / C_{Inulin} = 1$	Clearance of substance x = clearance of inulin	Substance x is also a glomerular marker
$C_x / C_{Inulin} < 1$	Clearance of substance x is lower than clearance of inulin	Substance x is not filtered (e.g.: albumin), or filtered and reabsorbed (e.g.: Na^+, Cl^-)
$C_x / C_{Inulin} > 1$	Clearance of substance is higher than clearance of inulin	Substance x is filtered and secreted (e.g.: Organic acids/bases)

Section 4 – Glomerular Filtration

4.0 – The Filtration Barrier

I. Mechanical barriers

Direction of solutes	Layers of the filtration barrier	Description of layer	Filtrated substances
Endothelial lumen ↓ Bowman space	**Fenestrated capillaries** 	Blood vessel endothelium	- Water - Dissolved solutes[1] - Plasma proteins - <u>Not</u> red blood cells
	Basement membrane 	Consists of 3 layers: 1. Interna 2. Densa 3. Externa	- Water - Dissolved solutes - <u>Not</u> plasma proteins[2]
	Podocytes 	Specialized epithelium on Bowman capsule where the cells have foot processes arranged around the capillaries to form small filtration slits	

[1] For example glucose, sodium, urea

[2] The basement membrane is the first barrier to not allow plasma proteins to pass which makes it the *<u>most significant component</u>* of the filtration barrier!

II. Negative charge

- Negatively charged glycoproteins on the filtration barrier helps filtrate the blood by repelling negatively charged molecules, like plasma proteins.
- Small solutes like Na^+, K^+ or HCO_3^- are too small to be affected by this electrostatic component of the filtration barrier.
- The main function of this negative charge of the glomerular barrier is to repel the plasma proteins that are small enough to slip through the physical filtration membrane.

4.1 – Starling Forces

- The starling equation describes the fluid movement inside the glomerulus, which is driven by the Starling pressures.

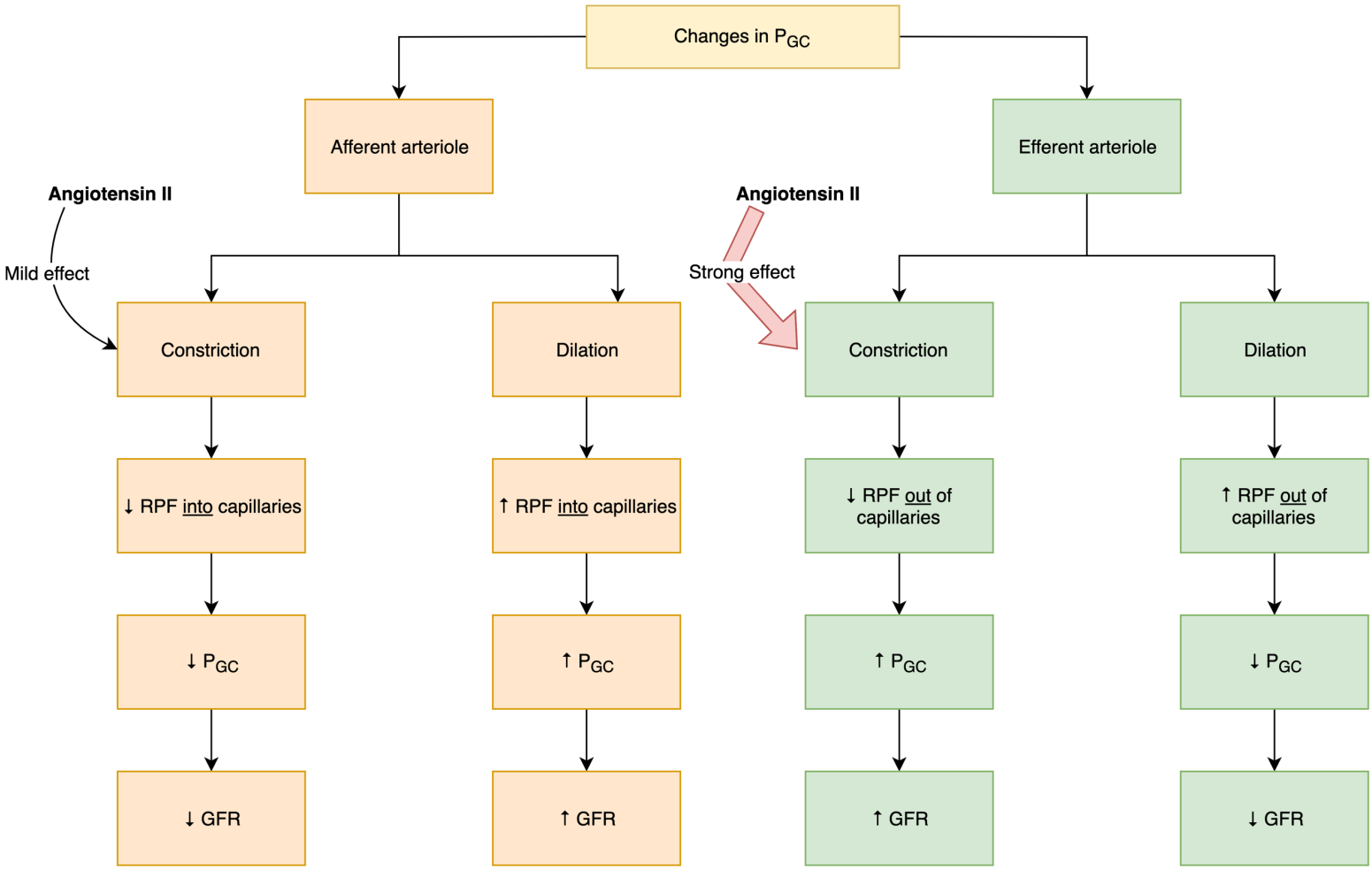
	$GFR = K_f [(P_{GC} – P_{BS}) – \pi_{GC}]$			
Net ultrafiltration pressure (the driving force)	**K_f**	The filtration coefficient	Describes the water permeability[1] of the glomerular capillaries ↑ K_f = ↑ Water permeability	K_f of the glomerular capillaries is very high compared to the systemic capillaries, because a lot more fluid must be filtered through the glomerular capillaries
	P_{GC}	The hydrostatic pressure (P) of glomerular capillaries ($_{GC}$)	The pressure the blood exerts against the glomerular capillary wall Favors filtration ↑ P_{GC} = ↑ Filtration rate	Higher in the glomerular capillaries compared to the systemic capillaries. Normally, hydrostatic pressure decreases along the length of capillaries, but it is constant in the glomerular capillaries.
	P_{BS}	Hydrostatic pressure in the Bowman's space	The pressure the filtrate in the Bowman capsule exerts on the glomerular capillaries Opposes filtration ↑P_{BS} = ↓ Filtration rate	For filtration to occur, P_{BS} must be less than P_{GC}
	π_{GC}	Oncotic pressure in glomerular capillaries	Ability of capillaries to retain fluid, determined by protein concentration in the blood Opposes filtration ↑π_{GC} = ↓ Filtration rate	Increases as fluid is filtered out of the capillaries until filtration equilibrium is reached and no more solutes can be filtered. Essentially makes it progressively more difficult for water to leave the closer it comes to the end of the glomerular capillaries.
Glomerular filtration rate = The product of the water permeability of glomerular capillaries and net ultrafiltration pressure making up the driving force. The net ultrafiltration pressure always favors movement of fluids out of the glomerular capillaries. ↑ Net ultrafiltration pressure = ↑ Filtration rate				

[1]Fancy word that means water permeability: Hydraulic conductance

4.1.0 – Changes in starling forces

I. P_{GC} – Hydrostatic pressure in the glomerular capillaries

- The hydrostatic pressure in the capillaries change when the afferent and efferent arterioles constrict or dilate.



CLINICAL CORRELATION

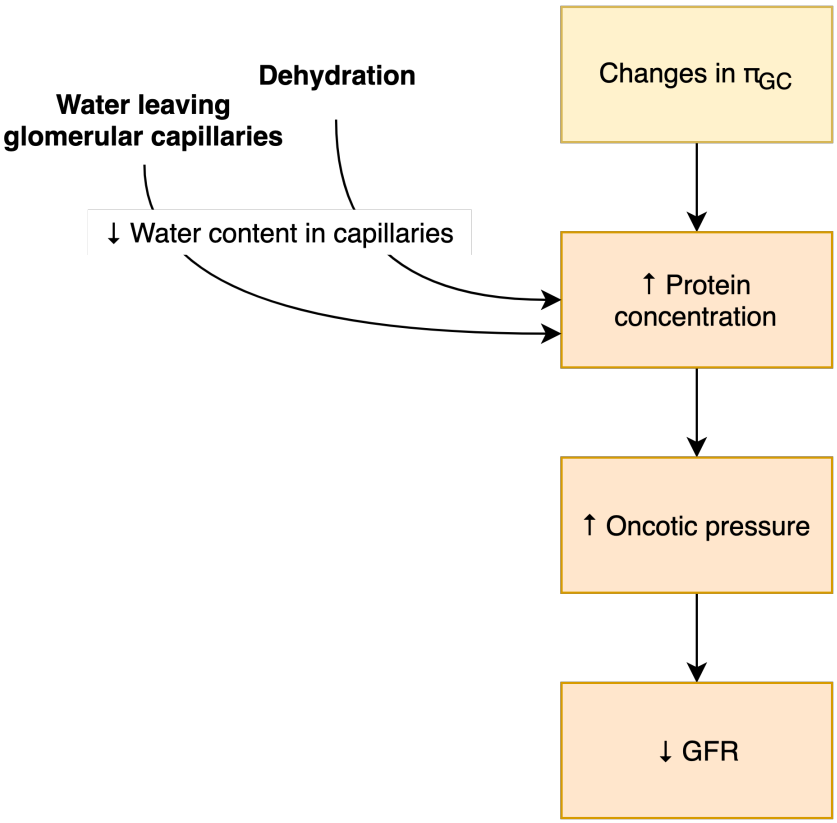
Kidney function and blood loss

When the pressure in the glomerular capillaries is low, the GFR will be reduced and kidney function can be lost. Angiotensin II prevents this from happening by always causing more constriction of the efferent arteriole than the afferent arteriole, maintaining sufficient hydrostatic pressure.

During major hemorrhage, the levels of angiotensin II will be very high and protect the kidneys!

II. π_{GC} – Oncotic pressure

- The oncotic pressure in the capillaries changes when the plasma protein concentration changes



III. P_{BS} – Hydrostatic pressure in the Bowman space

- The oncotic pressure in the Bowman space changes if there's an obstruction of urine flow
- Backflow of urine into kidney leads to an increased hydrostatic pressure in the Bowman space and results in ↓ GFR

IV. Summary

Effect	GFR	RPF	GFR/RPF
Constriction of afferent arteriole	↓	↓	–
Constriction of efferent arteriole	↑	↓	↑
↑ Plasma protein concentration	↓	–	↓
↓ Plasma protein concentration	↑	–	↑
Blockage or constriction of the ureter	↓	–	↓

GFR = Glomerular filtration rate, RPF = Renal plasma flow, "–" = No change

- GFR/RPF = Filtration fraction. Describes how much of the fluid that passes through the glomerular capillaries actually reach the renal tubules.

4.2 – Regulation of Renal Blood Flow

- Regulation of renal blood flow (RBF) occurs mainly by changing the resistance of arterioles:

I

	Afferent arteriole	Efferent arteriole
Constriction	↓ RBF + GFR	↑ RBF + GFR
Dilation	↑ RBF + GFR	↓ RBF + GFR

- Substances released in response to rapid decrease in blood pressure (e.g.: major bleeding):
  1. Catecholamines by the sympathetic nervous system (SNS)
  2. Angiotensin II
  3. Prostaglandins
- Substances released in volume expansion:
  1. Atrial natriuretic peptide (ANP) is secreted in response to stretching of the atria

Endogenous substances affecting RBF	Afferent arteriole	Efferent arteriole	RBF
Circulating catecholamines[1]	**Constriction**[2]	Constriction	↓
Angiotensin II (AT-II)	Constriction	**Constriction**	↑/↓
ANP[3]	**Dilation**	Constriction	↑
Prostaglandins	Dilation	Dilation	↑
Dopamine	**Dilation**	Dilation	↑

[1] Released when SNS is activated

[2] Greater effect is indicated by bold letters

[3] Also includes related substances, like brain natriuretic peptide (BNP)

- *Circulating catecholamines:* Stimulates α_1 receptors on afferent and efferent arterioles. The concentration of α_1 receptors is higher on the afferent arteriole than the efferent arteriole, causing the constrictor effect of catecholamines to be greatest at the afferent arteriole.

  In situations of major blood loss, baroreceptors will be stimulated causing activation of the SNS. The increases SNS activity Increases blood pressure (BP), but the kidneys will suffer due to the resulting low GFR.

- *Angiotensin II:* The efferent arteriole is more sensitive to AT-II than the afferent arteriole. As a consequence, the effect AT-II has on GFR depends on the blood levels of AT-II:
  Normal serum AT-II levels: Constriction of only efferent arteriole leads to ↑ GFR
  High serum AT-II levels (as seen during hemorrhage): Constriction of efferent and afferent arterioles leads to ↓ GFR

- *Atrial natriuretic peptide:* ANP has a stronger dilatory effect on the afferent arteriole than the efferent. Therefore, the net effect of ANP is decreased vascular resistance and increased RBF.

- *Prostaglandins:* Produced and released in the kidneys. Prostaglandins are released by the same stimuli that stimulates the SNS and AT-II release, and opposes the decrease in RBF produced by the SNS and AT-II. In the setting of extremely low blood pressure, prostaglandins are responsible for protecting the RBF and thereby preventing renal failure.

CLINICAL CORRELATION

NSAIDs and ACE inhibitors and acute kidney injury

ACE inhibitors (ACE-I) are commonly used antihypertensive drugs, and they function by inhibiting the production of AT-II. NSAIDs, e.g.: ibuprofen, inhibits production of prostaglandins and many are sold over the counter.

At normal levels, AT-II protects GFR by constricting the efferent arteriole, while prostaglandins protect the GFR by dilating the afferent arteriole. A patient using ACE-I will have decreased GFR due to decreased constriction of the efferent arteriole. If the same patient takes NSAIDs, the production of prostaglandins that normally dilates the afferent arteriole will also be inhibited.

The result will be constriction of the afferent arteriole (action of NSAIDs) and dilation of the efferent arteriole (action of ACE-I), which can lead to a large enough decrease in GFR to precipitate acute kidney injury.

- *Dopamine:* Dilates the renal arterioles at low levels, making it useful as medication in the setting of severe hemorrhage. It also dilates arterioles in other vital organs, like the heart and brain.

4.3 – Measurement of Glomerular Filtration Rate

- Observation of clearance rate of glomerular markers is how we measure the GFR
- Characteristics of good glomerular markers:
    1. Must be freely filtered
    2. Cannot be reabsorbed or secreted
    3. Cannot alter GFR when administered

$$GFR = \frac{[U]_{Inulin} \times V}{[P]_{Inulin}} = C_{inulin}$$

I. Inulin – The ideal glomerular marker

- Neutral molecule that is unbound to proteins in blood
- Small enough to be freely filtered
- Must be infused (i.e.: not produced in the body)
- Not reabsorbed or secreted in the renal tubules (i.e.: Exogenous substance)

$[U]_{Inulin}$	Urine concentration of inulin
V	Urine flow rate
$[U]_{Inulin}$ x V	Excretion rate of inulin
$[P]_{Inulin}$	Plasma concentration of inulin
C_{Inulin}	Clearance of inulin

- Changes in flow rate (V) will not cause changes in GFR. This can be explained by the inversely proportional relationship between urine concentration of inulin ($[U]_{Inulin}$) and urine flow rate (V). When the flow rate increases, the urine will be diluted and $[U]_{Inulin}$ will decrease proportionately with the increase in V.

- Increased $[P]_{Inulin}$ will not cause ↓ GFR because when $[P]_{Inulin}$ increases, the filtration rate of inulin will increase as well. This causes $[U]_{Inulin}$ x V to increase, so when $[P]_{Inulin}$ increases, $[U]_{Inulin}$ x V will increase proportionally and GFR will stay the same.

- Although inulin is an ideal glomerular marker, it's rarely used in the clinical setting because it must be infused. Creatinine is preferred, because it's an endogenous substance that is secreted only to a small extent in the renal tubules.

II. Blood urea nitrogen (BUN) and serum creatinine

- Both of these substances are filtered across the glomerular capillaries.
- An increase in the serum concertation of BUN or creatinine indicates that the glomerular filtration isn't functioning properly and this can be used in diagnosing renal disease.

CLINCAL CORRELATION

Prerenal acute kidney injury (AKI)

Prerenal AKI causes increased BUN and serum creatinine because of decreased perfusion of the kidneys due to problems in the systemic circulation (i.e. hypovolemia). The state of increased blood levels of nitrogen-containing compounds is called "azotemia".

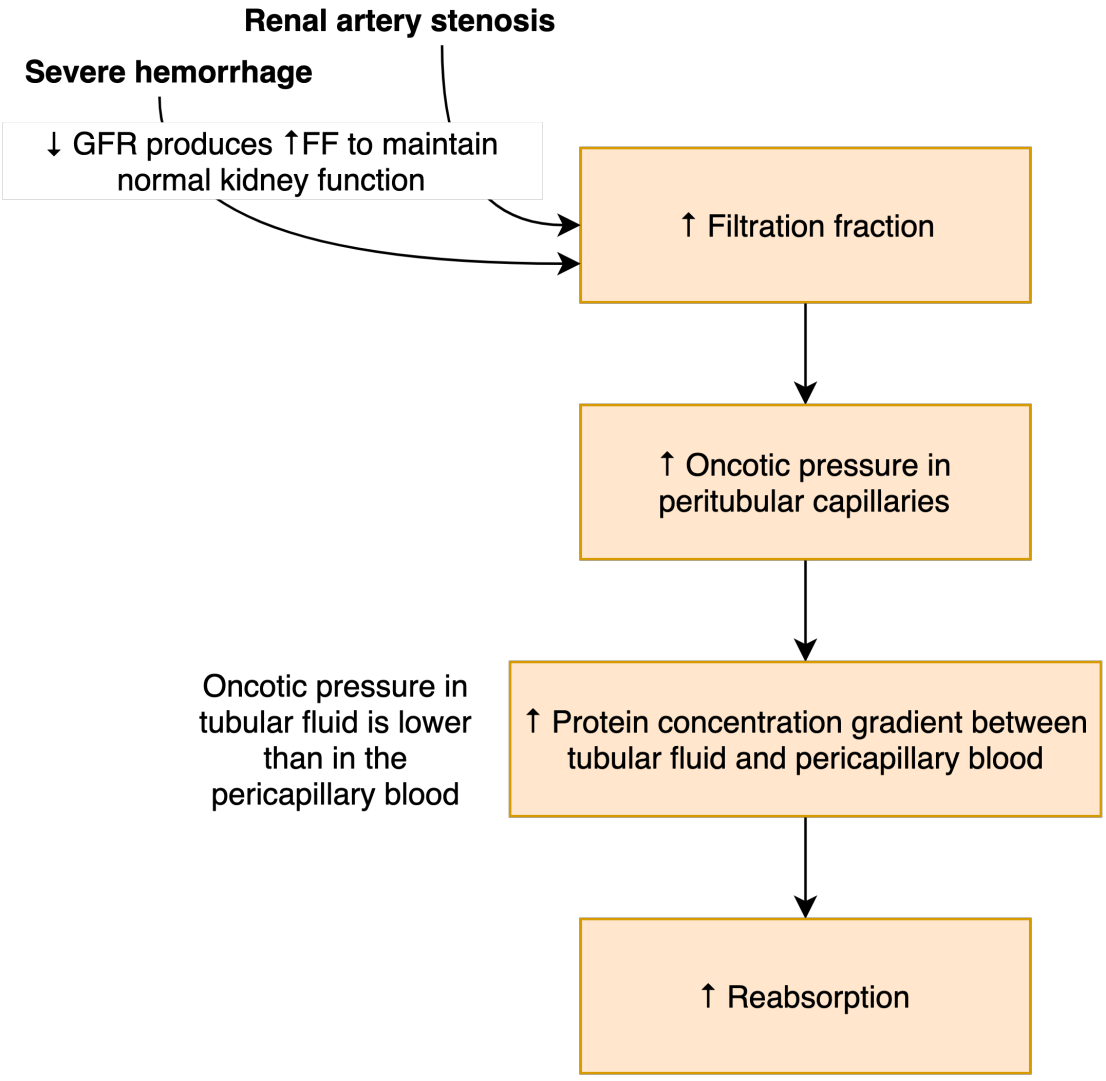
Urea is reabsorbed to some extent in the tubules, while creatinine is not. This means that a higher elevation in BUN than serum creatinine can be an indication of hypovolemia.

Specifically, a BUN/creatinine ratio > 20 is the reference value for prerenal AKI. To compare, renal causes of failure will increase BUN and creatinine equally, because the kidneys ability to reabsorb BUN is limited. In intrinsic renal failure the BUN/Creatinine ratio will be < 20.

4.4 – Filtration Fraction

- Filtration fraction (FF) express the relationship between glomerular filtration rate (GFR) and renal plasma flow (RPF)
- In other words, the filtration fraction is the % of plasma that is filtered into the proximal tubule
- Normally 20% of plasma filtered ⟶ Normal FF = 0.2
- The 80% of plasma that is not filtered becomes the peritubular blood flow, where reabsorption of solutes occurs.

$$\text{Filtration fraction} = \frac{\text{GFR}}{\text{RPF}}$$



4.5 – Test Yourself

1) What is the order of the layers in the glomerular filtration barrier?

1:_____

2:_____

3:_____

2) What is the main purpose of negative charge in the glomerular filtration barrier?

a) Repels ions like Na^+ and HCO_3^-

b) Repelling the plasma proteins that are small enough to pass through the basement membrane

c) It has no effect

d) It attracts the solutes like Cl^- and urea

e) b and d

3) Which of the starling forces favors glomerular filtration? Choose the answers you think are correct.

☐ Water permeability of the glomerular capillaries

☐ The hydrostatic pressure in the glomerular capillaries

☐ The hydrostatic pressure in the Bowman space

☐ Oncotic pressure in the glomerular capillaries

4) How does angiotensin II protect the kidneys during major hemorrhage?

_____

_____

_____

5) What happens to the GFR (increased or decreased) when:

a) Afferent arteriole constricts_____

b) Afferent arteriole dilates _____

c) Efferent arteriole constricts _____

d) Efferent arteriole dilates _____

6) How will renal blood flow be affected (increased or decreased) by secretion of these substances? Fill in the empty boxes.

Endogenous substances affecting RBF	RBF
Circulating catecholamines[1]	
Angiotensin II (AT-II)	
Atrial natriuretic peptide[3]	
Prostaglandins	
Dopamine	

7) Why should we never give NSAIDs with ACE inhibitors?

a) They both increased blood pressure and the patient can go into hypertensive emergency

b) NSAIDs will counteract the effect of ACE inhibitors

c) They both decrease GFR, which can precipitate acute kidney injury

d) They both increase permeability of the glomerular basement membrane which can lead to proteinuria

8) What are the characteristics of and ideal glomerular marker? Can you give an example of an ideal glomerular marker? Why do we not routinely use this marker?

9) What does the filtration fraction describe?

10) How much plasma is normally filtered into the renal tubules?

a) 10%

b) 20%

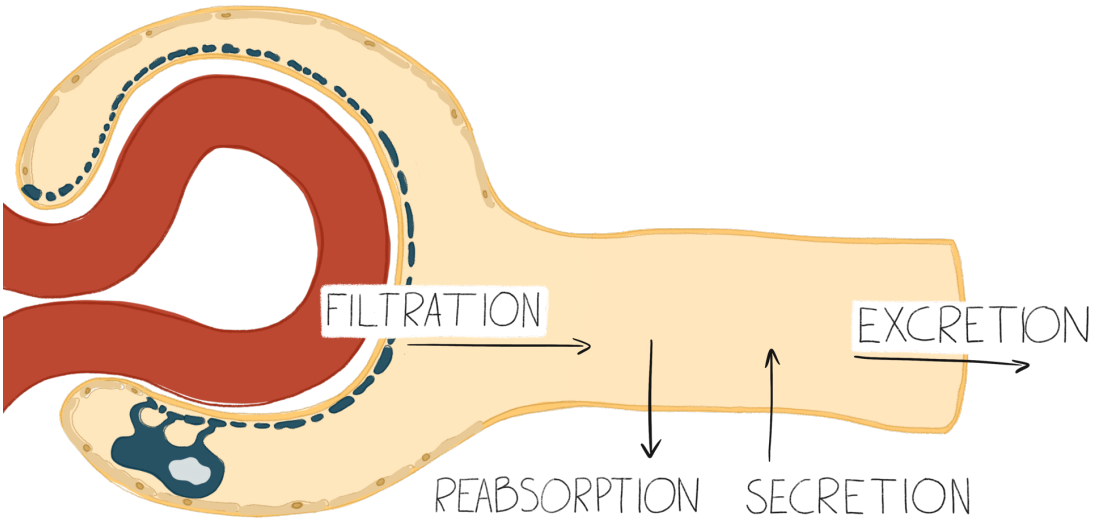
c) 30%

d) 40%

e) 50%

Section 5 – Reabsorption and Secretion

5.0 – Overview



Filtration	Reabsorption	Secretion	Excretion
A fluid similar to interstitial fluid is filtered across the glomerular capillaries into bowman space.	Water and many solutes are reabsorbed from the tubules into the peritubular capillaries. If this did not occur, we would rapidly lose important solutes into the urine.	Some substances, like K^+ and organic acids/bases, are secreted into the tubules from the peritubular capillaries.	The sum of filtration, reabsorption and secretion. To determine if a solute has been secreted or reabsorbed, we can compare the excretion rate with the filtered load.
Filtered load = GFR x $[P]_x$ $[P]_x$ = Plasma concentration of solute x	Reabsorption/excretion rate = Filtered load – Excretion rate		Excretion rate = V x $[U]_x$ V = Volume $[U]_x$ = Urine concentration of solute x

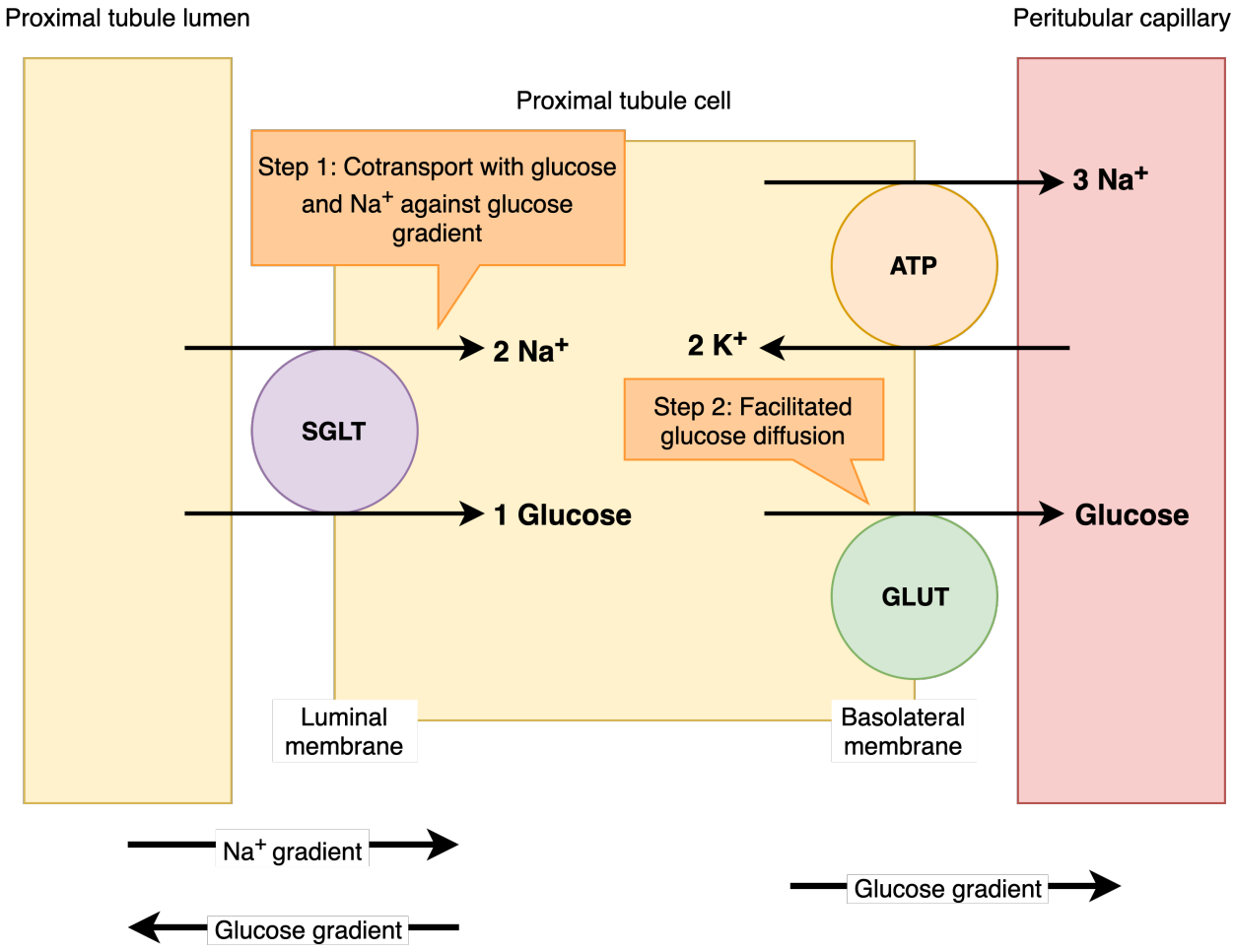
5.1 – Reabsorption

I. Mechanisms of reabsorption of solutes

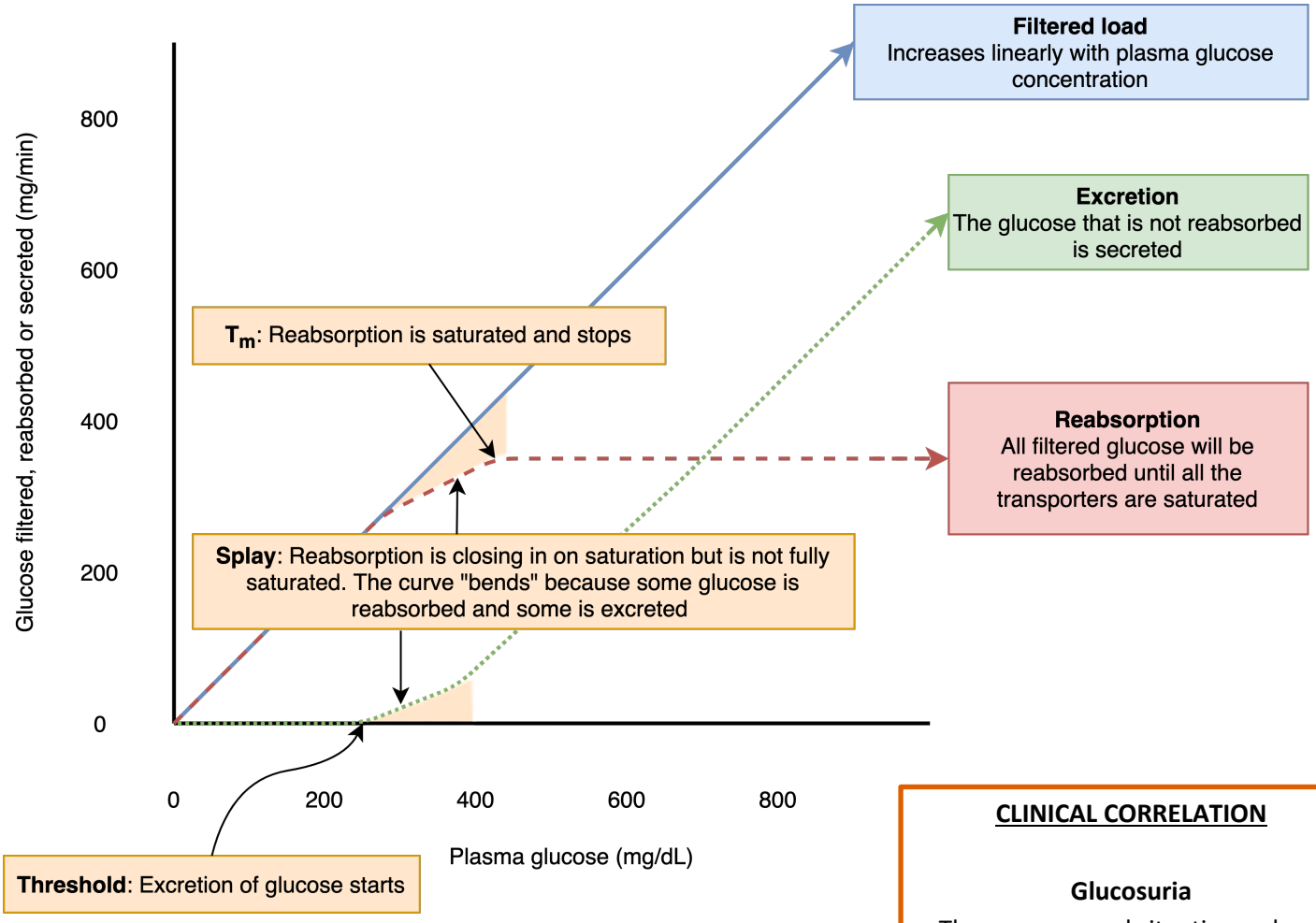
- Passive diffusion (e.g.: Water)
- Active transport (e.g.: Sodium)
- Cotransport (e.g.: Glucose)

5.1.0 – Secondary active transport: Glucose

- Reabsorption of glucose is a two-step process:
    1. Glucose enters the tubular cell against its electrochemical gradient via Na^+ cotransport.
    2. From the tubular cell, glucose diffuse with its gradient into the peritubular capillary with the help of a transporter
- The Na^+ gradient is maintained by the Na^+/K^+-ATPase on the basolateral membrane
- The Na^+/Glucose cotransport on the luminal membrane is called secondary active transport because it relies on the Na^+/K^+-ATPase on the basolateral membrane to maintain the Na^+ concentration gradient.



I. The glucose titration curve



- At plasma glucose concentrations < 200 mg/dL – all the filtered glucose will be reabsorbed
- At plasma glucose concentration > 350 mg/dL – all the glucose transporters are saturated, and no more glucose can be reabsorbed.

Hypotheses for splay	
Low affinity of Na^+/Glucose cotransporters	Heterogeneity of nephrons
If a glucose molecule detaches from its transporter when reabsorption is close to saturation (T_m), it will be less likely to find a new transporter to bind to, as most of them are occupied. This will lead to some glucose being excreted before all the transporters are saturated.	The T_m value is an average value, which means that all nephrons don't have the same T_m value. Some nephrons might reach their T_m value at lower plasma glucose concentrations, and glucose will be excreted into the urine before the average T_m value is reached.

CLINICAL CORRELATION

Glucosuria

There are several situations where glucose can be found in urine.

Diabetes Mellitus

Lack of insulin leads to high blood glucose, saturation of transporters and glucosuria.

Pregnancy

GFR is increased during pregnancy, and the filtered load of glucose can exceed the reabsorption capacity of the nephron.

Defects in Na^+/Glucose cotransporters

Decreases the T_m so more glucose is excreted into the urine.

5.1.1 – Passive reabsorption: Urea

I. Pattern of urea reabsorption

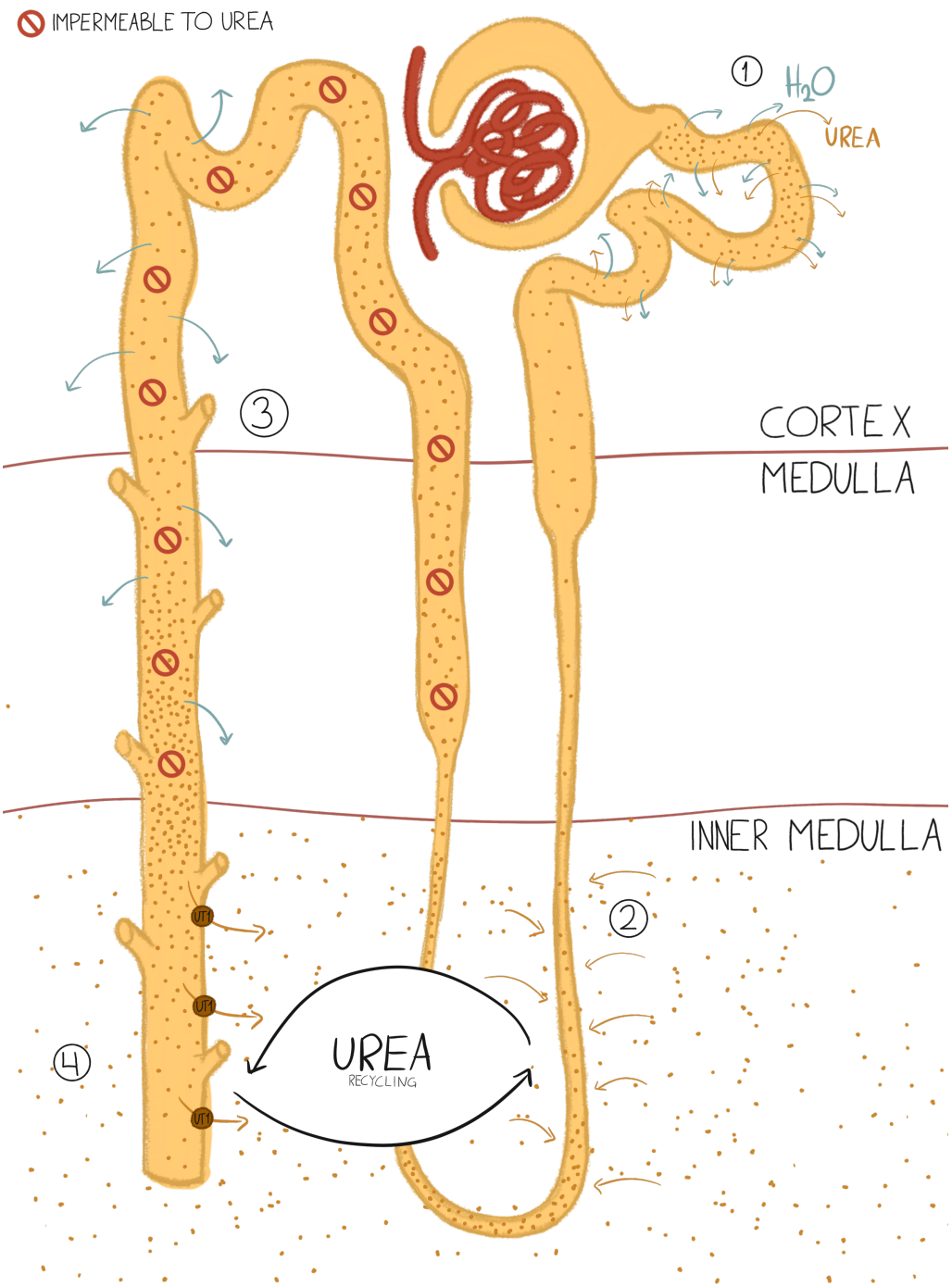
- Urea is freely filtered across the glomerular capillaries and concentration in the initial concentration is identical to the peritubular blood. This means, there's no driving force for reabsorption of urea until some of the filtered water is reabsorbed in the tubule.
- Because urea follows water, the pattern of urea reabsorption follows the pattern of water reabsorption as a general rule: ↑ Water reabsorption = ↑ Urea reabsorption

1 – Proximal tubule
In the proximal tubule, water diffuses out of the tubule, and urea follows also by simple diffusion. The gradient driving urea reabsorption is maintained by the water leaving the tubules.

2 – Thin descending limb
Urea concentration is very high in the inner medulla and urea diffuses into the tubule. The urea concentration in the inner medulla is from the urea leaving the inner medullary collecting duct.

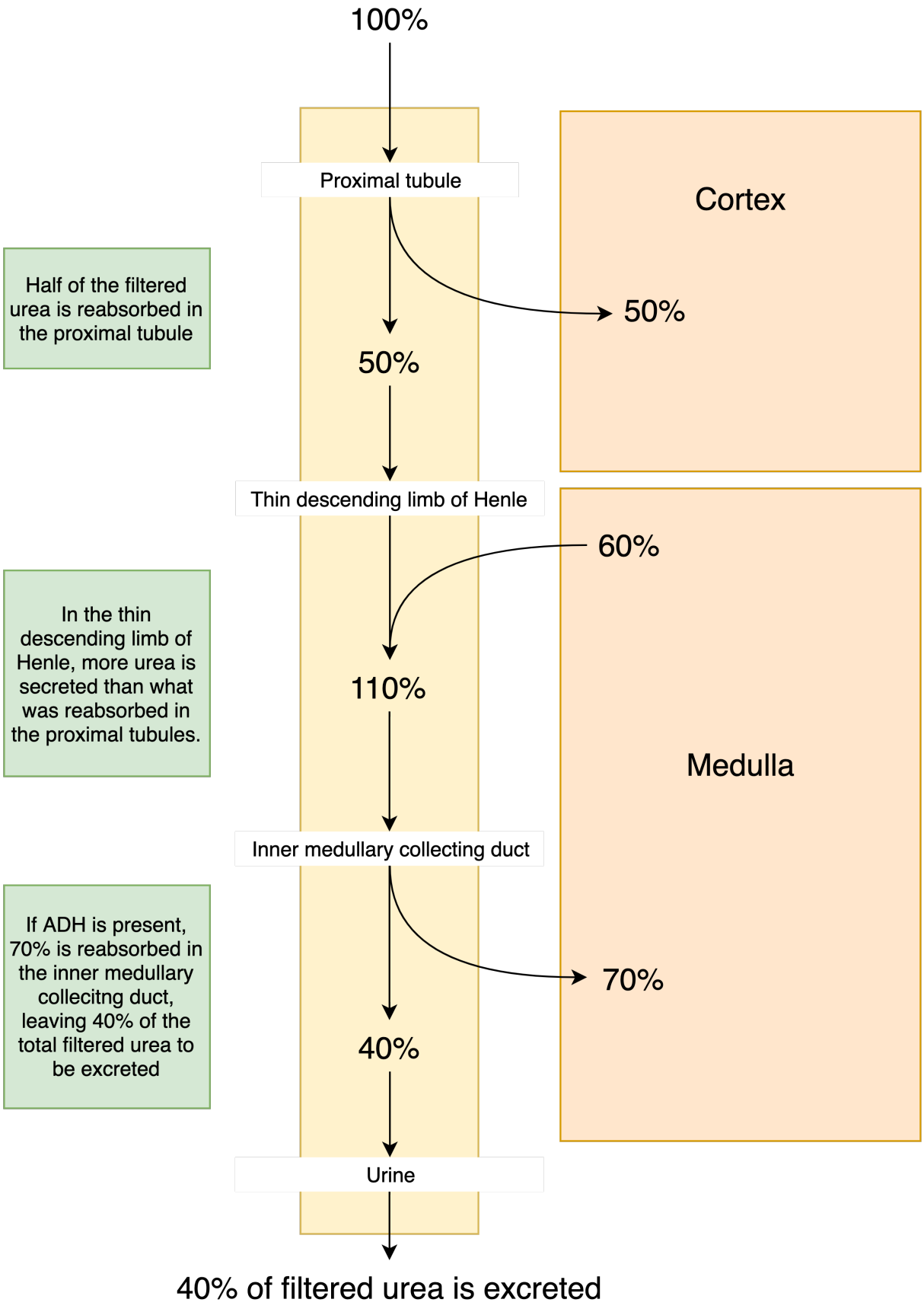
3 – Distal tubule, cortical and outer medullary collecting duct
ADH stimulates water reabsorption, but these segments are impermeable to urea. Urea stays in the tubule and its concentration becomes very high.

4 – Inner medullary collecting duct
The nephron is now permeable to urea, and the urea gradient out of the tubule is high. Urea diffuses out of the tubules via transporters called urea transporter 1 (UT1).
ADH also stimulates the facilitated diffusion of urea by upregulating UT1 on the inner medullary collecting ducts.



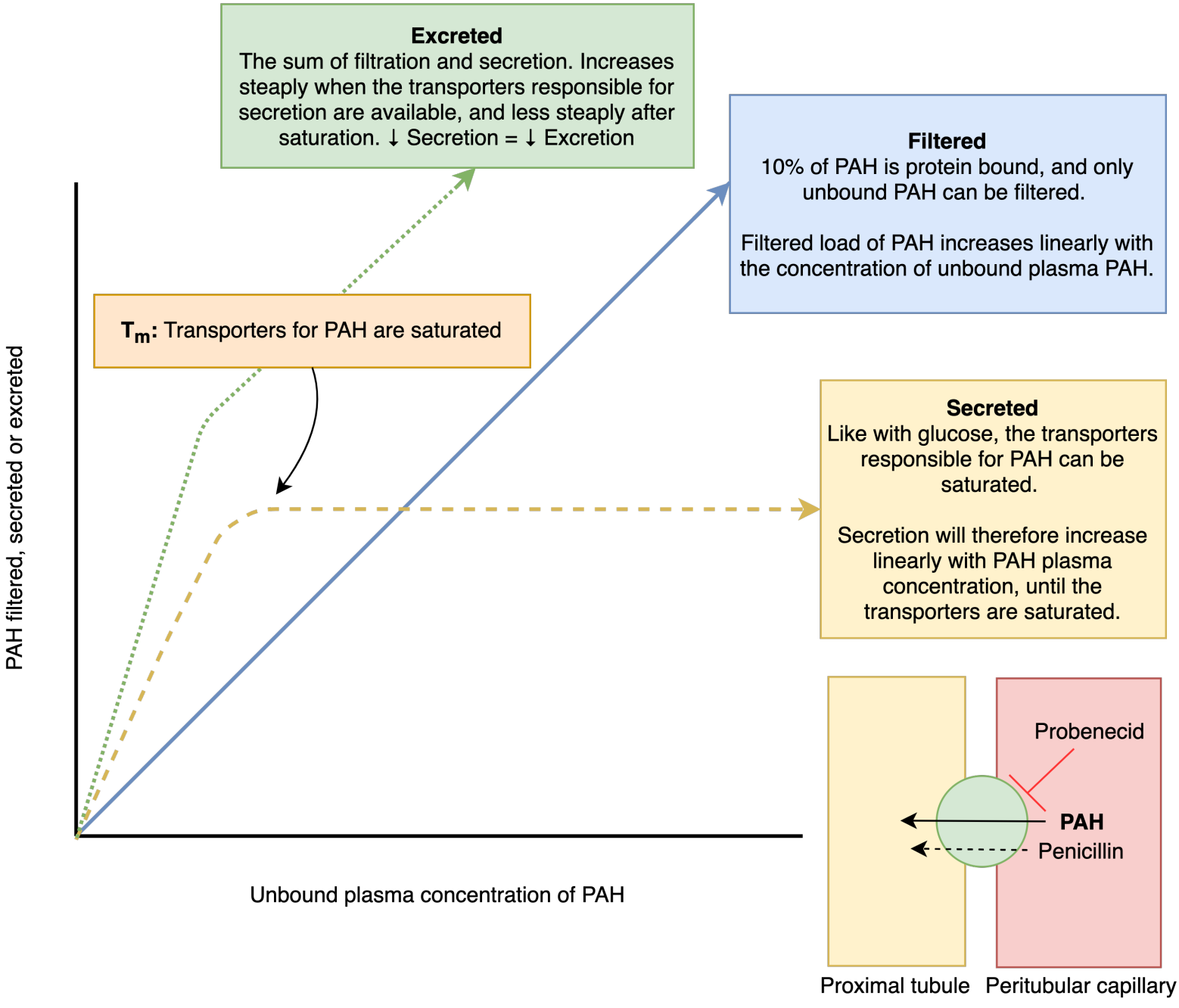
The urea in the inner medulla contributes to the corticopapillary osmotic gradient, which will be explained in section 9.

I. Filtered load of urea remaining in the tubules at different sections of the nephron



5.2 – Secretion: Para-Aminohippuric Acid

- Both filtered at the glomerular capillaries and secreted in the tubules
- Can be illustrated in a curve as with the example of reabsorption of glucose.
- Penicillin is secreted through the PAH carrier
- Probenecid (a drug used mostly in gout) inhibits the PAH transporter



5.3 – Non-Ionic Diffusion

- The kidneys excrete weak acids and bases by non-ionic diffusion

	Weak acids	Weak bases
	Exist in acid form (HA) and a conjugate base form (A^-)	Exist in a base form (B) and a conjugate acid form (BH^+)
	Natural forms (uncharged)	
	HA (e.g.: H_2CO_3)	B (e.g.: NH_3)
	Response to pH changes	
Low pH	HA (H_2CO_3) predominates	BH^+ (NH_4^+) predominates (charged)
High pH	A^- (HCO_3^-) predominates (charged)	B (NH_3) predominates

Notice how the acid becomes charged when pH increases, and the base becomes charged when the pH decreases.

- Two important principles:
  1. The relative concentrations of charged and uncharged weak acids/bases is determined by the urine pH
  2. Only uncharged species can diffuse across the tubular epithelial cells

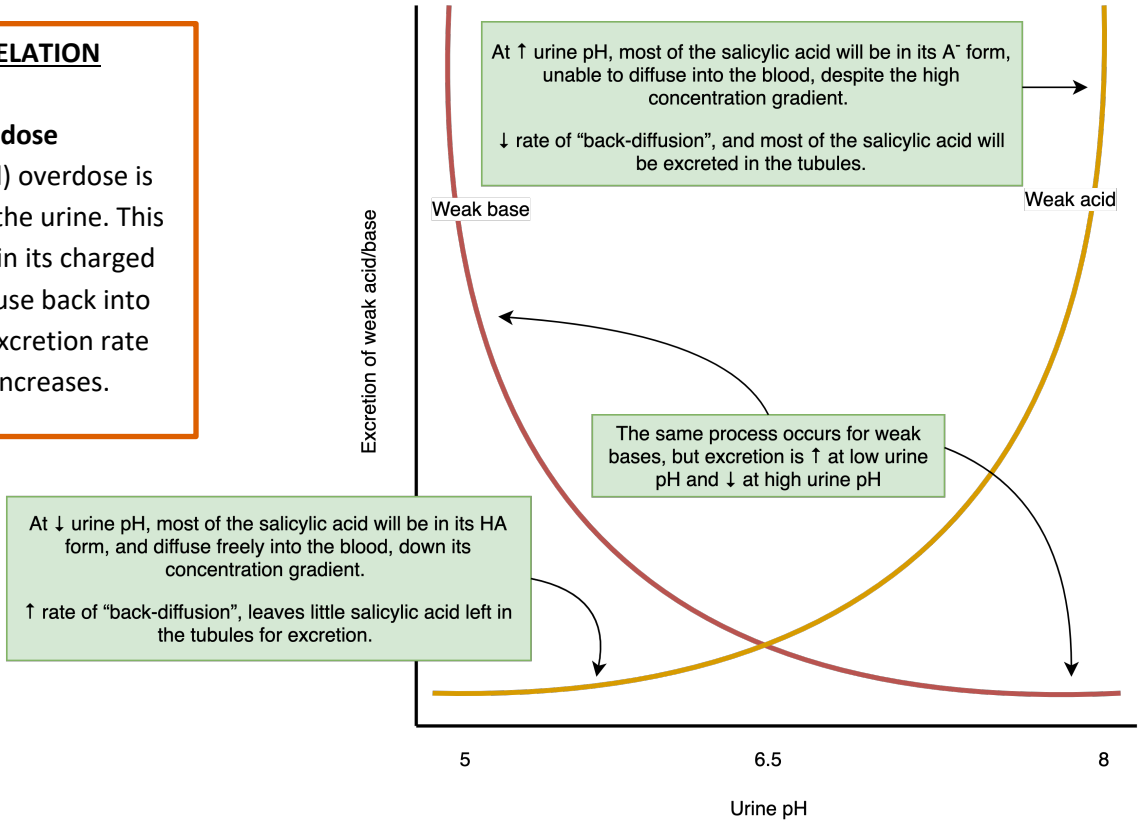
I. Example of non-ionic diffusion: Salicylic acid

- Salicylic acid is a weak acid, and it's filtered and secreted in a similar manner as PAH. This produces a high urine concentration and a low blood concentration of salicylate (i.e. a large concentration gradient).

CLINICAL CORRELATION

Aspirin overdose

Aspirin (salicylic acid) overdose is treated by alkalizing the urine. This makes the acid stay in its charged form, unable to diffuse back into the blood and the excretion rate (and clearance) increases.



5.4 – Test Yourself

1) How can we calculate the reabsorption and secretion rate?

2) Which ion is glucose dependent on to be reabsorbed in the tubules?

a) Na^+
b) Mg^{2+}
c) Cl^-
d) HCO_3^-
e) Ca^{2+}

3) What is secondary active transport?

4) What is the T_m value in the setting of glucose reabsorption?

a) When the filtered load is at its maximum
b) When excretion of glucose start
c) When all the glucose transporters are saturated
d) The point where the affinity of the glucose transporters to glucose is at their highest

5) Which parts of the nephron are permeable to urea?

6) Which hormone stimulates facilitated diffusion of urea at the inner medullary collecting duct?

7) Which drug is secreted through the transporter responsible for secretion of para-aminohippuric acid?

8) Explain why we can use alkalization of urine as a way to treat aspirin overdose.

Section 6 – Sodium Balance

6.0 – Introduction

- Renal mechanisms of sodium reabsorption are crucial for maintenance of the ECF volume, normal blood volume and normal blood pressure.
- The kidneys are responsible for maintaining the sodium balance, making sure that sodium intake matches sodium excretion.

Notice:

- Na^+ content = Total amount of Na^+ in the body
- Na^+ concentration = Amount of Na^+ dependent on amount of fluids

Sodium balance	Definition	Comment
Positive sodium balance	Excretion < intake →ECF volume expansion→ ↑ Blood volume and arterial pressure	Can lead to edema
Negative sodium balance	Excretion > intake →ECF volume contraction → ↓Blood volume and arterial pressure.	

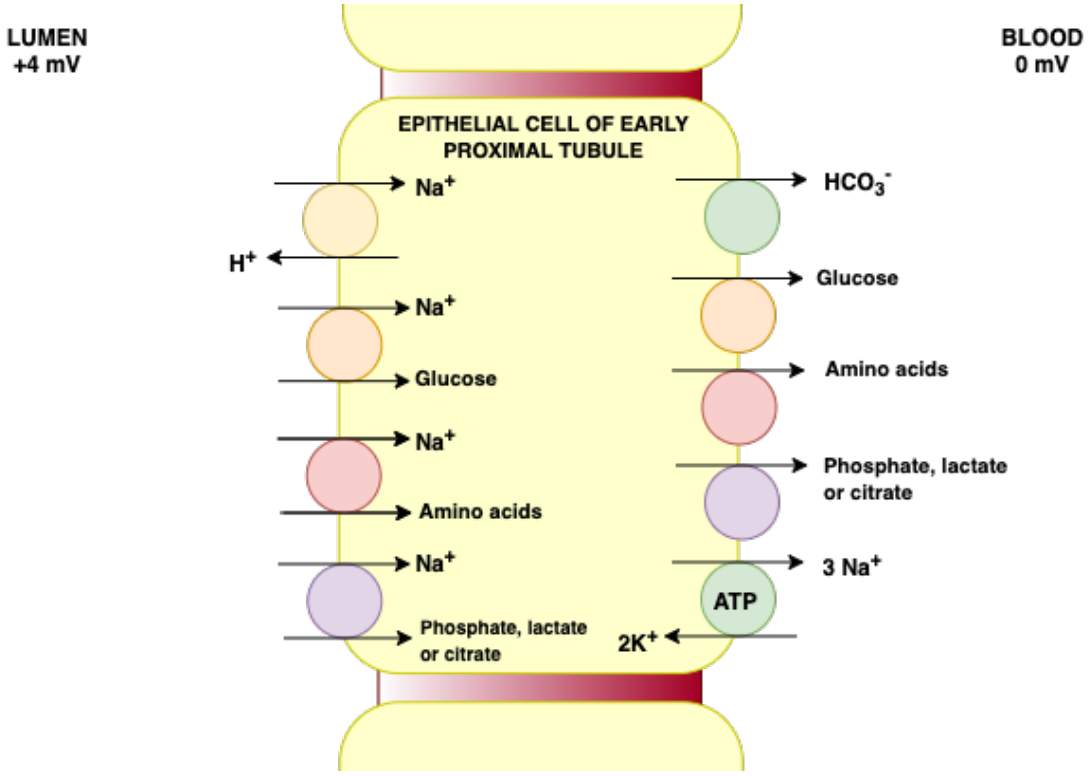
6.1 – Proximal Convoluted Tubule

- Main function isosmotic reabsorption of sodium and water.
- Reabsorbs ≈ 67% of filtered Na^+ and water.

6.1.0 – Early proximal convoluted tubule (EPCT)

I. Reabsorption

- 100% of filtered glucose
- 100% of amino acid
- 85% of filtered bicarbonate
- Most of phosphate, citrate and lactate
- Extensive sodium reabsorption



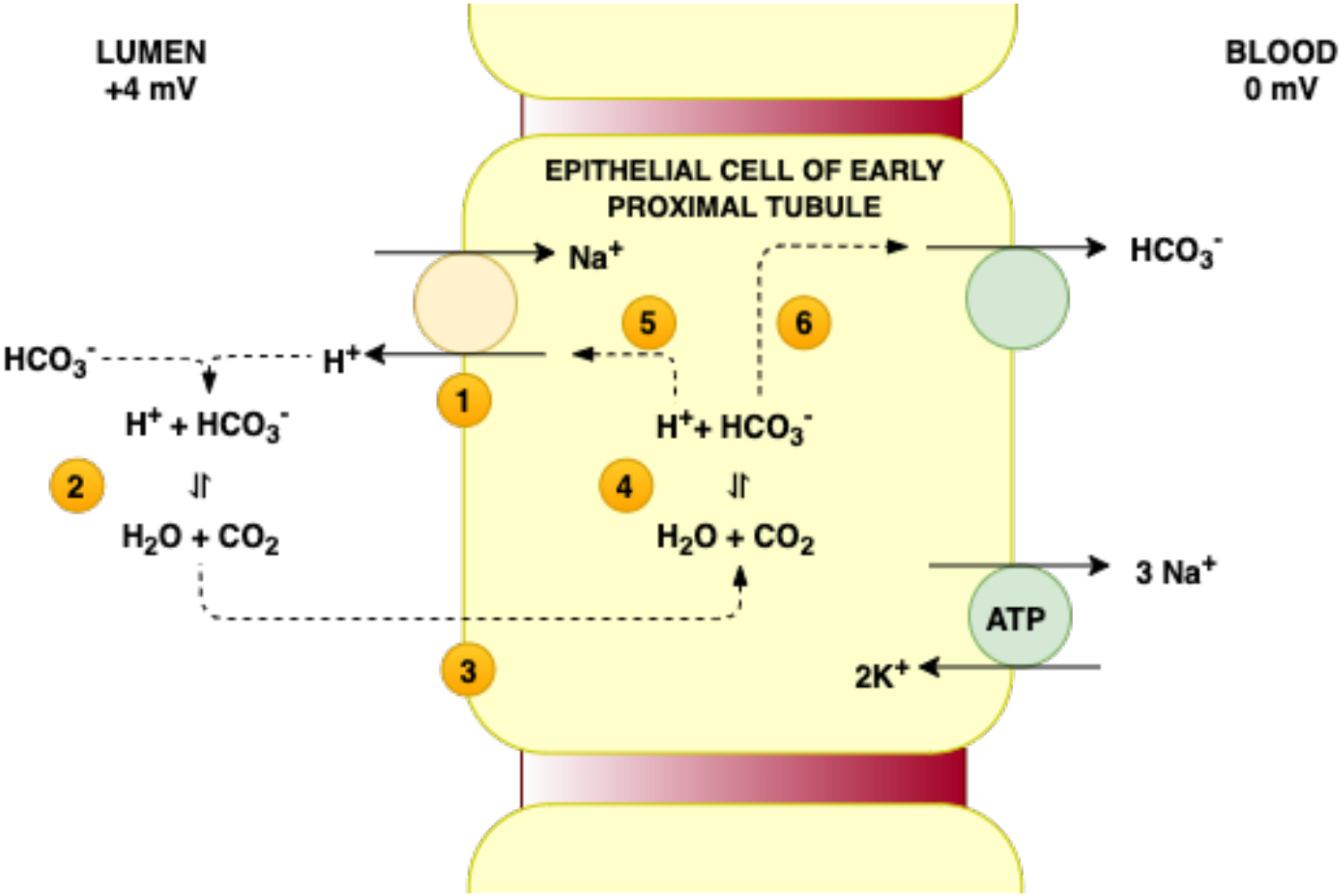
Luminal membrane	Basolateral membrane
Reabsorption driven by Na^+ transmembrane gradient 1. Sodium moves with the gradient 2. Organic compounds are transported against their electrochemical gradient.	1. Organic compounds and **bicarbonate** is absorbed into blood via facilitated diffusion 2. Sodium is actively transported into blood by "the housekeeper" Na^+, K^+ - ATPase

II. Hormonal influence

- Parathyroid hormone (PTH) inhibits Na^+-phosphate cotransport
- Angiotensin II stimulates Na^+-H^+ exchange

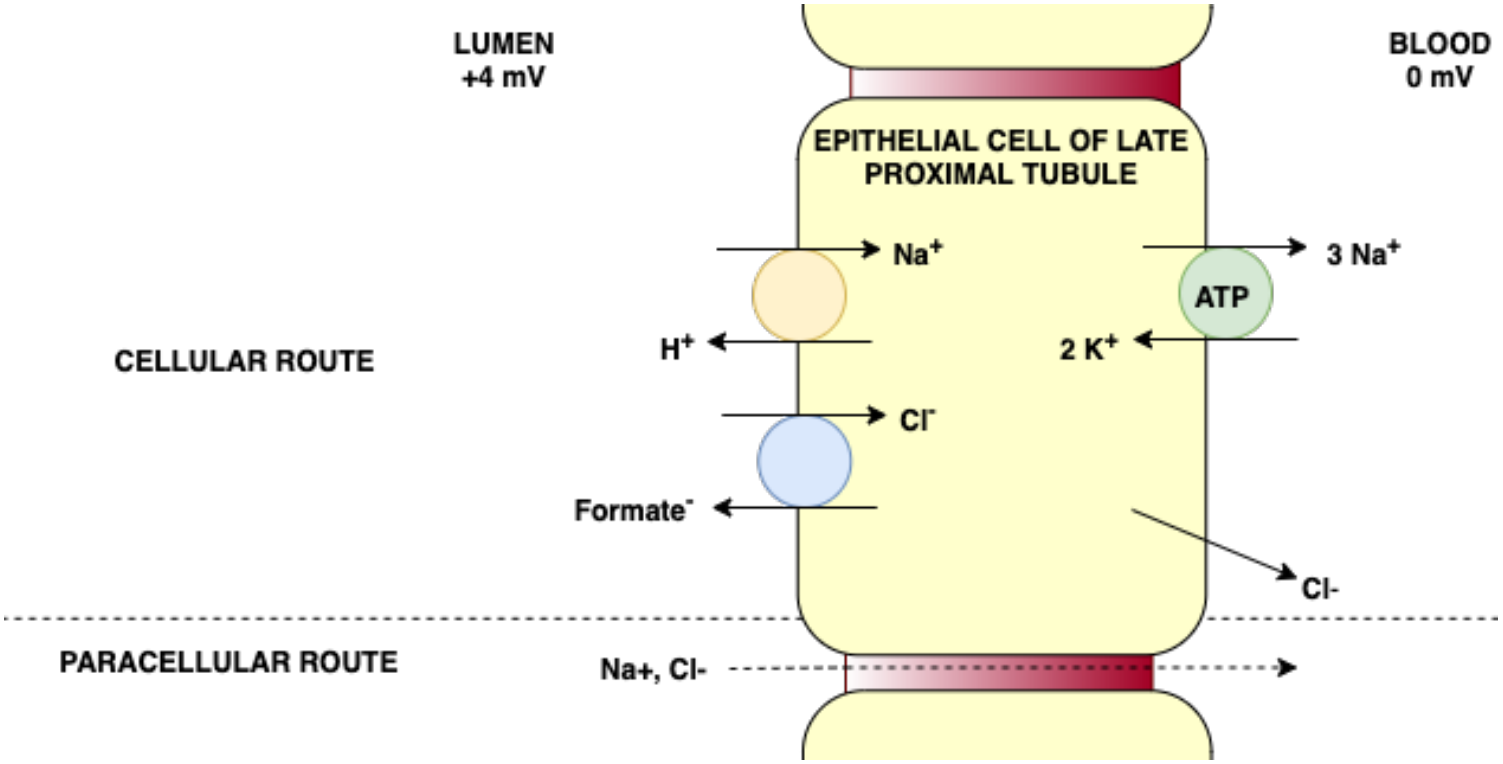
III. Bicarbonate reabsorption

1. Sodium (Na^+) is absorbed from lumen in exchange for hydrogen (H^+)
2. Hydrogen combines with bicarbonate – creating water and CO_2
3. Water and CO_2 diffuses back into the epithelial cell of the proximal tubule
4. Water and CO_2 is then reconverted to H^+ and HCO_3^-
5. H^+ is transported to the lumen via the Na^+-H^+ exchanger
6. HCO_3^- is reabsorbed to blood via facilitated diffusion



6.1.1 – Late proximal convoluted tubule (LPCT)

- Primarily reabsorption of NaCl
- Filtrate in the LPCT has high concentration Cl^- and low concentration of HCO_3^-



NaCl is reabsorbed from LPCT lumen in 2 ways:

Cellular route	Paracellular route
1. NaCl is reabsorbed from lumen via Na^+ - H^+ exchanger, and Cl^--Formate$^-$ anion exchanger. 2. Cl^- reabsorption is driven by the high luminal Cl^- concentration 3. From the cell to blood Na^+ is transported by Na^+, K^+ - ATPase and Cl^- diffuses.	1. The tight junctions between the proximal tubule epithelial cell are permeable to water and small solutes (e.g.: NaCl) 2. Cl^- is able to diffuse between the cells from lumen to blood 3. Cl^- diffusion establishes a Cl^- diffusion potential where lumen is positive compared to the blood 4. The lumen-positive potential difference drives Na^+ reabsorption

6.1.2 – Important concepts of the proximal convoluted tubule

Isosmotic reabsorption	Solute (Na^+ , HCO_3^- , Cl^-) and water reabsorption are coupled in the proximal convoluted tubule
TF/P ratios along PCT	Tubular fluid/Plasma (TF/P) ratio compares concentration of a solute in tubular fluid compared to the concentrations in plasma. At the beginning of the proximal tubule TF/P = 1 for all solutes. The ratio changes as water and solutes begins to be reabsorbed. 1. *TF/P < 1* → HCO_3^-, glucose and amino acids - Amount of reabsorbed water < solute → concentration of the solute decreases (↓) in the tubular fluid 2. *TF/P = 1* → Na^+ - Amount of reabsorbed water = solute → concentration remains the same 3. *TF/P >1* → Cl^- in the EPCT and Inulin - Amount of reabsorbed water > solute → concentration of the solute increases (↑) in the tubular fluid
Glomerulotubular balance	Ensures that a constant fraction of what is filtrated is reabsorbed by the proximal tubule. Important to ensure right fraction of reabsorption (ca 67%) with ↑/↓ in *filtered load.* - ↑ Filtered load: ↑ GFR→ ↑ Filtration fraction→ ↑π_C →↑ Reabsorption - ↓ Filtered load: ↓ GFR→ ↓ Filtration fraction→ ↓ π_C →↓ Reabsorption[1] -
Changes in ECF volume	*Glomerulotubular balance can be altered by ↑/↓ in ECF volume* 1. *ECF volume expansion* → ↓ fractional reabsorption in the PCT - Aids in excretion of excess NaCl and water when there is ECF expansion[2] 2. *ECF volume contraction* → ↑ fractional reabsorption in the PCT - Aids ↑ reabsorption of solute and water as a protective mechanism[3] - Causes contraction alkalosis[4] due to RAAS activation and Angiotensin II[5] effect of PCT.

[1] π_c = Starling forces in the peritubular capillary blood.

[2] E.g. with saline infusion

[3] E.g. in vomiting or diarrhea.

[4] Metabolic alkalosis secondary to volume contraction

[5] Angiotensin II stimulate Na^+–H^+ exchange which increases reabsorption of, water and $\underline{HCO_3^-}$

6.2 – Loop of Henle

- Responsible for countercurrent multiplication, which is important for concentration and dilution of urine.

I. The parts of the loop of Henle

Thin descending limb	Thin Ascending limb	Thick Ascending limb
Permeable to water and small solutes (as NaCl and urea)	Permeable to NaCl Impermeable to water	Net reabsorption of Na^+, K^+ and Cl^- Impermeable to water
Passive diffusion of solutes	Passive diffusion of solutes	Active reabsorption by Na^+-K^+-$2Cl^-$ cotransporter.
Water moves out, solutes move in	Solutes moves out, water remains in the lumen	Solute is reabsorbed, water remains in the lumen
Filtrate becomes more *hyper*osmotic as it moves down the thin descending limb	Filtrate becomes *hypo*osmotic as it moves up the thin ascending limb	Tubular fluid become more diluted

II. Thick ascending limb

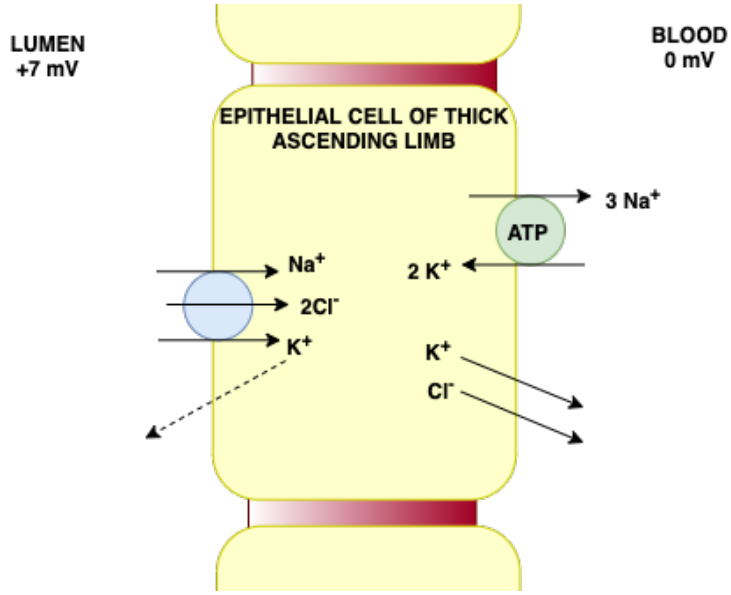
- Ca 25% of filtered Na^+ is reabsorbed
- Reabsorption of Na^+ is load dependent
    1. Higher volume in the filtrate = higher volume of Na^+ reabsorbed.
    2. Limits Na^+ excretion if there is malfunction/inhibition of the PCT
- Some K^+ diffuses back into the lumen → lumen-positive potential difference
    - This drives reabsorption of divalent cations (Ca^{2+} & Mg^{2+})

CLINICAL CORRELATION

Loop diuretics

Loop diuretics (i.e. furosemide and ethacrynic acid) inhibits the Na^+-K^+-$2Cl^-$ cotransporter by attaching to the Cl^- binding site.

Loop diuretics are very potent diuretics and at maximal dosage they can completely block NaCl reabsorption in the thick ascending limb. They are amongst others used in treatment of heart failure, hypertension and edematous states (i.e. ascites)



6.3 – Early Distal Tubule

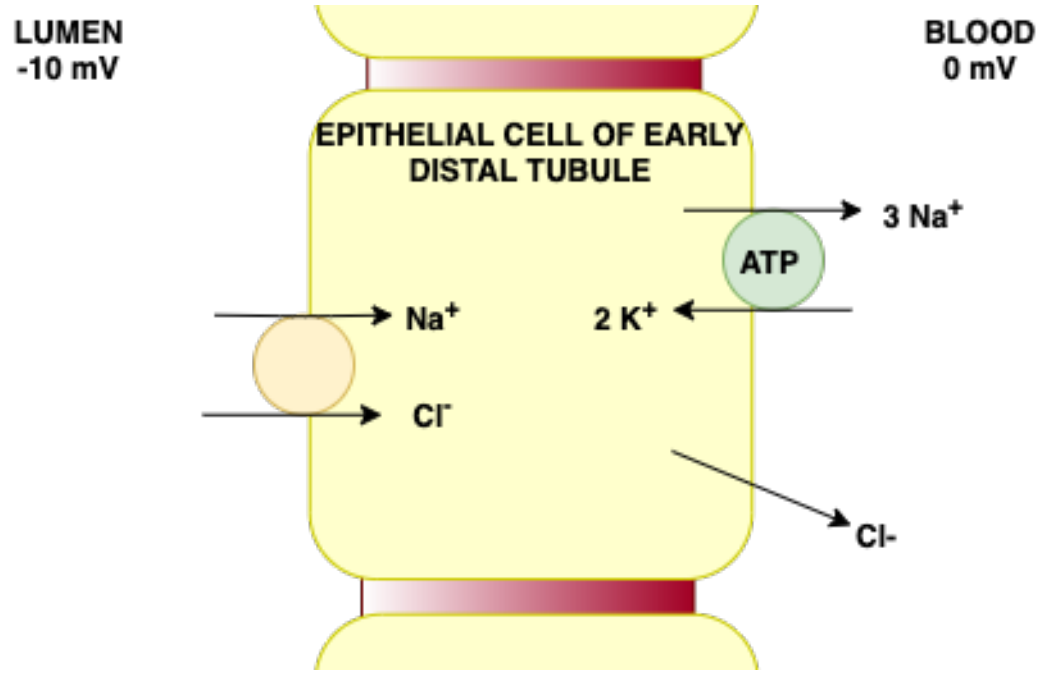
Terminal nephron = distal tubule and collecting duct

I. Reabsorption

- Net reabsorption of NaCl
- Reabsorb 5% of filtered Na^+
- Reabsorption of sodium is load dependent.
- Impermeable to water → further diluting the filtrate

Luminal membrane: Na^+-Cl^- cotransporter (driven by Na^+ gradient)

Basolateral membrane: Na^+ – K^+ exchanger; Cl^- diffusion



CLINICAL CORRELATION

Thiazide diuretics

Thiazide diuretics (i.e. hydrochlorothiazide) inhibit the reabsorption of sodium in the early distal convoluted tubule. They target the NaCl cotransporter on the luminal membrane.
Thiazide diuretics are used in the treatment of conditions as hypertension and mild heart failure.

6.4 – Late Distal Tubule and Collecting Duct

- Anatomically and functionally similar
- 3% of filtered Na^+
- Last segment of the nephron to influence amount of sodium that is excreted.

I. α-intercalated cells

- K^+ reabsorption
- H+ secretion

II. Principal cells

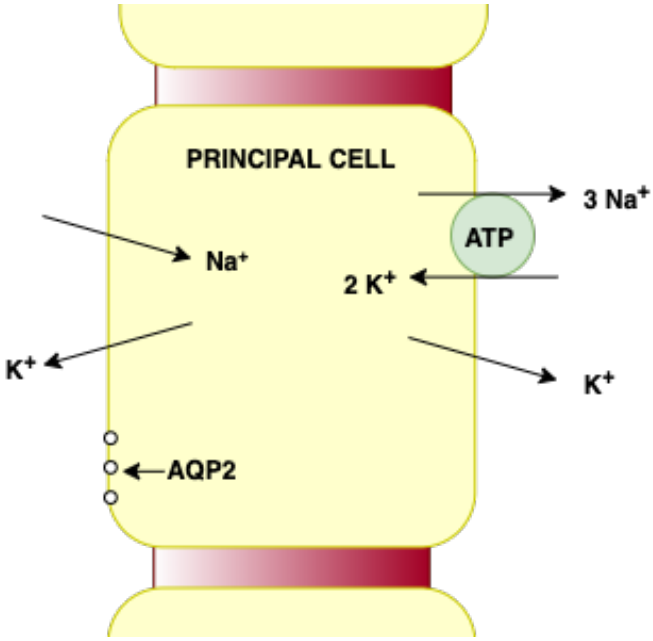
- Na^+ reabsorption
- K^+ secretion
- Water reabsorption

Luminal membrane:

1. Epithelial sodium channel (ENaC)
2. Sodium diffuses down its electrochemical gradient
3. Potassium diffusion
4. Aquaporin 2 channels in the presence of ADH

Basolateral membrane:

1. Na^+, K^+ - ATPase



III. Hormonal influence on the principal cells

- Aldosterone
  - Induce synthesis of proteins involved in sodium reabsorption → causes increased sodium reabsorption.
- Antidiuretic hormone (ADH)
  - Adjusts water permeability of the principal cells by inserting aquaporin 2 channels in the luminal membranes.

CLINICAL CORRELATION

Potassium-sparing diuretics

Sodium reabsorption by the principal cells is inhibited by potassium-sparing diuretics (e.g. spironolactone, amiloride). Potassium-sparing diuretics reduce K^+ wasting and can be used as treatment of hypokalemia caused by other diuretics.

Spironolactone is an aldosterone antagonist and inhibits production of new proteins and can also be used in the treatment of aldosteronism.

NB! With these drugs you have to watch out for hyperkalemia

6.5 – Regulation of Na^+ Balance

The kidney register changes in blood pressure, and will always work to restore blood pressure to normal by directly altering the sodium excretion.

↑ Na^+ ⟶ ECF volume ⟶ ↑ Blood volume ⟶ ↑ Blood pressure

I. Renal mechanisms regulating Na^+ excretion

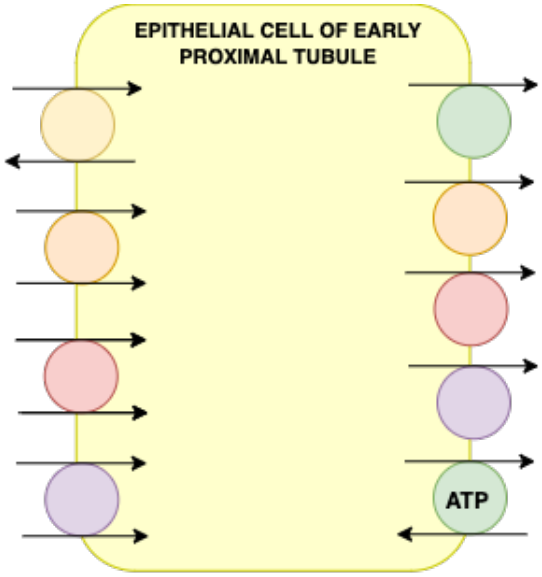
Sympathetic nerve activity	Baroreceptors (aortic and carotid sinus) register decrease in arterial pressure Causes vasoconstriction of afferent arteries and increased proximal tubule Na reabsorption
ANP[1]	Secreted from atria in response to ↑ ECF volume causing: 1. Vasodilation of afferent arterioles 2. Vasoconstriction of efferent arterioles 3. ↑ GFR 4. ↑ Na^+ reabsorption in late distal tubule and collecting duct
Starling forces in peritubular capillaries[2]	↑ECF volume→ dilute π_c → Inhibit renal Na^+ reabsorption ECF volume→ concentrate π_c → Stimulate renal Na^+ reabsorption
Renin-Angiotensin-Aldosterone system	A decrease in blood pressure activates RAAS - Angiotensin II stimulates Na^+-H^+ exchanger in PCT, increasing sodium absorption - Aldosterone stimulates Na^+ reabsorption in the late distal tubule and collecting duct.

[1] See section 4.2 – Regulation of renal blood flow

[2] See section 4.1 – Starling Forces

6.6 – Test Yourself

1) Draw in the movement of solutes in the epithelial cell of the early proximal tubule



2) Glomerulotubular balance ensure that the right fraction of filtered load is reabsorbed. Fill in the correct arrows for the mechanism of glomerulotubular balance:

↑ Filtered load: GFR→ __Filtration fraction→ __π_C → _Reabsorption

3) Fill in the blanks

	Thin descending limb	Thin Ascending limb	Thick Ascending limb
Permeability of tubule to solutes and water	Permeable to water and small solutes (as NaCl and urea)		
Type of transport across the membrane		Passive diffusion of solutes	
Direction of movement of water and solute			Solute is reabsorbed, water remains in the lumen
Osmolarity/concentration of filtrate	Filtrate becomes more **hyper**osmotic as it moves down the thin descending limb		

4) Aldosterone

a) Increases sodium secretion

b) Increases sodium reabsorption

c) Decreases sodium reabsorption

d) Decrease sodium secretion

5) Name the segment of the nephron, and transporter affected by Thiazide diuretics.

6) PTH inhibits which transporter in the early proximal tubule?

7) What is the main function of the late proximal tubule?

8) Explain the term isosmotic reabsorption

Section 7 – Potassium Balance

7.0 – Introduction

- Maintenance of potassium balance is important for normal function of excitable tissues such as nerves, skeletal and cardiac muscle.

I. Body K^+

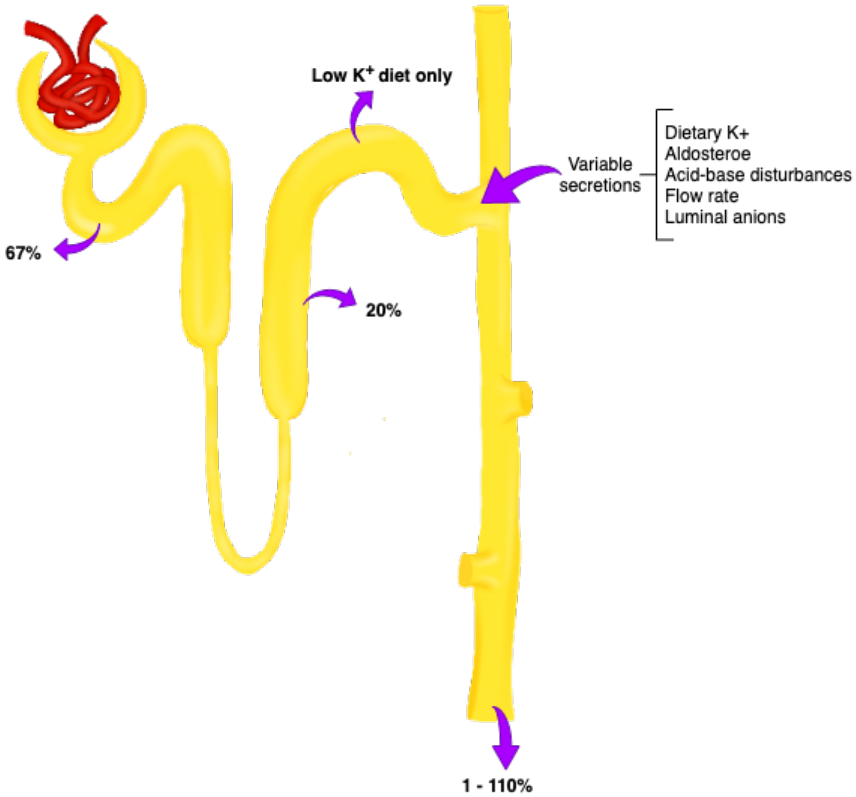
- Most of the total body K^+ is located in the ICF:
  ICF = 98%
  ECF = 2%

II. Potassium concentration gradient

- K^+ concentration gradient sets the resting membrane potential.
- Intracellular K^+ concentration (150 mEq/L) >> extracellular concentration (4.5 mEq/L)
- The concentration gradient is maintained by the Na^+ -K^+ ATPase that is present in all cell membranes.

III. Potassium balance

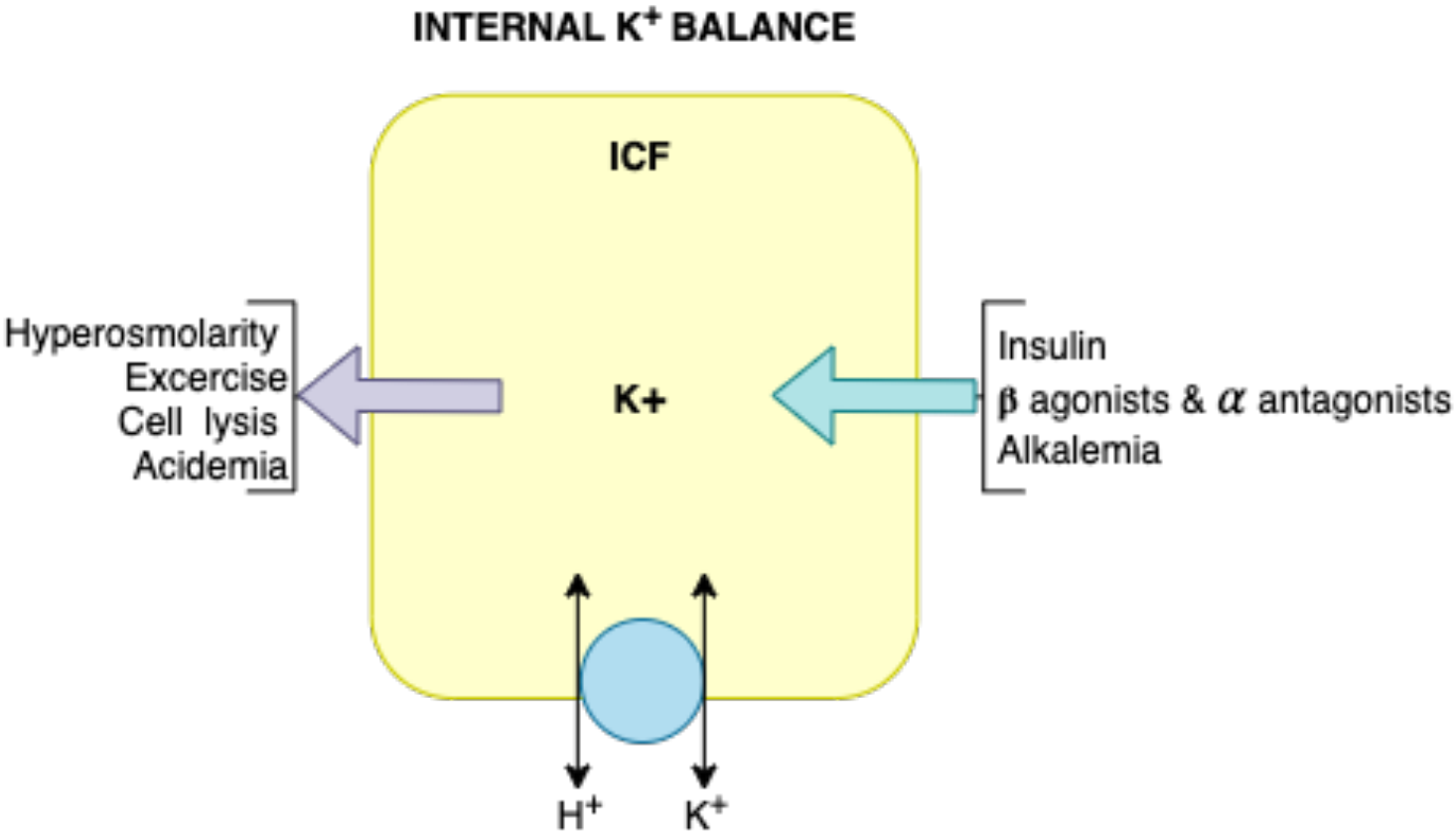
- *Internal K^+ balance:* The distribution of K^+ across cell membranes
- *External K+ balance:* The renal mechanisms that ensures that urinary excretion of K^+= K^+ dietary intake



7.1 – Internal K^+ Balance

7.1.0 – Factors altering the internal K^+ balance

K+ into cell ⟶ Hypokalemia	K+ out of cell ⟶ Hyperkalemia
- High levels of insulin - Alkalemia – blood ↓ [H^+] - β_2 agonists & α antagonists	- Low levels of insulin - Acidemia – blood ↑ [H^+] - α agonists & β_2 antagonists - Hyperosmolarity - Cell lysis - Exercise



7.1.1 - The mechanisms that alter the distribution of K^+

I. Insulin

- Stimulates K^+ uptake into cells by increasing the activity of Na^+- K^+ ATPase.
- Ensures uptake of dietary K^+ into the cells following a meal so K^+ does not remain in the ECF and produce hyperkalemia.
- In deficiency of insulin (e.g. DM type 1) there is decreased uptake of K^+ into cells, which may produce hyperkalemia.

II. Acid-base abnormalities

- H^+-K^+ exchange is a useful mechanism for controlling internal K^+ balance
- ICF has considerable buffering capacity for H^+, by making H^+ enter or leave the cells.
- H^+ must be accompanied by an anion, or exchanged for another cation (e.g. K^+) to preserve electroneutrality

Alkalemia – blood $[H^+] \downarrow \rightarrow H^+$ leaves the cells and K^+ enters the cells → hypokalemia
Acidemia – blood $[H^+] \uparrow \rightarrow$ H^+ enters the cells and K^+ leaves the cells → hyperkalemia

- Acid-base disturbances that do not produce a K^+ shift are:
    1. Respiratory acidosis and respiratory alkalosis → primary disturbance in CO2.
        - Because CO2 is lipid soluble, it freely crosses cell membranes
    2. Several forms of metabolic acidosis are caused by an excess of an organic acid (e.g., lactic acid, ketoacids, salicylic acid), which does not require a K^+ shift.
        - When an organic anion(-), such as lactate, is available to enter the cell with H^+, electroneutrality is preserved K^+

III. Adrenergic agonists and antagonists

- β2 agonists & α antagonists → ↑ Na+–H+ ATPase activity → K+ move into cells (may cause hypokalemia)
- α agonists & β2 antagonists → ↓ Na+–H+ ATPase activity → K+ move out of cells (may cause hyperkalemia)

IV. Hyperosmolarity

- Shift of K^+ out of cells (Water drags K+ out of the cells)

V. Cell lysis

- High $[K^+]$ in cell = high amount of K^+ released with breakdown of cell membranes → hyperkalemia
- Examples of cell lysis include burns, rhabdomyolysis, chemotherapy.

VI. Exercise

- The depletion of cellular ATP stores opens K^+ channels in the muscle cell membranes and K^+ moves out of the cells down its electrochemical gradient.
- Strenuous exercise can result in hyperkalemia in:
    1. Patients on β_2 antagonists
    2. Patients with impaired renal function

7.2 – External K^+ Balance

- Urinary excretion of K^+ = Dietary K^+ (Minus some K^+ that is lost via gastrointestinal tract or sweat)

I. K^+ balance

- *Positive balance:* Excretion < Intake
  - Hyperkalemia can occur
- *Negative balance:* Excretion > intake
  - Hypokalemia can occur

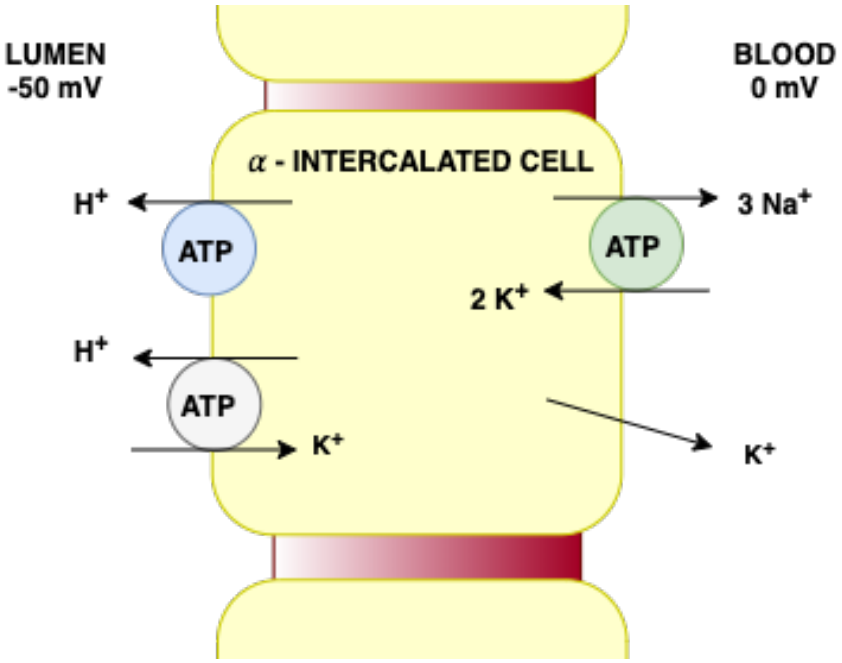
- As dietary intake of potassium varies a great deal, from day to day and from person to person, the mechanisms controlling K^+ balance needs to be very flexible.

II. Filtration and reabsorption

Glomerulus	K^+ Is freely filtered across the glomerular capillaries
Proximal convoluted tubule	Reabsorbs about 67% of the filtered load of K^+ as a part of the isosmotic fluid reabsorption
Thick ascending limb	Reabsorbs 20% of filtered K^+ via Na^+- K^+-$2Cl^-$ cotransporter. K^+ is then both reabsorbed by K^+ channels, and diffuses into the lumen – creating the lumen-positive potential difference
Late distal convoluted tubule and collecting ducts	Responsible for adjusting K^+ excretion to match dietary intake. ↓ Dietary K^+ → K^+ is further reabsorbed by α- intercalated cells ↑ Dietary K^+ → K^+ is secreted by principal cells

7.2.0 – K^+ secretion and reabsorption in late distal tubule and collecting duct

α- intercalated cells

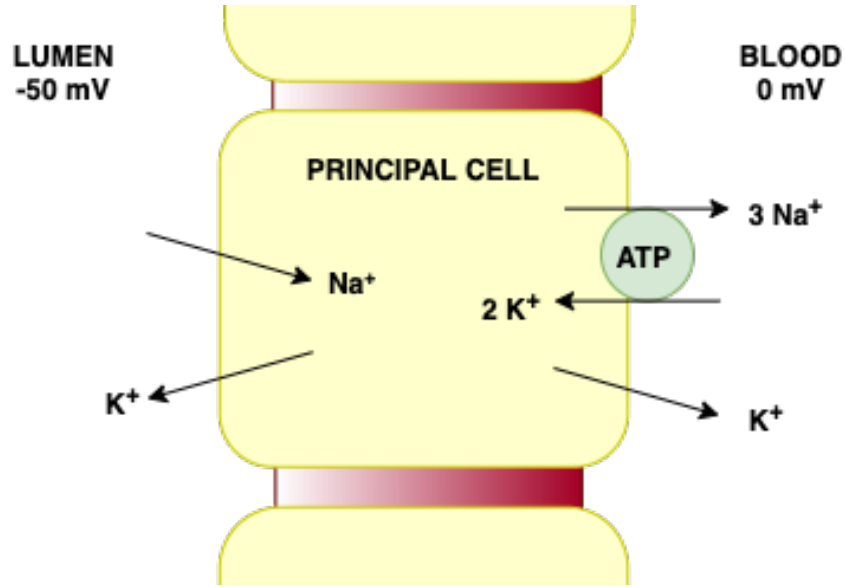


Reabsorption of K^+

H^+ - K^+ ATPase pumps H+ from the cell to the lumen, and K+ into the cell

K+ then diffuses into the blood via K+ channels

Principal cells



Secretion (and reabsorption) of K^+

Na^+ – K^+ ATPase pumps K+ into the cell

Both luminal and basolateral membranes have K+ channels. Most of K+ diffuses across the luminal membrane (secretion)

The *magnitude* of secretion is determined by the size of the electrochemical gradient across the luminal membrane.

7.2.1 – Factors that alter K+ secretion

- Any factor that ↑ electrochemical gradient → ↑ K^+ secretion
- Any factor that ↓ electrochemical gradient → ↓ K^+ secretion
- The electrochemical gradient across the luminal membrane can be increased either by ↑ the intracellular K^+ concentration or by ↓ the luminal K^+ concentration.

Dietary K^+	**High K^+ diet** - ↑ Intracellular [K^+] of principal cells → ↑ Excretion of K^+ in the urine **Low K^+ diet** - Low K^+ intake → ↓ Intracellular [K^+] of principal cells → ↓ Excretion of K^+ in the urine - ↑ reabsorption of K^+ by the α- intercalated cells → ↓ Excretion of K^+ in the urine
Aldosterone	Aldosterone causes ↑ secretion of K^+ by the principal cells via: 1. ↑Na^+ entry into the principal cells 2. ↑ Quantity of Na^+-K^+ ATPases This leads to ↑ intracellular K^+ as more sodium needs to be transported out, and there are more transporters Aldosterone also ↑ the number of K^+ channels on the luminal membrane
Acid-base disturbances	***Alkalosis*** → ↑ ***K^+ secretion*** Deficit of H^+ in ECF → H^+ leaves the cell for buffering → K^+ enters cell → ↑ Intracellular [K^+] → ↑ K^+ secretion → Hypokalemia **Acidosis** → ↓ **K^+ secretion** Excess of H^+ in ECF → H^+ enter the cell for buffering → K^+ leaves cell → ↓ intracellular [K^+] → ↓ K^+ secretion → Hyperkalemia

Factors that alter K+ secretion continued:

Diuretics	*Loop diuretics & Thiazide diuretics* → ↑ K^+ excretion 1. Loop and thiazide diuretics inhibit sodium reabsorption at thick ascending limb and loop of Henle. This causes more sodium to be delivered to the LDCT and collecting duct. - ↑ Na^+ reabsorption by principal cells → ↑ K^+ secretion as more K^+ is pumped into the cell by $Na^+ – K^+$ ATPase - **!** Hypokalemia is an important side effect of treatment with these diuretics 2. Loop diuretics also inhibit Na^+-K^+-$2Cl^-$ cotransport in thick ascending limb, and thereby inhibits some of the K+ reabsorption. - The decrease of absorption and increased secretion causes profound kaliuresis and hypokalemia with use of loop diuretics. 3. Increased flow rate = luminal K^+ concentration is diluted → increasing driving force for K+ secretion
K^+ sparing diuretics	Inhibits the action of aldosterone on principal cells → inhibits K^+ secretion. Mainly used in combination with loop or thiazide diuretics to minimize K^+ wasting.
Luminal anions	Presence of large anions in the lumen of the distal tubule and collecting duct increases K^+ secretion due to increased electronegativity of the lumen.

7.3 – Test Yourself

1) Fill in the table: Factors altering the internal K^+ balance

K+ into cell → Hypokalemia	K+ out of cell→ Hyperkalemia

2) In which segments of the nephron is potassium reabsorbed?
a) Proximal tubule, thick ascending limb, collecting duct
b) Proximal tubule, thin descending limb and distal convoluted tubule
c) Proximal tubule, thick ascending limb late distal tubule and collecting duct
d) Proximal tubule, thick ascending limb early distal tubule

3) How does K^+ sparing diuretics inhibit K^+ secretion?

4) In which segments of the nephron is potassium secreted?

5) How does acidemia and alkalemia affect K^+ distribution?

6) Chemotherapy and rhabdomyolysis can cause hyperkalemia, how?

7) What happens with the K^+ excretion in a low K^+ diet?

8) Which factors alter K^+ secretion?

Section 8 – Phosphate, Calcium and Magnesium Balance

8.0 – Phosphate Balance

- Phosphate plays a critical part in the body, as a constituent of bone and as a buffer for H^+ in urine.

Phosphate in the body	**Bone matrix:** 85% **ICF:** 15% **ECF:** < 0,5%
Plasma Phosphate	In the ECF phosphate serves as a buffer for H^+. 10% of phosphate in ECF is bound to plasma, the rest (90%) is freely filtered in the glomerulus.
Phosphate reabsorption	85% of filtered phosphate is reabsorbed 15% is excreted There is a limited amount of transporters, which makes the mechanism saturable. Phosphate has a transport maximum (T_m), and any phosphate not reabsorbed at T_m is excreted.
PCT	70% in PCT, and 15% in proximal straight tubule (PST) Na^+-Phosphate cotransporter in luminal membrane of the proximal tubule cells[1]
Urinary buffering	Unabsorbed phosphate serves as a urinary buffer for H+.
Parathyroid hormone (PTH)	PTH Regulates absorption from PCT by inhibiting the Na^+-Phosphate cotransporter Inhibition of the transporter causes *phosphaturia*[2]

[1] It is uncertain whether phosphate is reabsorbed in other segments

[2] ↑phosphate excretion

8.1 – Magnesium Balance

Plasma Mg^{2+}	20% is bound to plasma
Filtration	80% is filterable
Reabsorption	95% reabsorbed 5% excreted
PCT	30% of filtered load is reabsorbed
Thick ascending limb	60% of filtered load is reabsorbed Driven by the LPPD[1] created by the Na^+-K^+-$2Cl^-$ cotransporter.
Distal tubule	5% is reabsorbed

[1]LPPD = Lumen-positive potential difference

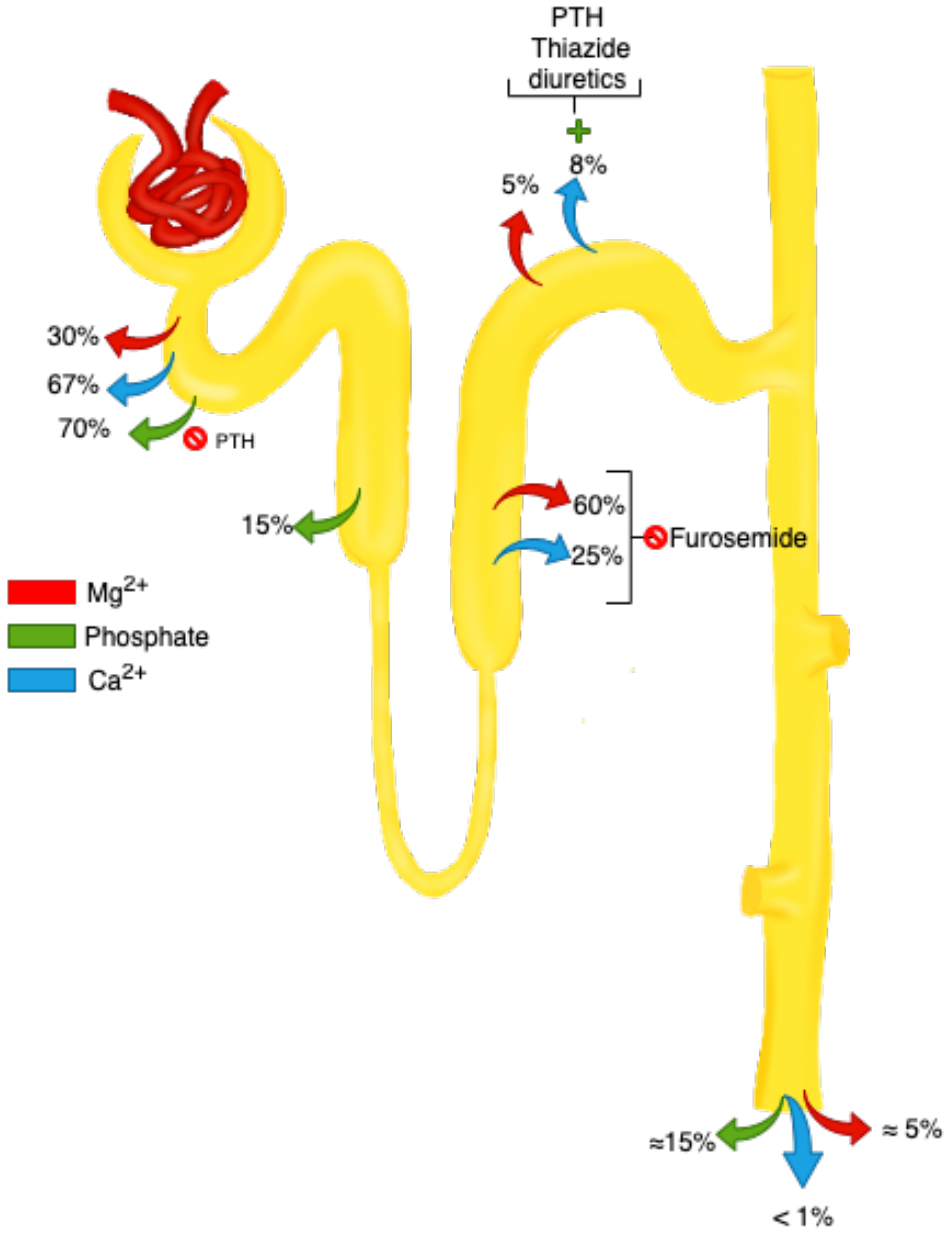
8.2 – Calcium Balance

Calcium in the body	**Bone matrix:** 99% **ECF & ICF** 1% **Total plasma Ca^{2+}** 5 mEq/L (10 mg/dL)
Plasma Ca^{2+}	40% bound to plasma protein 10% bound to anions (e.g. phosphate, citrate) 50% free
PTH	Regulates plasma Ca^{2+}
Filtration	60% of total plasma Ca^{2+} is filtered in the glomerulus *Filtered load Ca^{2+} = GFR × Total plasma Ca^{2+} × 0,60* The 40% bound to plasma protein cannot be filtered
Reabsorption	99% is reabsorbed 1% is excreted
PCT	**67%** of filtered load is reabsorbed Coupled to Na reabsorption: 1. Volume expansion inhibits Na^+ reabsorption → ↓ Ca^{2+} reabsorption 2. Volume contraction stimulates Na^+ reabsorption → ↑Ca^{2+} reabsorption
Loop of Henle	**25%** of filtered load is reabsorbed Coupled to Na reabsorption, and dependent on the LPPD[1] LPPD is created by the Na^+-K^+-$2Cl^-$ cotransporter. Ca^{2+} reabsorption occurs via paracellular routes
Distal tubule	**8%** of filtered load is reabsorbed Site of regulation of Ca^{2+} reabsorption Not coupled to Na^+ reabsorption *Thiazide diuretics and PTH* ↑Ca^{2+} reabsorption in EDCT[2]

[1]LPPD = Lumen-positive potential difference

[2]EDCT = Early distal convoluted tubule

8.3 – Phosphate, Calcium and Magnesium Balance



CLINICAL CORRELATION

Loop diuretics and hypomagnesemia

When *Loop diuretics* (e.g. furosemide) act on the Na^+-K^+-$2Cl^-$ cotransporter, they eliminate the lumen-positive potential difference. inhibiting the reabsorption of Mg^{2+} (same as with Ca^{2+}).

Use of *Loop diuretics* increases magnesium excretion, and may cause hypomagnesemia.

CLINICAL CORRELATION

Treatment of hypercalcemia

When *Loop diuretics* (e.g. furosemide) act on the Na^+-K^+-$2Cl^-$ cotransporter, they eliminate the lumen-positive potential difference. inhibiting the reabsorption of Ca^{2+} as well as the reabsorption of Na^+. Due to this mechanism, *Loop diuretics* can be used to treat *hypercalcemia.*

8.4 – Test Yourself

True or false	True	False
Thiazide diuretics and PTH increases Ca^{2+} reabsorption in the early distal convoluted tubule		
PTH causes decreased excretion of phosphate		
Thiazide diuretics can be used to treat hypercalcemia		
Calcium reabsorption in the proximal convoluted tubule is coupled to Na^{+} reabsorption		

1) Where can we find most of the phosphate in the body?

2) Where is most of the phosphate reabsorbed?

3) Where is most of magnesium reabsorbed?

4) By what mechanism can Loop diuretic cause hypomagnesemia?

5) How does changes in volume affect calcium reabsorption?

Section 9 – Water Balance

9.0 – Regulation of Body Fluid Osmolarity

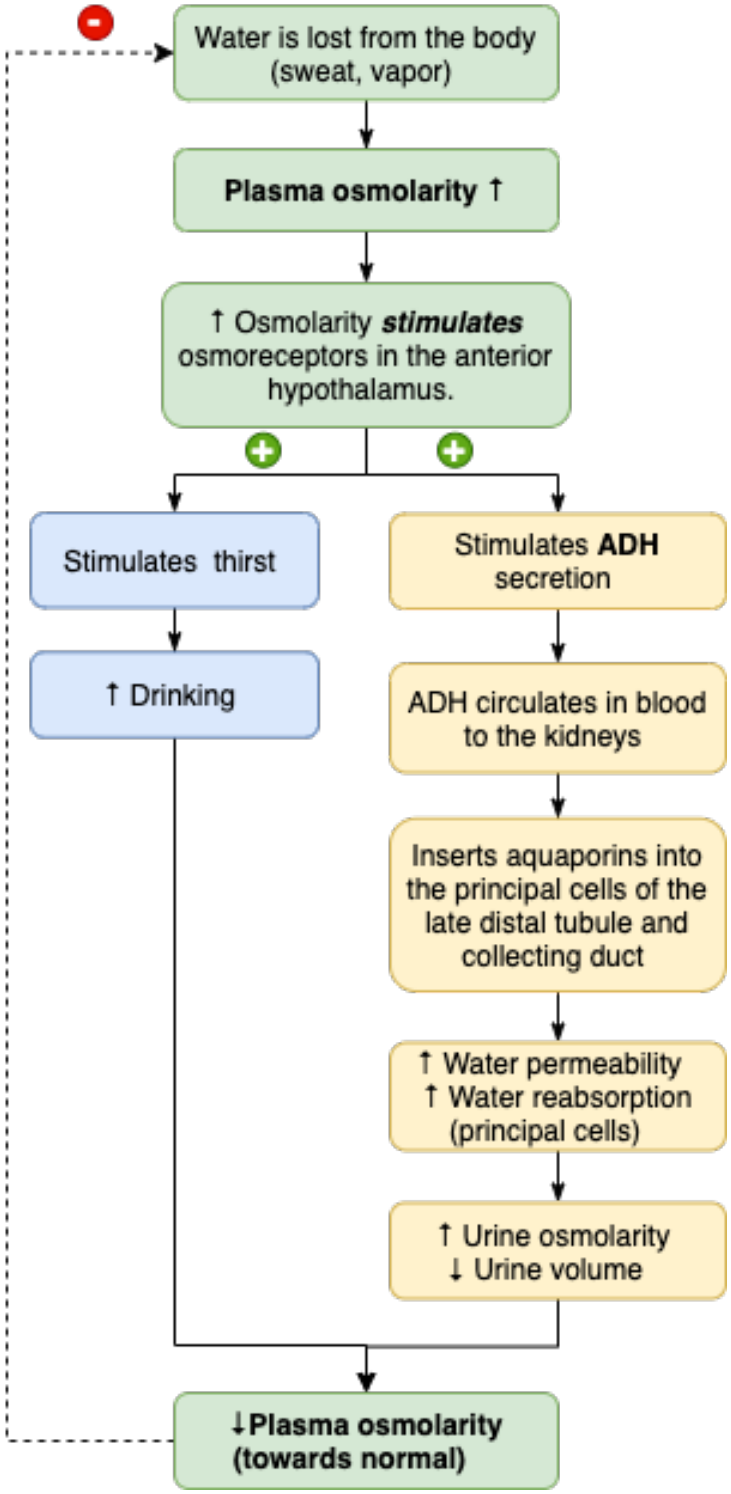
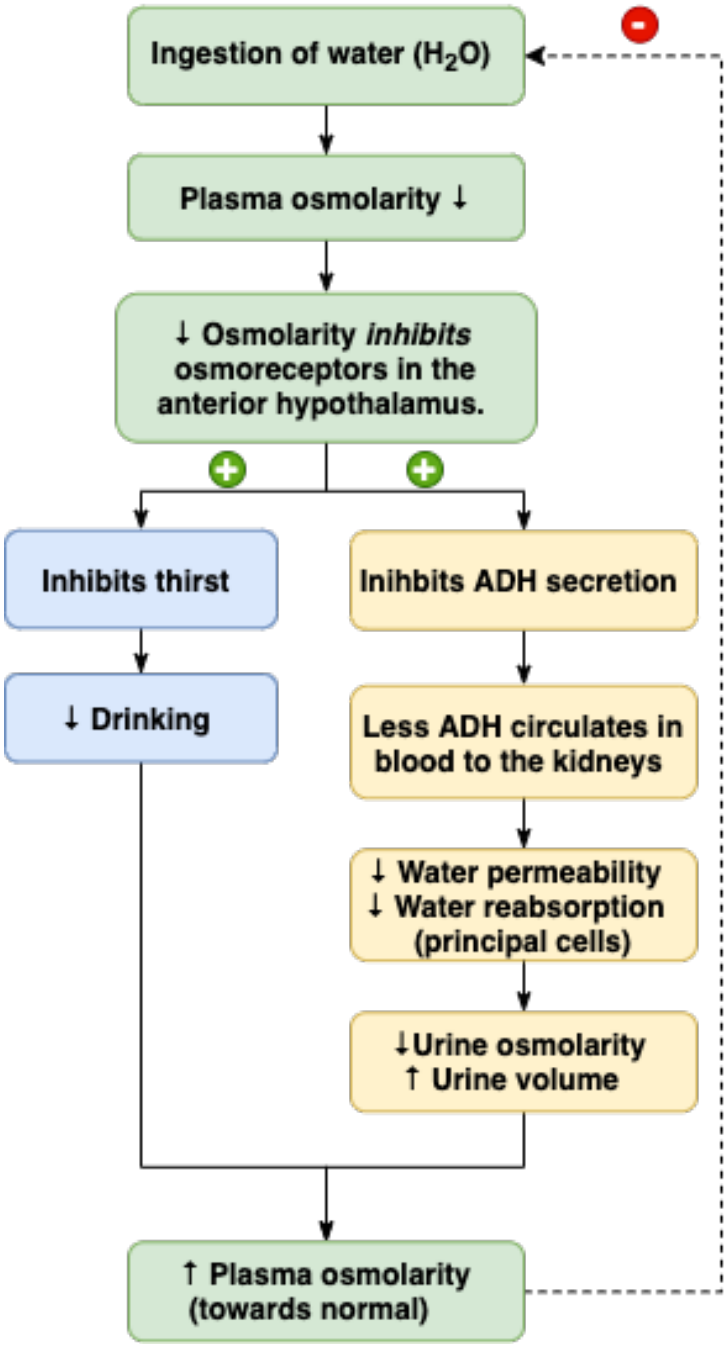
9.0.0 – Urine osmolarity

- Body fluid osmolarity is maintained at 290 mOsm/L by osmoregulation.
- Deviations from this initiates hormonal responses altering water reabsorption by the kidneys.

Isosmotic urine	Urine osmolarity = Blood osmolarity
Hyperosmotic urine	Urine osmolarity > Blood osmolarity
Hypoosmotic urine	Urine osmolarity < Blood osmolarity

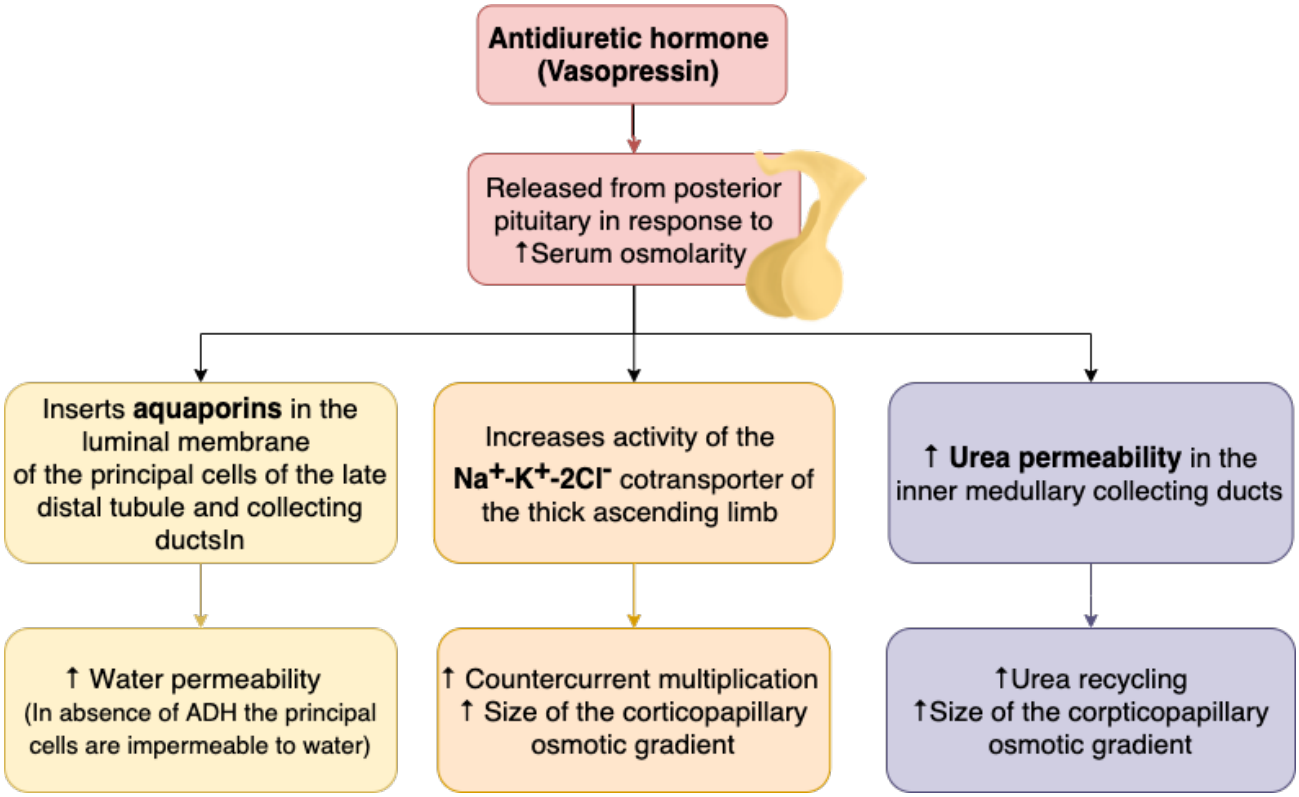
9.0.1 – Water balance

- Regulated in the late distal tubule and collecting duct
- Variations in water reabsorption produce variations in urine osmolarity.
- Urine osmolarity can vary from 50 to 1200 mOsm/L

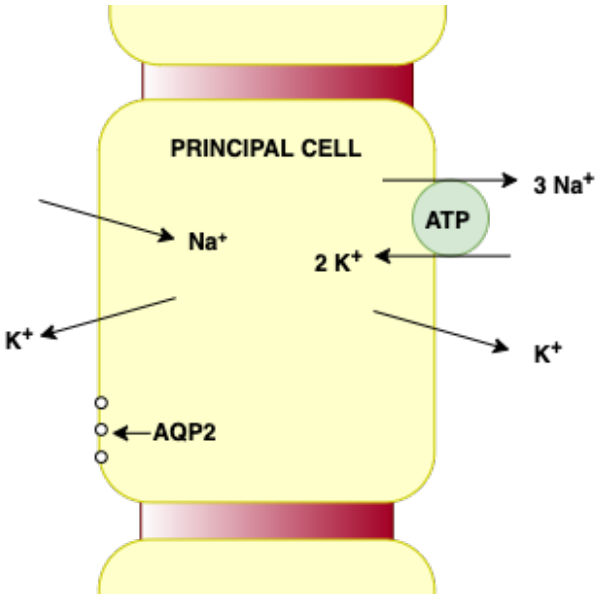
Response to water deprivation	Response to water ingestion
	

9.1 – Antidiuretic Hormone

I. Three actions on the renal tubule



II. Principal cell of late distal convoluted tubule with aquaporin 2 at luminal membrane



9.2 – Corticopapillary Osmotic Gradient

- Critical for the kidneys participation in osmoregulation

I. Gradient of osmolarity in the interstitial fluid of the kidney from the cortex to the papilla

- Osmolarity in the cortex = 300mOsm/L
- Osmolarity of the interstitial fluid progressively increases as the fluid moves from the cortex through the outer medulla, inner medulla and ends in the papilla.
- Osmolarity at the papilla can be up to 1200 mOsm/L

II. Mechanism contributing to the corticopapillary osmotic gradient

- Solutes that contribute to the osmotic gradient are NaCl and urea and they are deposited in the interstitial fluid through
    1. Urea recycling
    2. Countercurrent multiplication

III. ADH effect on corticopapillary gradient

- High levels of ADH increases corticopapillary gradient by:
    1. Enhancing the single effect of countercurrent multiplication
    2. Enabling urea recycling in the inner medulla

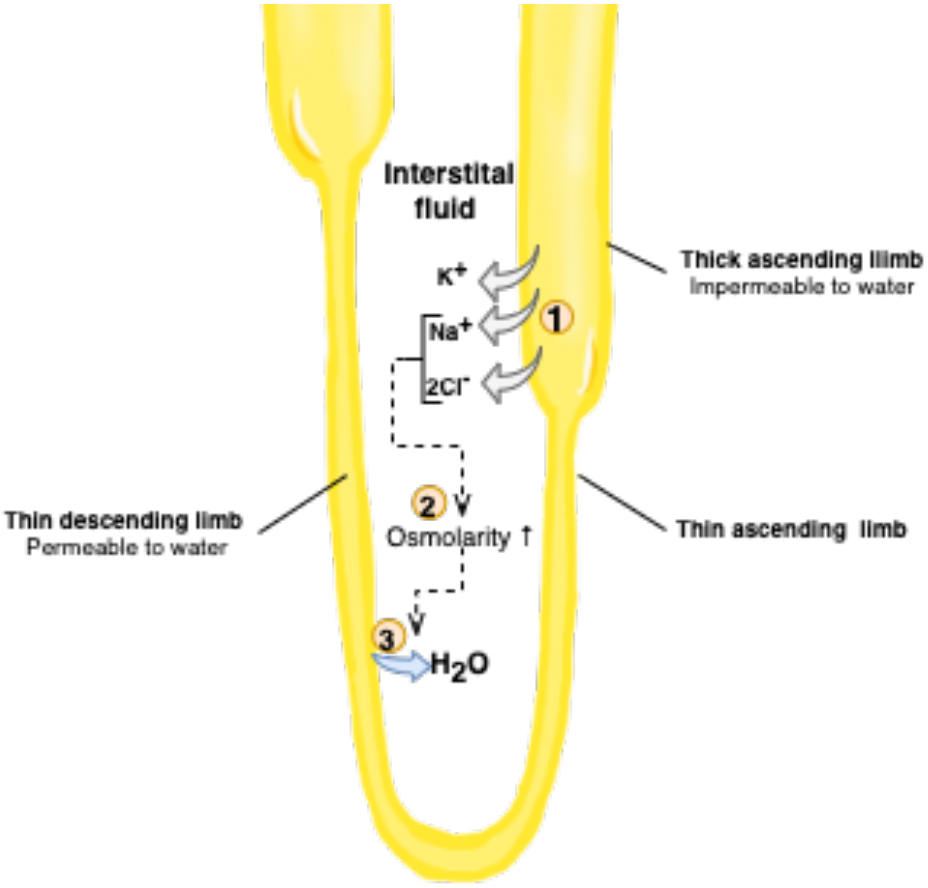
9.2.0 – Countercurrent multiplication

- A function of the loop of Henle
- Deposits NaCl in the interstitial fluids in the deeper regions of the kidney
- Builds a gradient of osmolarity through repeating two steps:
    1. Single effect
    2. Flow of the tubular fluid

I. Single effect

1. Thick ascending limb reabsorbs NaCl (via the Na^+-K^+-$2Cl^-$-pump)
    - It is impermeable to water and the tubular fluid is diluted by continued reabsorption of NaCl
2. Reabsorbed NaCl increases the osmolarity of Interstitial fluid
3. The Descending limb is permeable to water → water flows out until its osmolarity increases to the level of the adjacent interstitial fluid

Result: Osmolarity of the ascending limb *decreases*, and osmolarities of the interstitial fluid and the descending limb *increase*



II. ADH enhances the single effect by increases Na^+-K^+-$2Cl^-$-pump activity

- High ADH e.g. in dehydration→ corticopapillary osmotic gradient is augmented
- Low ADH e.g. in central diabetes insipidus → corticopapillary osmotic gradient is diminished

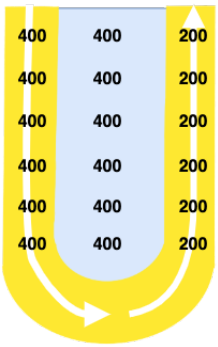
III. Flow of the tubular fluid

1. Flow through the nephron is continuous
2. Fluid entering the descending limb of loop of Henle = 300 mOsm/L
3. New fluid pushes the existing fluid further down the nephron
4. The high osmolarity fluid (created by single effect) in the descending limb move down to the bend of the loop of Henle.

IV. Mechanism of countercurrent multiplication

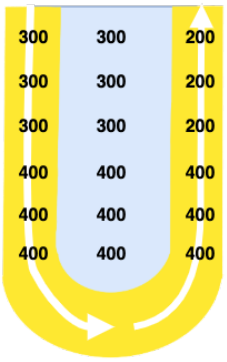
- The 2 steps are repeated until full corticopapillary gradient is established. Each repetition increases (multiplies) the gradient. Size of the corticopapillary osmotic gradient depends on the length of the loop of Henle

Step 1 – Single effect



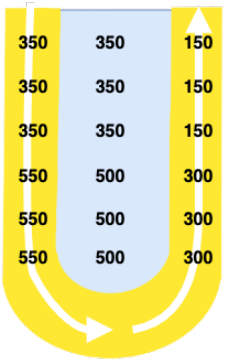
1. NaCl is reabsorbed without water from the ascending limb and is deposited in the surrounding interstitial fluid
2. Interstitial fluid increases to 400 mOsm/L
3. Fluid in descending limb equilibrates with the interstitial fluid and its osmolarity also becomes 400 mOsm/L
4. Ascending limb is diluted to 200 mOsml/L

Step 2 – Flow of fluid



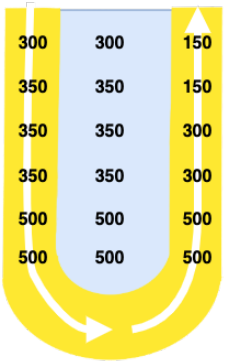
1. New fluid Osmolarity 300 mOsm/L enters descending limb from the PCT
2. Fluid in the nephron shifts, which displaces fluid from the ascending limb.
3. High osmolarity fluid – 400 mOsm/L moves down to the bend of the loop

Step 3 – Single effect



1. NaCl is reabsorbed without water from the ascending limb and is deposited in the surrounding interstitial fluid
2. Osmolarity of the interstitial fluid and descending limb fluid increases – adding to the gradient that was already established
3. Osmolarity of the fluid of the ascending limb decreases further (is diluted)

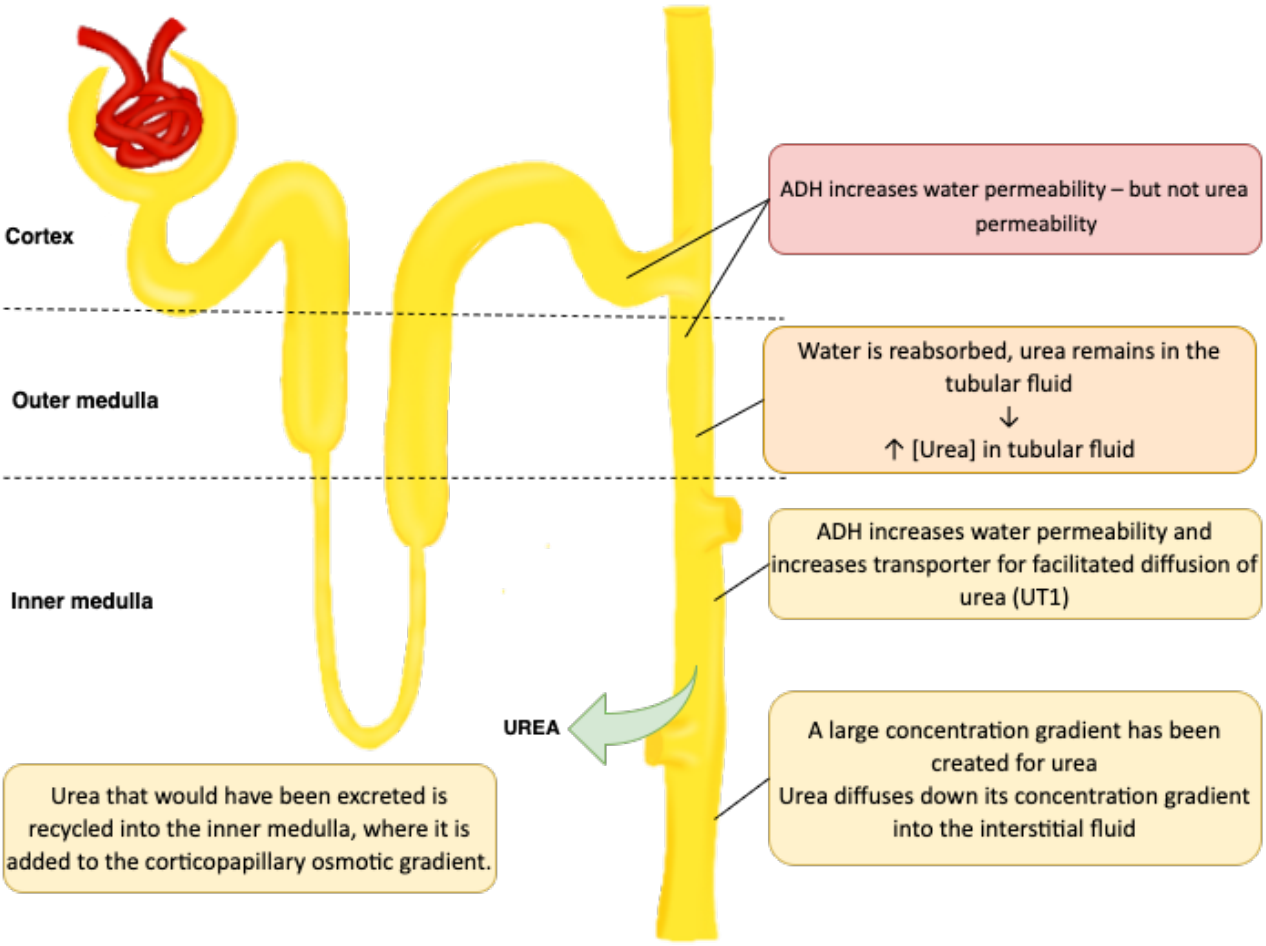
Step 4 – Flow of fluid



1. New fluid Osmolarity 300 mOsm/L enters descending limb from the PCT
2. Fluid in the nephron shifts, which displaces fluid from the ascending limb.
3. High osmolarity fluid in descending limb is pushed down toward the bend of the loop of Henle.
4. Gradient is now larger than in step 2

9.2.1 – Urea recycling

- Second process contributing to establishing the corticopapillary osmotic gradient



See section 5 – Reabsorption and secretion, part 5.1.1 – Passive reabsorption: Urea

I. Urea and the corticopapillary gradient

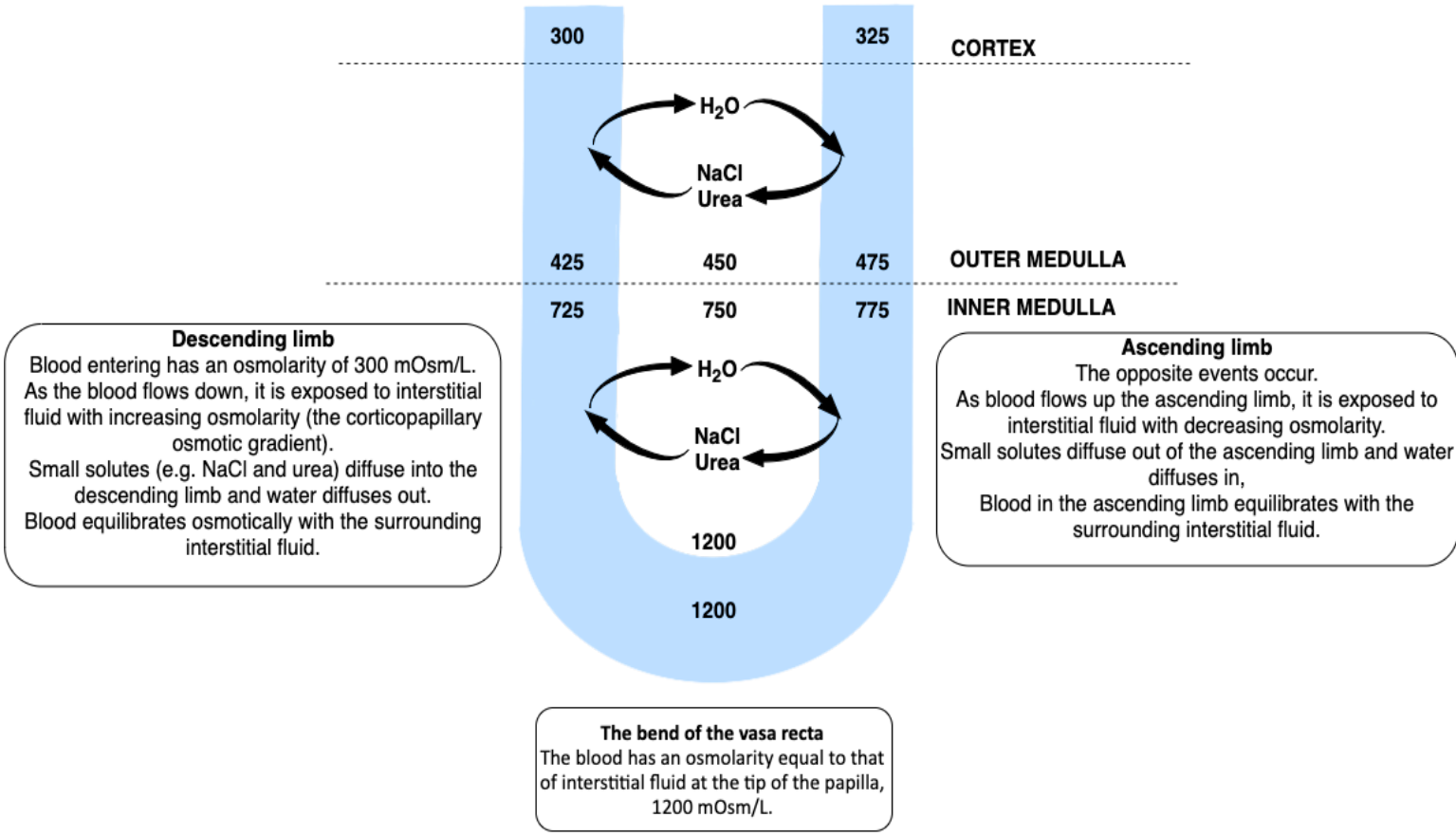
- Urea is deposited in the inner medulla, and increases the osmolarity of the interstitial fluid.
- The urea deposition adds to the corticopapillary gradient

II. ADH

- Urea recycling is dependent on ADH
    1. *High ADH* (e.g. in dehydration) → permeability incresseas→ urea is recycled into the inner medulla → adding to the corticopapillary osmotic gradient
    2. *Low ADH* (e.g. in central diabetes insipidus) → no permeability → urea is not recycled

9.2.2 – Vasa recta

- Capillaries serving the medulla and papilla of the kidney
- Follow the same course as the loop of Henle
- Participate in countercurrent exchange
    - Purely passive process that helps maintain the corticopapillary gradient
        1. The vasa recta are freely permeable to small solutes and water
        2. Blood flow is slow, and solutes and water can move in and out allowing efficient countercurrent exchange



I. Blood leaving the vasa recta

- Blood leaving the vasa recta has an osmolarity of 325 mOsm/L, which is higher than the osmolarity of the blood that entered it. This is because some of the solute from the corticopapillary osmotic gradient is absorbed and will be transported back into the systemic circulation.
- This could remove the corticopapillary osmotic gradient, but due to continuous countercurrent multiplication and urea recycling the gradient usually stays intact.

9.3 – Hyperosmotic and Hypoosmotic Urine

9.3.0 – Hyperosmotic urine

- Hyperosmotic urine = urine osmolarity > blood osmolarity
- Produced when levels of *ADH* is high (e.g. in SIADH or dehydration)
- Urine becomes hyperosmotic by making the osmolarity of tubular fluid in the collecting ducts equal to the high osmolarity of the corticopapillary gradient.
- Final urine osmolarity will be equal to the osmolarity at the bend of the loop of Henle

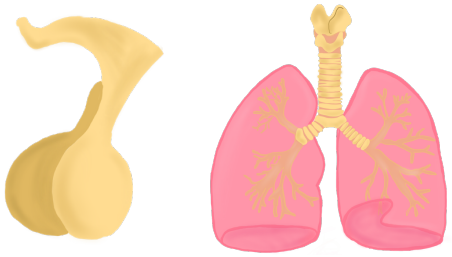
CLINICAL CORRELATION

Syndrome of inappropriate ADH (SIADH)

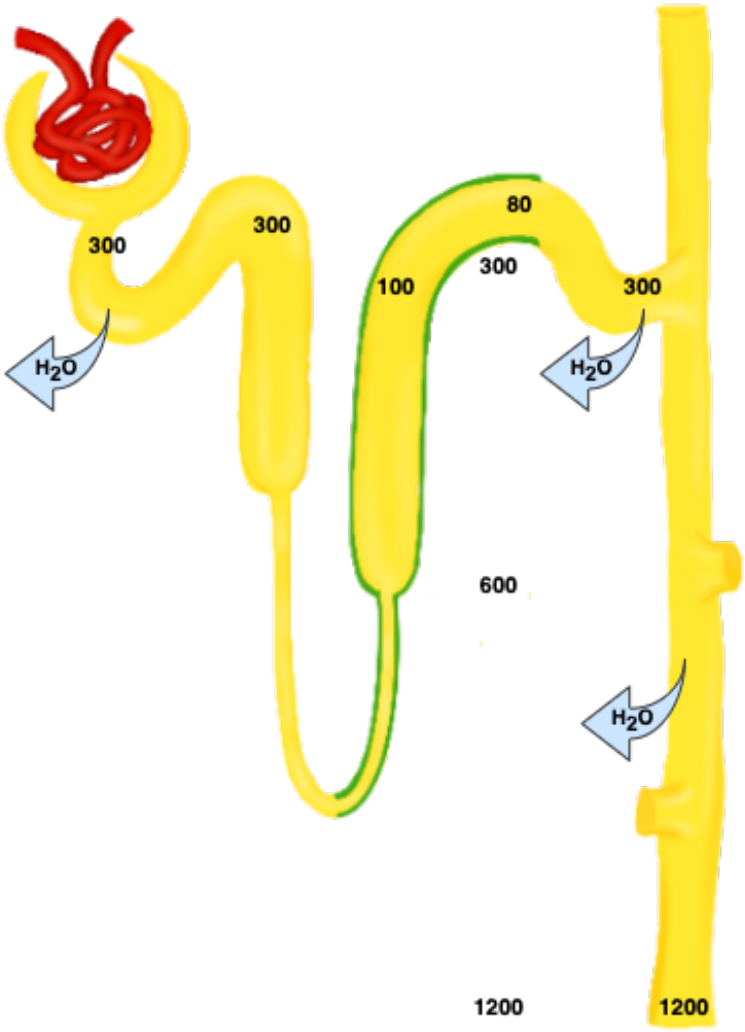
SIADH is a condition with excess secretion of ADH, due head trauma or ectopic secretion (e.g. from a lung tumor).

The high levels of ADH makes the urine hyperosmotic and dilutes the plasma osmolarity. This causes hyponatremia and depending on severity and rapidity of onset, the neurologic consequences can include confusion, lethargy, weakness, generalized seizures, and coma. The normal feedback mechanism with low plasma osmolarity will not occur, as ADH is secreted autonomously.

Treatment of SIADH consists of administration of a drug such as demeclocycline, which inhibits the ADH action on the renal principal cells.



I. Production of hyperosmotic urine



Proximal convoluted tubule
Isosmotic reabsorption
Osmolarity = 300 mOsm/L

Thick ascending limb (diluting segment)
Impermeable to water
Sodium is reabsorbed by Na-K-2Cl cotransporter
Solute is reabsorbed, water is left behind
Osmolarity of fluid leaving the segment is 100 mOsm/L

Early distal tubule (cortical diluting segment)
Impermeable to water
NaCl is reabsorbed by Na-Cl cotransporter
Osmolarity of fluid leaving the segment is 80mOsm/L

Late distal tubule
Principal cells:
Permeable to water in presence of ADH
Osmolarity of tubular fluid is low – water is reabsorbed by osmosis
Reabsorption of water continues until osmolarity of tubular fluid is equal to the osmolarity of interstitial fluid (300 mOsm/L)

Collecting ducts (Same mechanism as late distal tubule)
Principal cells:
Permeable to water in presence of ADH
Osmolarity of interstitial fluid ↑ down the collecting duct
Water continues until osmolarity of tubular fluid = osmolarity of interstitial fluid
Final urine will reach the osmolarity at the papilla e.g. 1200 mOsm/L

9.3.1 – Hypoosmotic urine

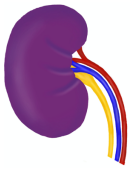
- Hypoosmotic urine = urine osmolarity < blood osmolarity
- Produced when levels of *ADH are low*. A normal response to water drinking or can be due to pathologies as central diabetes insipidus and nephrogenic insipidus.
- ! Corticopapillary gradient will be lower with absence of ADH

CLINICAL CORRELATION

Diabetes insipidus

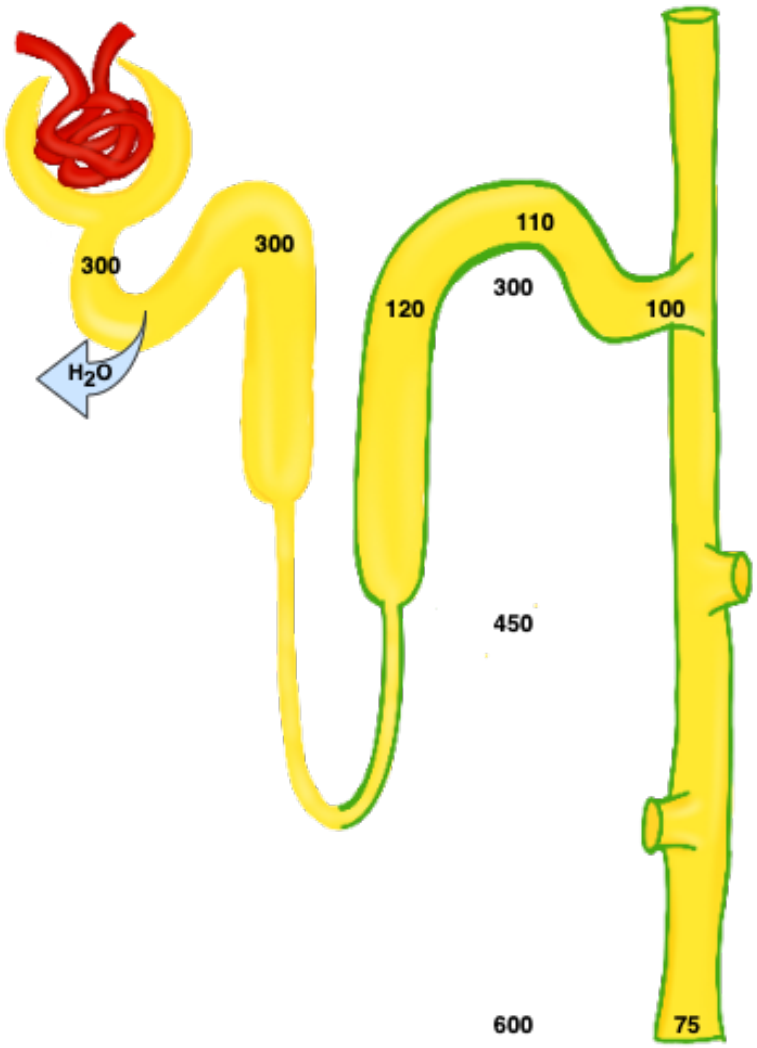
Diabetes insipidus is a condition that causes major water loss and high plasma osmolarity with hypernatremia and hypotonic urine due to no reabsorption of water in the distal tubule and collecting duct. The lack of water reabsorption causes large volumes of dilute urine to be excreted. Diabetes insipidus can be due central problems, or problems in the kidney.

1. **Central diabetes insipidus**
   - The posterior pituitary is unable to secrete ADH (e.g. due to head trauma or tumor)
   - Treatment consists of administrating an ADH analogue (e.g. desmopressin)



2. **Nephrogenic diabetes insipidus**
   - ADH secretion is functional, but there is a defect in principal cells response to ADH
   - ADH levels will be elevated in response to increased plasma osmolarity, but with no effect on the water reabsorption.
   - Thiazide diuretics are used to treat nephrogenic diabetes insipidus

I. Production of hypoosmotic urine



Proximal convoluted tubule
Unaffected by ADH
Isosmotic reabsorption
Osmolarity = 300 mOsm/L

Thick ascending limb (diluting segment)
Impermeable to water
Solute is reabsorbed, water is left behind

Sodium is reabsorbed by Na^+-K^+-$2Cl^-$ cotransporter
Activity of the cotransporter is lower no ADH, therefor osmolarity is lower than in the presence of ADH
Osmolarity of fluid leaving the segment is 120 mOsm/L

Early distal tubule (cortical diluting segment)
Impermeable to water
NaCl is reabsorbed by Na-Cl cotransporter
Osmolarity 110mOsm/L

Late distal tubule & Collecting ducts
! Impermeable to water in the absence of ADH
Water is not reabsorbed in response to the osmotic gradient
→ No osmotic equilibration
Some NaCl is reabsorbed
Final, not equllibrated urine, has an osmolarity of 75 mOsm/L

9.4 – Free Water Clearance

I. Free water = Distilled water free of solutes

- In the nephron, free water is generated in the diluting segments (thick ascending limb and early distal tubule) when solutes are reabsorbed without water.
- Free water clearance can be used as a measure for how the body regulates water.
    - Calculating free water clearance (C_{H20}) provides a method for measuring water loss, if water is reabsorbed or excreted.

II. Measurement of free-water clearance

- It is the difference between the urine volume and the clearance of osmoles.
    - Clearance of osmoles is the amount of water necessary to excrete the osmotic load in urine that is isotonic with plasma.

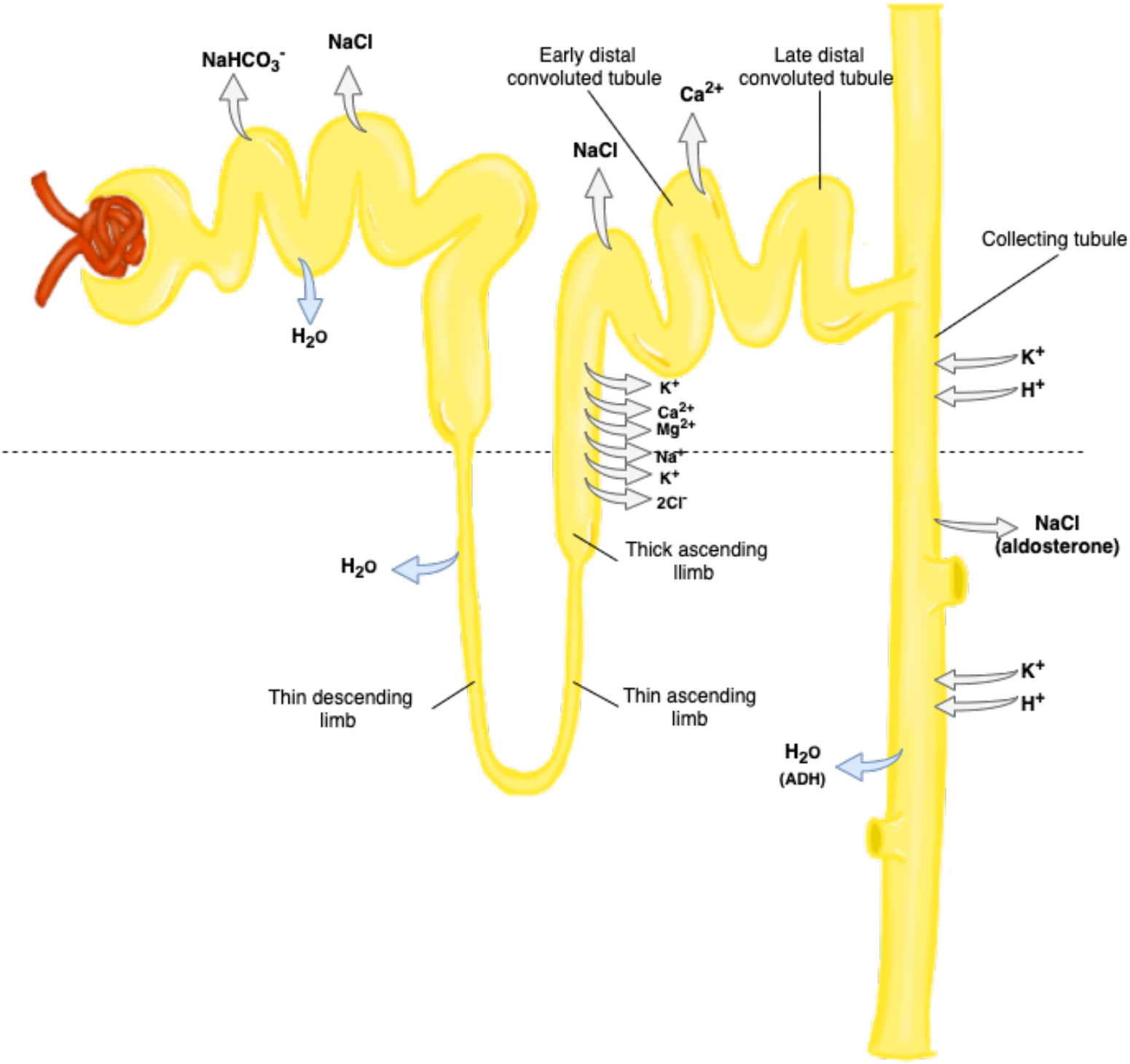
$$C_{H_2O}\left(\frac{mL}{min}\right) = \text{Urine flow rate}\left(\frac{mL}{min}\right) - \text{Clearance osmoles}\left(\frac{mL}{min}\right)$$

$$C_{H_2O}\left(\frac{mL}{min}\right) = \text{Urine flow rate}\left(\frac{mL}{min}\right) - \frac{\text{Urine osmolarity}\left(\frac{mOsm}{L}\right) * \text{Urine flow rate}\left(\frac{mL}{min}\right)}{\text{Plasma osmolarity}\left(\frac{mOsm}{L}\right)}$$

III. Significance of free water clearance

	ADH	Water permeability of LDCT and collecting duct	Water	Urine
Free water clearance is positive	ADH levels are low or ineffective	Impermeable to water	Solute-free water is *excreted*	Hypoosmotic
Free water clearance is negative	ADH levels are high	Permeable to water	Solute-free water is *reabsorbed* in the late distal tubule and collecting duct.	Hyperosmotic
	Loop diuretics		**Water**	**Urine**
Free water clearance = zero	Can occur with use of loop diuretics as they inhibit NaCl reabsorption in the thick ascending limb and then *no free water is generated* at this site.		No solute-free water is excreted	Isosmotic Ability to concentrate or dilute urine is impaired.

9.5 – Summary of Solutes and Water Balance



Segment/cell type	Major functions	Water permeability	Hormone Actions
Early proximal tubule	Isosmotic reabsorption of solute and water	Permeable	PTH inhibits Na^+-phosphate cotransport
Late proximal tubule	Isosmotic reabsorption of solute and water	Permeable	Angiotensin II stimulates Na^+ - H^+ exchange
Thick ascending Limb	Reabsorption of NaCl Dilution of tubular fluid Single effect of countercurrent multiplication Reabsorption of Ca^{2+} and Mg^{2+}	Impermeable	ADH stimulates Na^+ - K^+- $2Cl^-$ cotransport
Early distal tubule	Reabsorption of NaCl Dilution of tubular fluid	Impermeable	PTH stimulates Ca^{2+} reabsorption
Late distal tubule and collecting ducts			
Principal cells	Reabsorption of NaCl K^+ secretion Regulate water reabsorption	Permeable with ADH present	Aldosterone stimulates Na^+ reabsorption and K^+ secretion ADH stimulates water reabsorption (via aquaporins)
α-intercalated cells	K+ reabsorption H+ secretion	Not relevant	Aldosterone stimulates H^+ secretion

9.6 – Test Yourself

1) Underline correct word:

1. Ingestion of water inhibits/stimulates ADH secretion
2. In the presence of ADH principal cells are impermeable/permeable to water
3. Result of the single effect is that osmolarity of the ascending limb decreases/increases
4. SIADH is a condition with lack of/excess ADH secretion

2) Which two effects of ADH increases the corticopapillary gradient?

3) What is the major structural difference in production of hypersmotic Vs hyposmotic urine?

4) If free water clearance is positive, what can that tell us about the ADh levels and the state of the urine?

5) Explain the mechanism of countercurrent multiplication

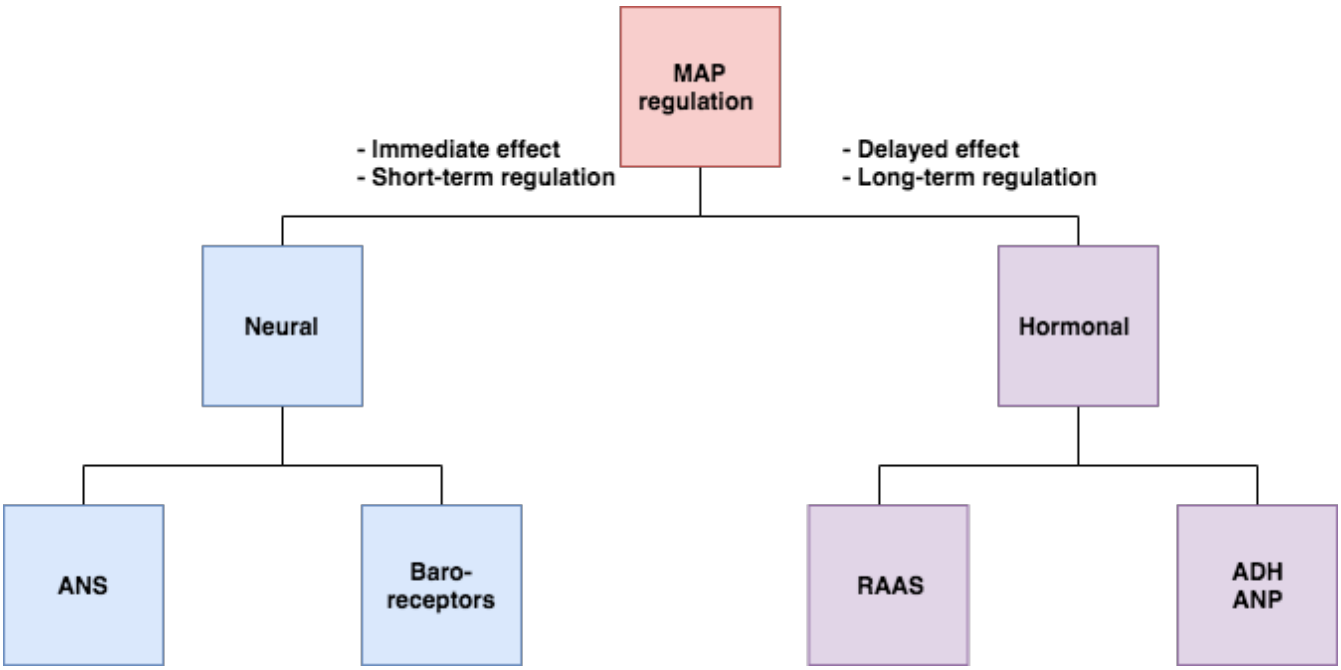
Section 10 - Renin-Angiotensin-Aldosterone System (RAAS)

10.0 – Introduction to RAAS

- This section will break down the renin-angiotensin-aldosterone system and its effect on blood pressure regulation.
- The Renin-Angiotensin-Aldosterone System regulates arterial pressure by regulating blood volume.
- RAAS is activated in response to a decrease in arterial pressure and produces a series of responses to attempt to restore the pressure to normal.
- The effects of this system is slower than the baroreceptor reflex because it is hormonally mediated.

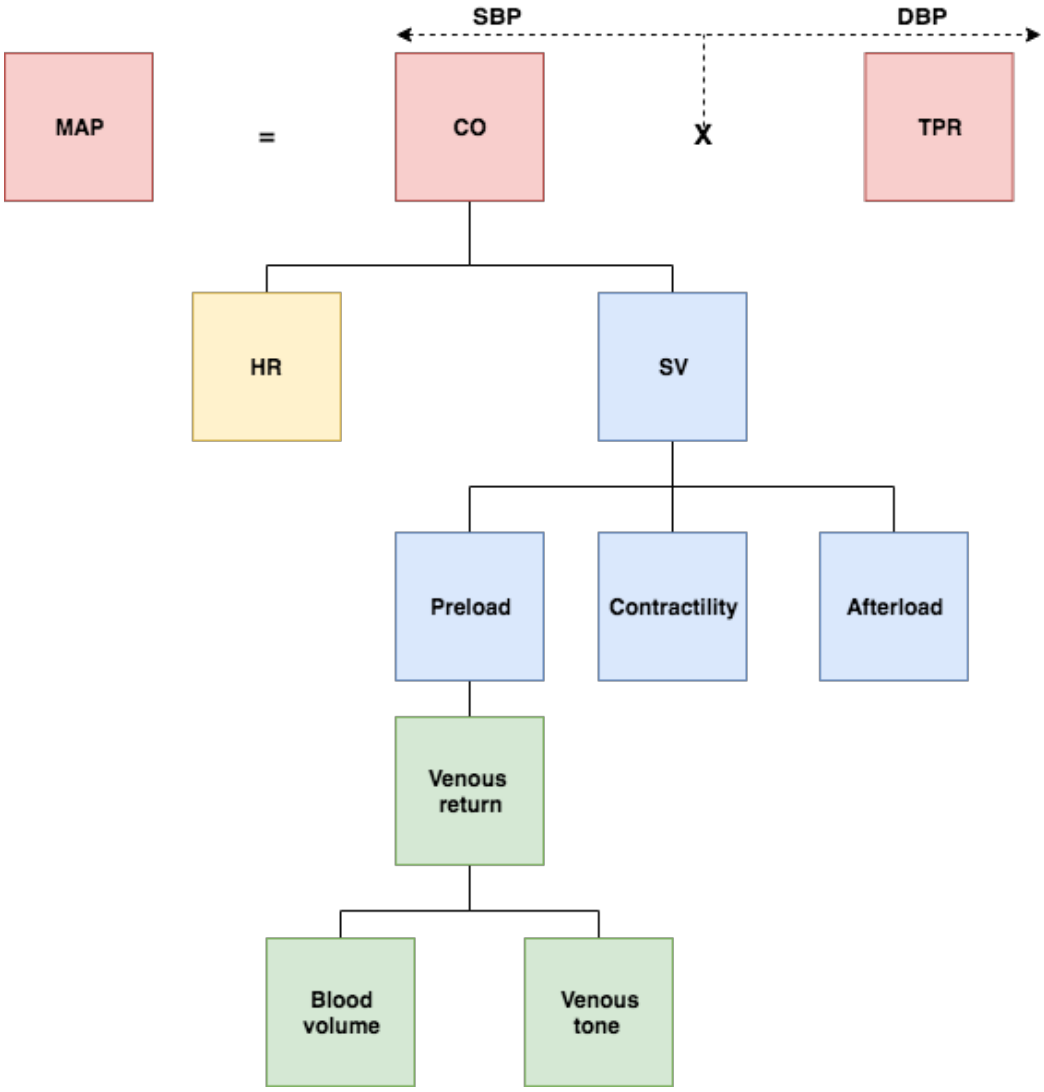
10.1 – Regulation of Blood Pressure

Recap from the *StudyAid Cardiovascular Physiology Booklet:*



10.1.0 – Mean arterial pressure

Recap from the *StudyAid Cardiovascular Physiology Booklet*:



10.2 – Extracellular Fluid

- Extracellular fluid (ECF) volume is determined primarily by the total amount of osmotically active solutes.
- Na^+ and Cl^- are the most osmotically active solutes in ECF. Changes in Cl^- are often secondary to changes in Na^+. Therefore the amount of Na^+ is the most important determinant of ECF volume.
- Mechanisms controlling Na^+ (e.g. aldosterone ⭐) are therefore the major mechanisms for sustaining ECF volume.

10.3 - Activation of RAAS

- RAAS is activated in response to decreased arterial pressure. It is activated through 3 different mechanisms all affecting the components of the juxtaglomerular apparatus
  1. ↓ Blood pressure
  2. ↓ NaCl in the DCT
  3. Sympathetic stimuli β_1

Juxtaglomerular apparatus		
Maintains GFR via RAAS		
Extraglomerular Mesangial cells (Lacis cells)	Pericytes located outside the glomerulus	Exact function is unknown, but it is thought to contribute in regulation of blood pressure
Juxtaglomerular cells	Modified smooth muscle cells of the afferent arteriole with mechanoreceptors	Juxtaglomerular cells register the changes in arteriolar pressure. ↓Blood pressure → prorenin → renin → Renin is released in the bloodstream. Juxtaglomerular cells can also be stimulated by the sympathetic nervous system acting on β_1 receptors
Macula densa cells	Modified region of tubular epithelium in the DCT	Macula densa cells sense NaCl delivery to distal convolute tubule (DCT) → ↑renin release[1]

[1] Presumably NaCl enter the macula densa cells via $Na^+/K^+/2Cl^-$ transporters in their apical membranes, and the increase signals to the juxtaglomerular cells to decreases renin secretion

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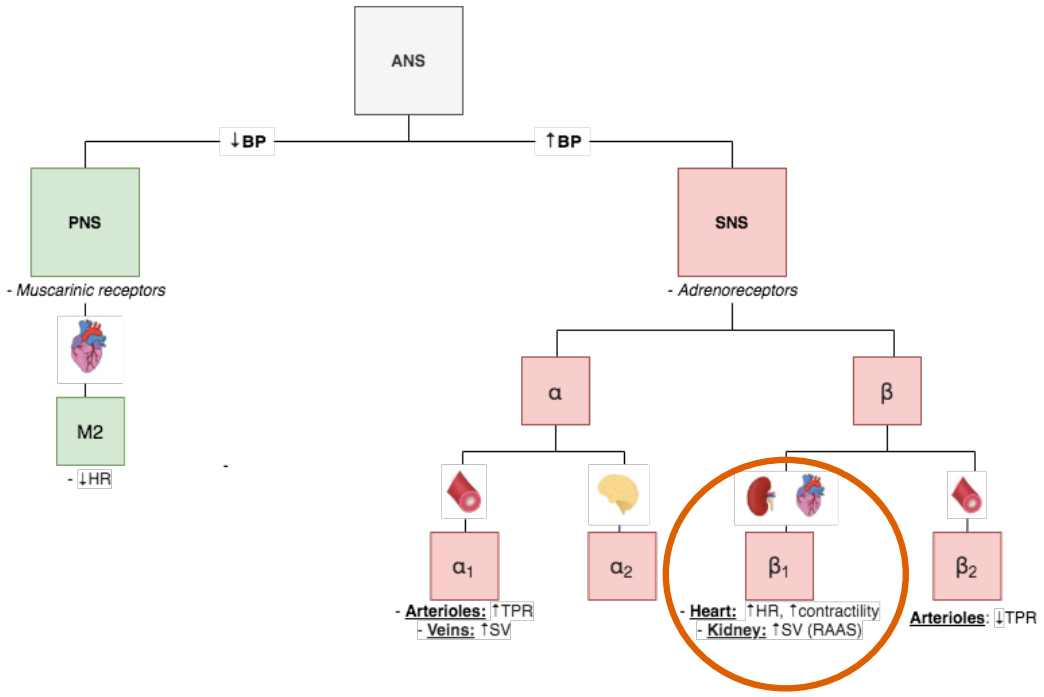
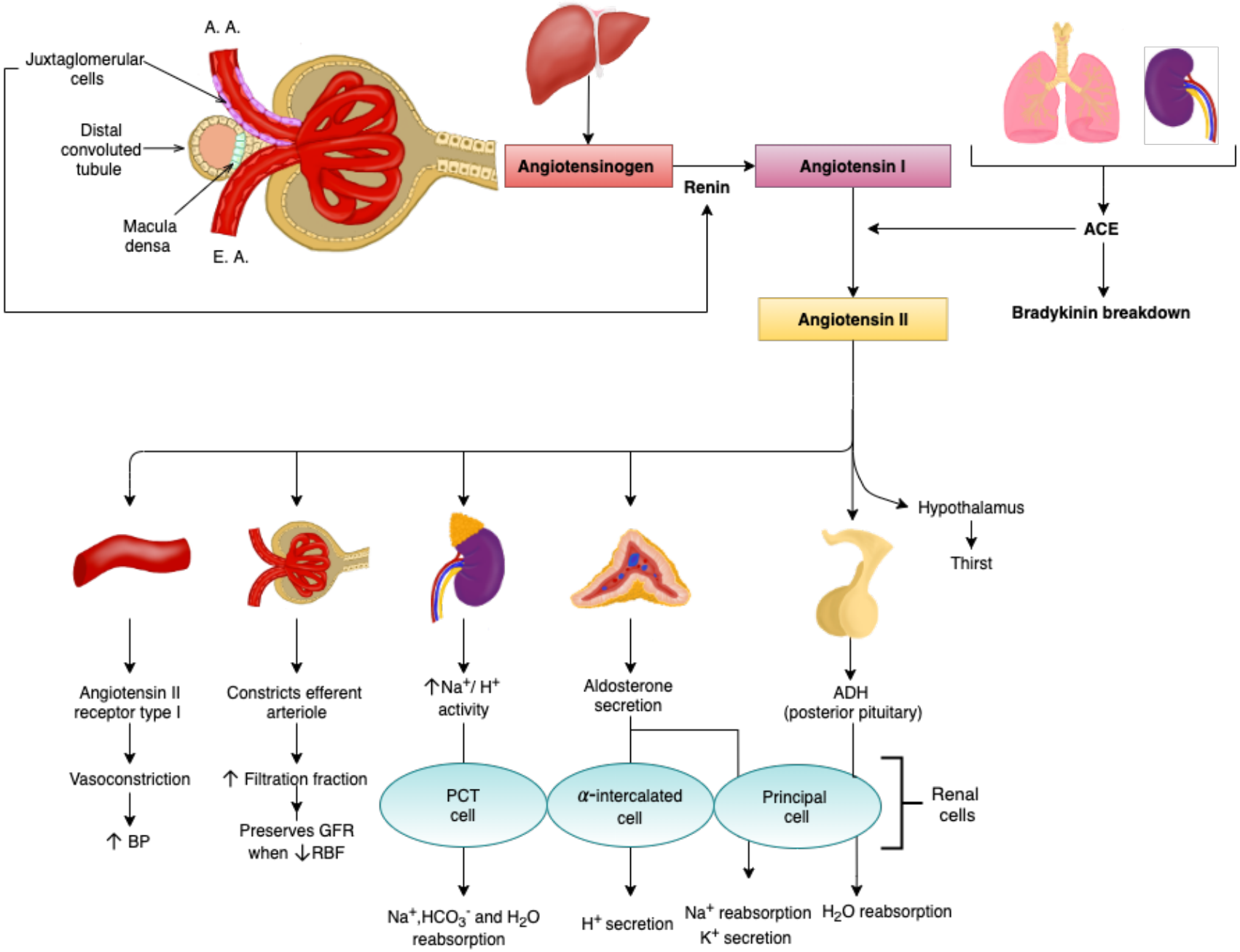
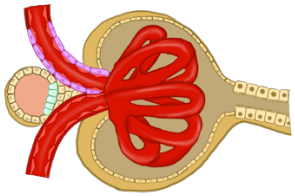
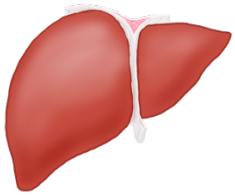



A. A.
Juxtaglomerular cells
Distal convoluted tubule
Macula densa
E. A.
Angiotensinogen
Renin
Angiotensin I
ACE
Bradykinin breakdown
Angiotensin II
Hypothalamus
Thirst
Angiotensin II receptor type I
Vasoconstriction
↑ BP
Constricts efferent arteriole
↑ Filtration fraction
Preserves GFR when ↓RBF
↑Na+/ H+ activity
Aldosterone secretion
ADH (posterior pituitary)
PCT cell
α-intercalated cell
Principal cell
Renal cells
Na+,HCO3- and H2O reabsorption
H+ secretion
Na+ reabsorption
K+ secretion
H2O reabsorption

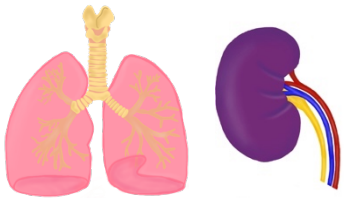
10.4 – Sequence of Events



Renin is an enzyme and it is released from the juxtaglomerular cells due to ↓BP, ↓GFR or ↑ sympathetic tone.



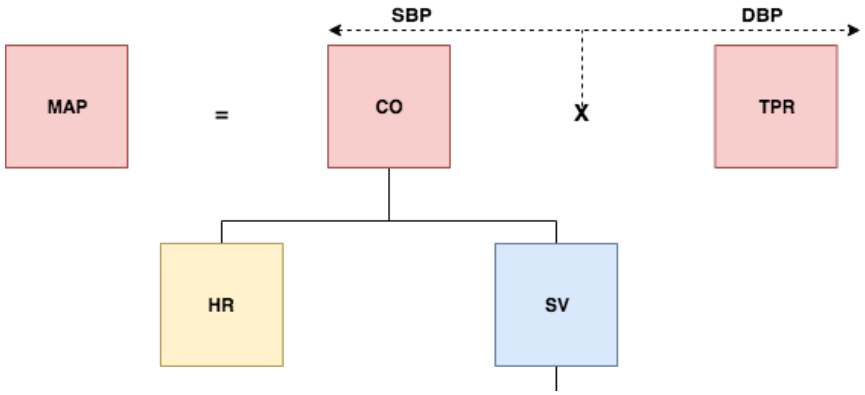
Angiotensinogen, which is produced by the liver, exists continuously in blood and is hydrolyzed to **Angiotensin I** by **renin**.



Angiotensin I is then converted by Angiotensin Converting Enzyme (ACE) to **Angiotensin II** in the lungs and kidneys.

10.5 – Functions of Angiotensin II

- RAAS affects MAP mainly by increasing the blood volume. ↑ blood volume = ↑blood pressure because of ↑ venous return → ↑ Cardiac output



Angiotensin II act on several structures:

1. *Zona glomerulosa cells*, in the adrenal cortex, which produces *Aldosterone*
2. *The hypothalamus,* and stimulates thirst and the release of *ADH* from posterior pituitary
3. *Systemic arterial vasculature,* causing systemic vasoconstriction
4. *Proximal convoluted tubule cells* (PCT cells), increasing Na+/H+ exchange
5. *Efferent arteriole,* causing vasoconstriction

All these effects contribute to increase the blood pressure:

⭐**Aldosterone**	Acts on the principal cells of the distal convoluted tubule and collecting ducts ↑ sodium reabsorption and potassium excretion → ↑ECF volume → ↑ blood volume ! Aldosterone is a mineralocorticoid, which requires gene transcription and new protein synthesis in the kidney → process requires hours to days → slow onset of action
ADH	Acts on the principal cells of the distal convoluted tubule and collecting duct and activates aquaporins → ↑ reabsorption of water → ↑ blood volume
Systemic Vasoconstriction	Increases the blood pressure by ↑ the peripheral resistance. ! Mean arterial pressure = Cardiac Output x Total Peripheral Resistance
PCT cells	↑reabsorption of Na+ and HCO3- → ↑ECF volume →↑ blood volume
Efferent arteriole	Vasoconstriction causes blood to back up into the capillary bed → ↑ glomerular hydrostatic pressure → =/↑GFR

10.6 – Test Yourself

1) Angiotensinogen is produced in
a) Liver
b) Kidney
c) Lungs
d) Juxtaglomerular cells

2) Which part of the nephron does aldosterone act on
a) Proximal convoluted tubule
b) Distal convoluted tubule
c) Collecting duct
d) c and d are correct

3) Renin secretion by Juxtaglomerular cells is increased by
a) Increasing mean blood pressure
b) Increasing GFR
c) Increasing sympathetic nerve activity
d) Increasing angiotensin II synthesis

4) ADH will be released from the posterior pituitary when there is a decrease in
a) Plasma Na+ concentration
b) Plasma volume
c) Plasma K+ concentration
d) Plasma pH

5) Which of the following statements about renin is true?
a) Its secretion leads to loss of sodium and water from plasma
b) Its secretion is stimulated by increased mean renal arterial pressure
c) It converts angiotensinogen to angiotensin I
d) It converts angiotensin I to angiotensin II

6) How does aldosterone increase blood pressure?

7) How does ADH increase water reabsorption?

8) Why does an increase in peripheral resistance increase the blood pressure?

9) Angiotensin I is converted to Angiotensin II by which enzyme?

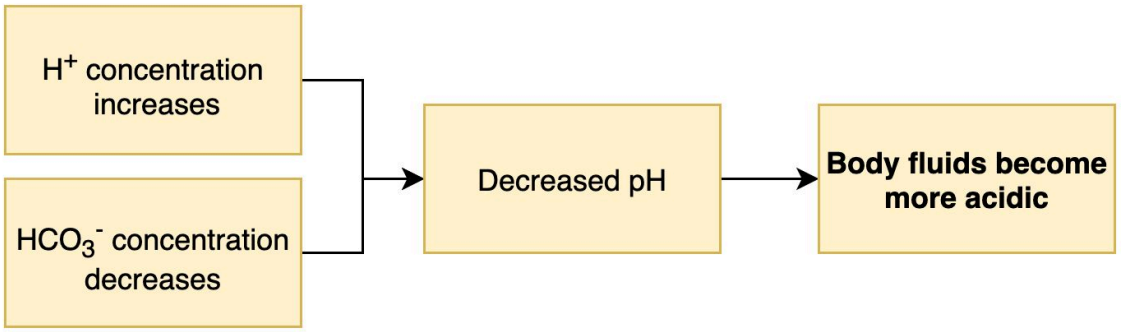
10) The secretion of renin can be activated through which type of receptor?

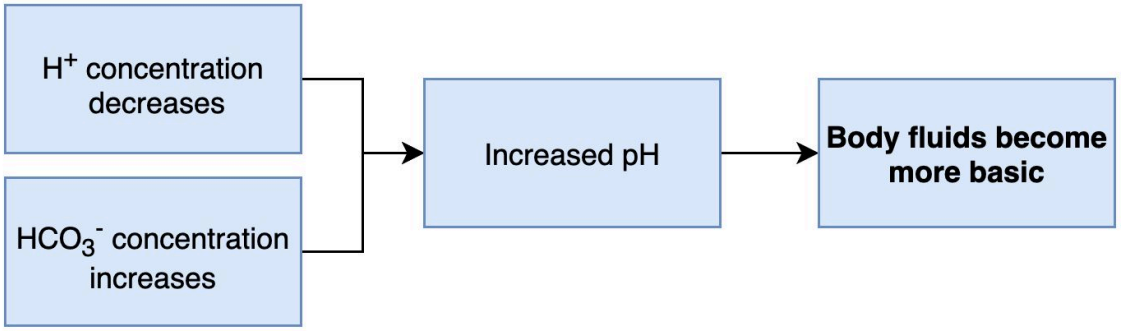
Section 11 – Introduction to Acid-Base Physiology

11.0 – pH of Body Fluids

I. Overview

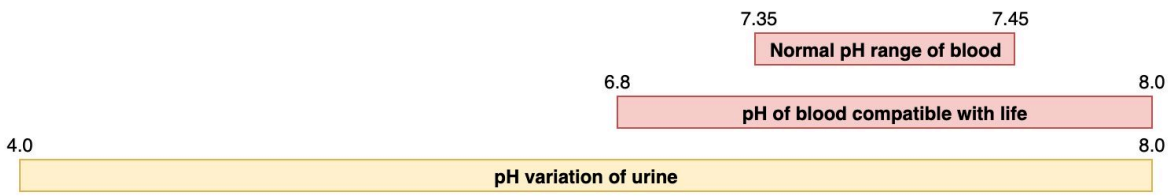
- Because the H^+ concentration in the body is extremely low, small changes in concentration can lead to a significant increase or decrease in the pH of body fluids.





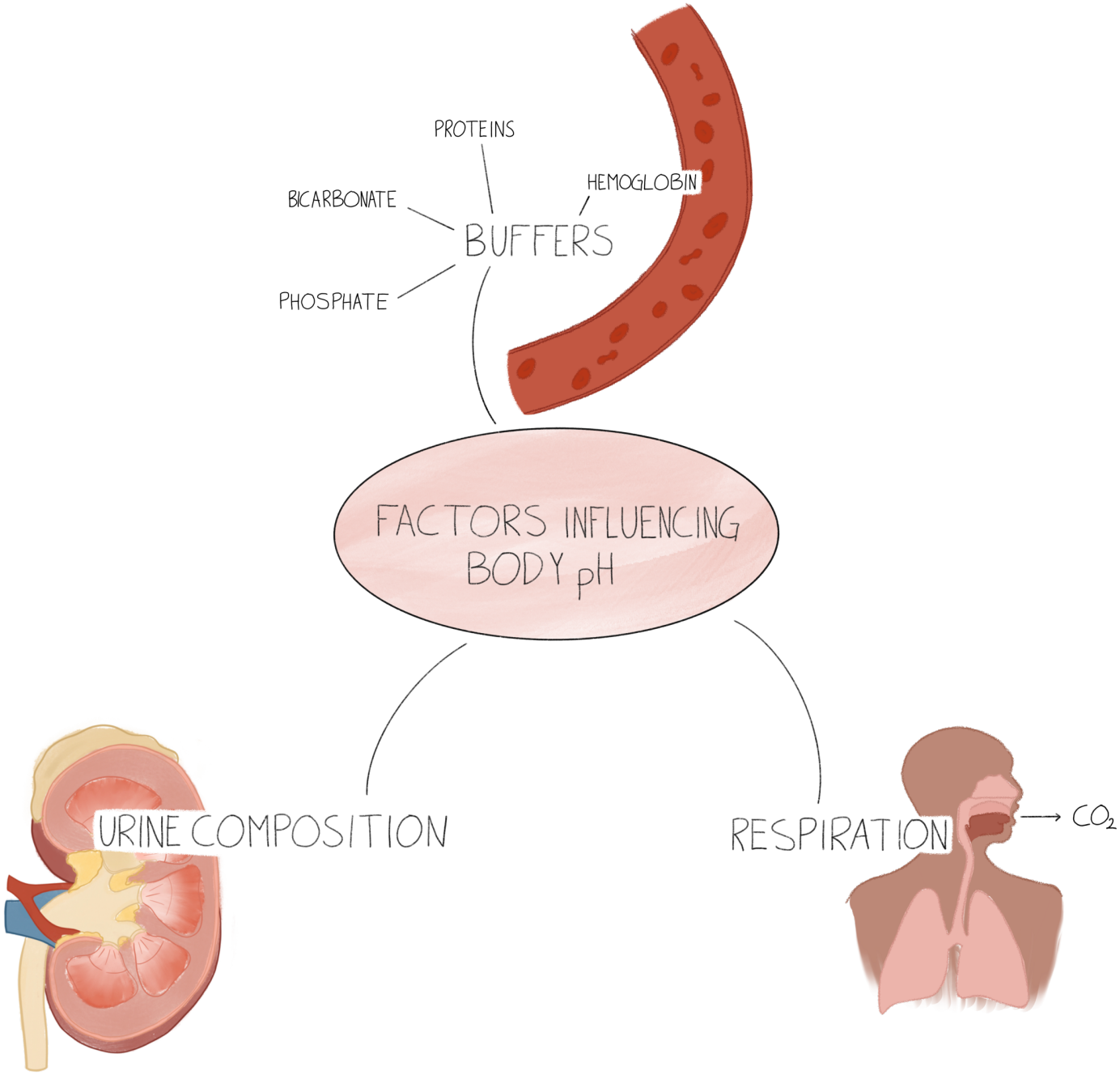
II. The pH range of blood

- Normal pH level of blood: 7.35 – 7.45
- Because venous blood contains more CO_2, it will have a pH slightly lower than arterial blood
- The kidneys greatly influence the pH of blood by either excreting H^+ or reabsorbing HCO_3^- The large pH variation of urine emphasizes this.



III. Factors that influence pH of body fluids

- Buffers in intracellular and extracellular fluid.
- Respiration where CO_2 is expired.
- The composition of urine – acid or base excreted in urine.



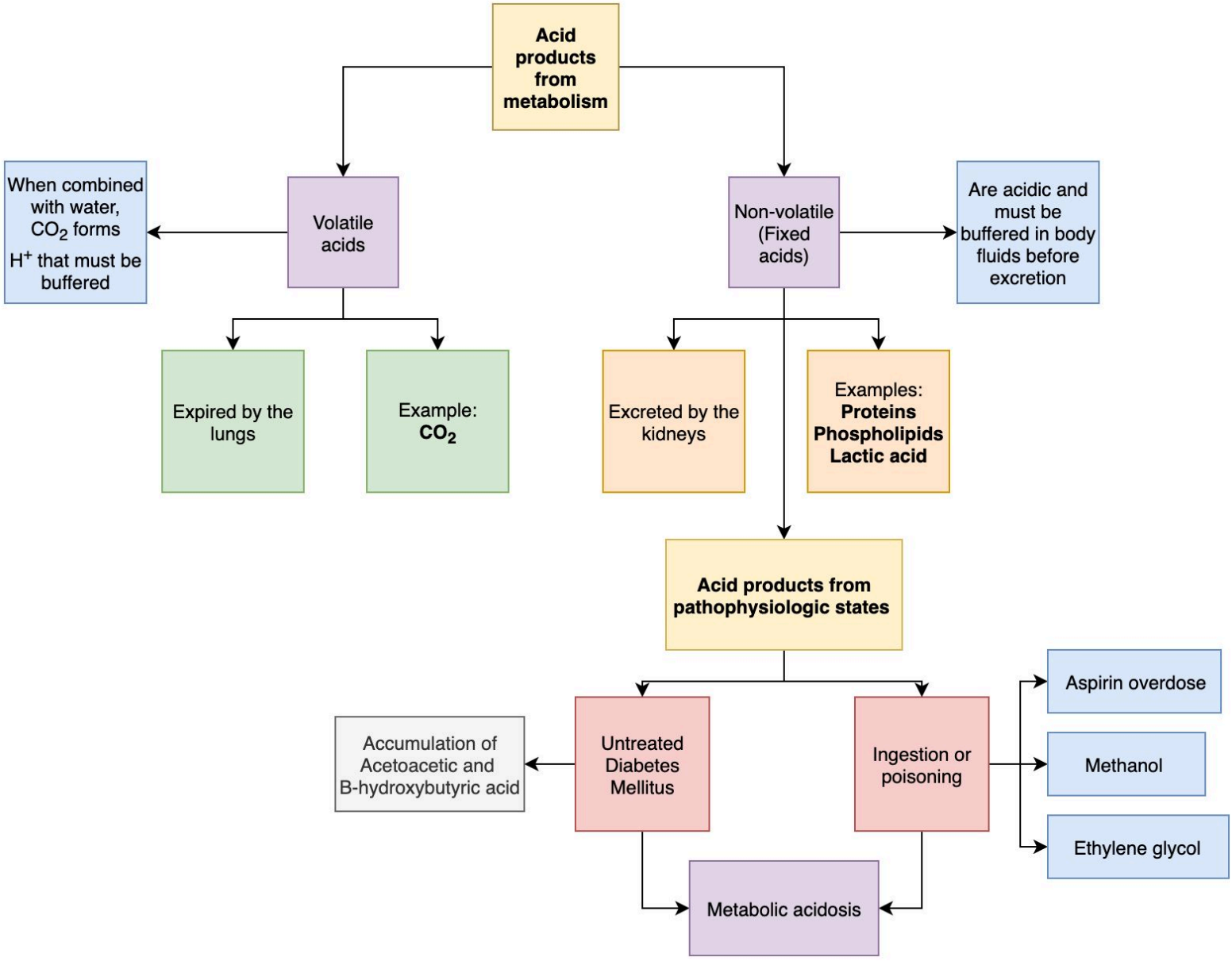
11.1 – Acid Production in the Body

I. Volatile acids

- Volatile: Acid that can be expired by the lungs

II. Non-volatile acids

- Non-volatile (or fixed) acids: Cannot be expired and must be excreted by kidneys



11.2 – Test Yourself

1) How are volatile acids removed from the circulation?

2) How are non-volatile (fixed) acids removed from the circulation?

3) What is true about venous blood?

a) It contains more CO_2 and will have pH slightly higher than arterial blood
b) It contains less CO_2 and will have pH slightly higher than arterial blood
c) It contains more CO_2 and will have pH slightly lower than arterial blood
d) It contains less CO_2 and will have pH slightly lower than arterial blood

4) Which one is a volatile acid?

a) Methanol
b) CO_2
c) Lactic acid
d) Phospholipids

Section 12 – Buffering

12.0 – Principles of Buffering

I. Definition

- A solution that can resist a change in pH when acidic or alkaline solutions are added to it.

12.1 – Extracellular Fluid Buffers

12.1.0 – Bicarbonate

I. Bicarbonate as a buffer

- $H^+ + HCO_3^- \rightarrow H_2CO_3 \rightarrow CO_2 + H_2O$
- Bicarbonate is the most important extracellular buffer

II. The pK of bicarbonate

- The pK of bicarbonate is 6.1
- In blood, most of the buffer will be in HCO_3^- rather than CO_2 form $\rightarrow$ HCO_3^- concentration is high

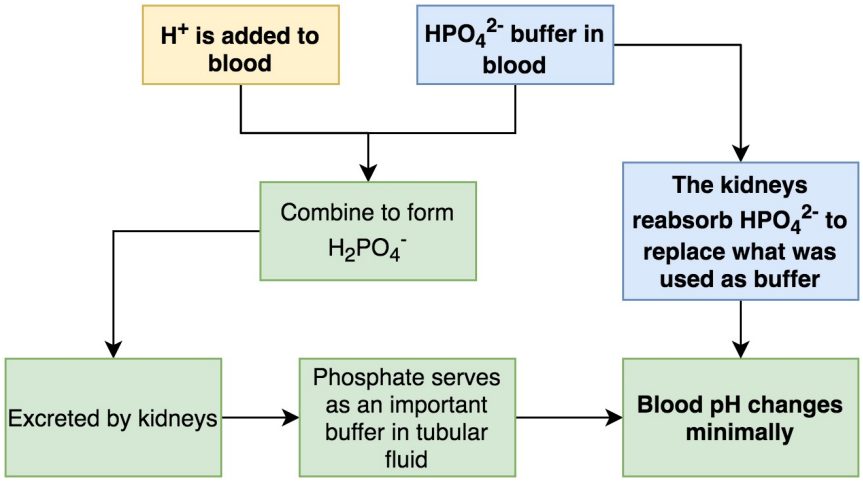
What is pK?

pK expresses the acidity or alkalinity of a substance. When pK of a substance is equal to pH of the solution, there will be equal concentrations of acidic and basic form of the substance.

12.1.1 – Inorganic phosphate

I. Phosphate as a buffer

- $H^+ + HPO_4^{2-} \rightarrow H_2PO_4^-$
- Phosphate is a major urinary buffer



II. The pK of phosphate

- The pK of phosphate is 6.8, so the pH range of 5.8 – 7.8 is closer to pH of blood than the pH range of bicarbonate (5.1 – 7.1). However, the concentration of bicarbonate is over ten times higher!

12.1.2 – Comparison of bicarbonate and inorganic phosphate

I. Why is bicarbonate a better buffer than phosphate?

- Phosphate concentration in blood is only 2 mmol/L, compared to 24 mmol/L bicarbonate.
- CO_2 can be expired by the lungs while $H_2PO_4^-$ must be excreted by the kidneys.

Extracellular buffer	Combines with H^+ to form	pK	Important aspects
Bicarbonate	$H^+ + \mathbf{HCO_3^-} \rightarrow H_2CO_3 \rightarrow \mathbf{CO_2} + H_2O$	6.1	- HCO_3^- concentration in the blood is high - CO_2 can rapidly be expired and thereby removed from the circulation - HCO_3^- can be excreted by the kidneys
Phosphate	$H^+ + \mathbf{HPO_4^{2-}} \rightarrow H_2PO_4^-$	6.8	- pK is within the pH range of blood. - phosphate is a major urinary buffer

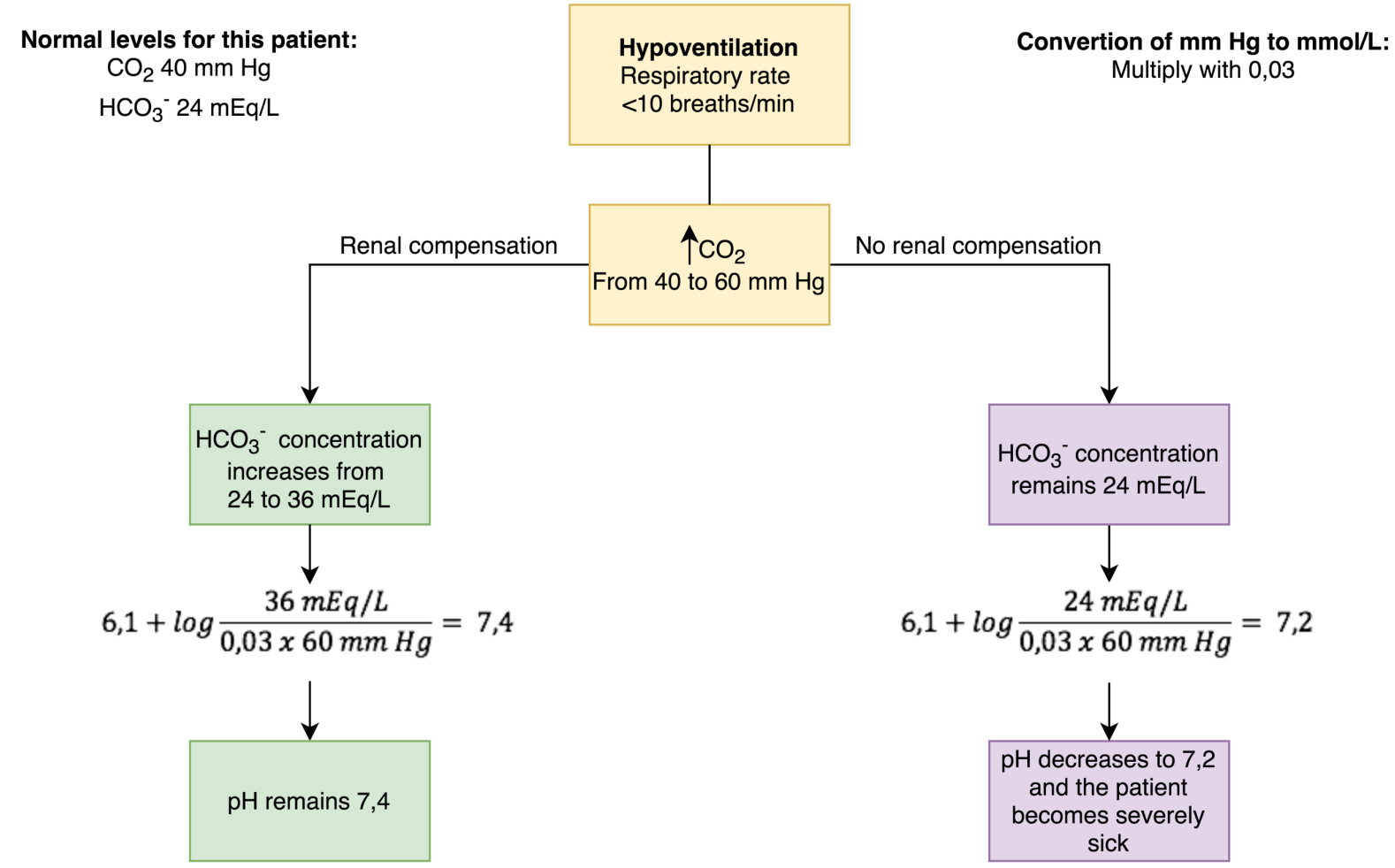
12.2 – The Henderson-Hasselbach Equation

$$\text{pH} = pK + log\frac{[A^-]}{[HA]}$$

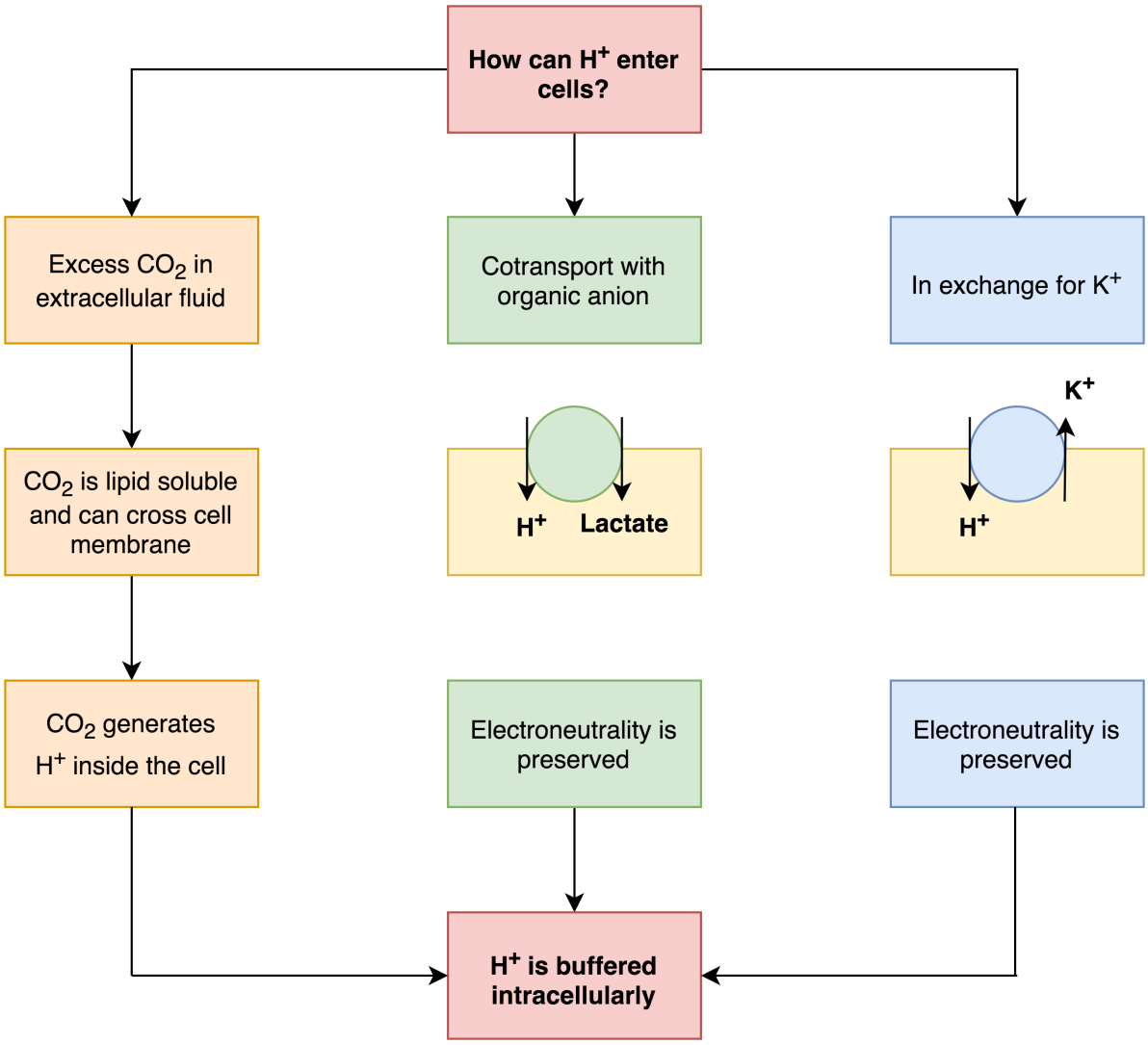
- Used to calculate the pH of a solution
- The relationship between the concentrations of acid/base is more important than the concentrations themselves

12.2.0 – Why is the Henderson-Hasselbach clinically relevant?

- Using what we have learned about bicarbonate, we will see what happens to pH when the concentrations of HCO_3^- and CO_2 change
- For the examples below, $[A^-]$ will be replaced by HCO_3^- because it is the basic component and [HA] will be replaced by CO_2 because it is the acid component



12.3 – Intracellular Buffers



Intracellular buffers	Examples	pK	
Organic phosphates	ATP ADP AMP 2,3-DPG	6.0 - 7.5	The phosphate groups (HPO_4^-) buffer H^+
Proteins	Hemoglobin	Oxygenated: 6.7 Deoxygenated: 7.9	Hemoglobin releases O_2 to tissues and receives CO_2 Inside RBCs[1], CA[2] converts CO_2 and H_2O to H^+ and HCO_3^- H^+ is buffered by deoxyhemoglobin

[1] RBC = Red blood cell

[2] CA = Carbonic anhydrase

12.4 – Test Yourself

1) Which of these statements is false?

a) If the patient is hypoventilating, bicarbonate must increase to maintain pH

b) Phosphate is the most important extracellular buffer

c) ATP and hemoglobin are examples of intracellular buffers

d) Concentration of bicarbonate is higher than concentration of phosphate in blood

2) How can H^+ enter cells?

a) CO_2 diffuses through the cell membrane, combines with H_2O and generates H^+ inside the cell

b) Co-transport with an organic anion such as lactate

c) In exchange for K^+

d) All the above

3) Which of the statements is true?

a) The concentrations of acid/base are more important than the relationship between them

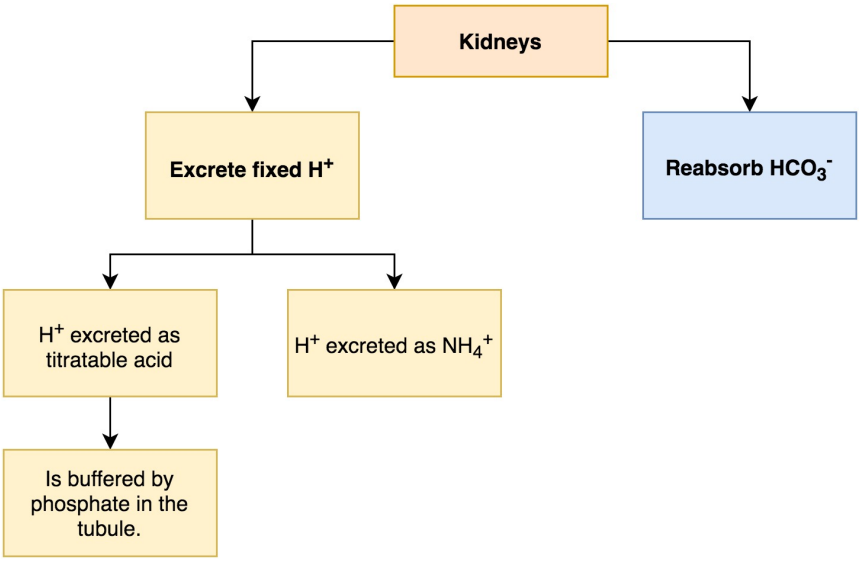
b) HCO_3^- can be expired by the lungs

c) Phosphate serves as an important buffer in the kidney tubules

d) All the above

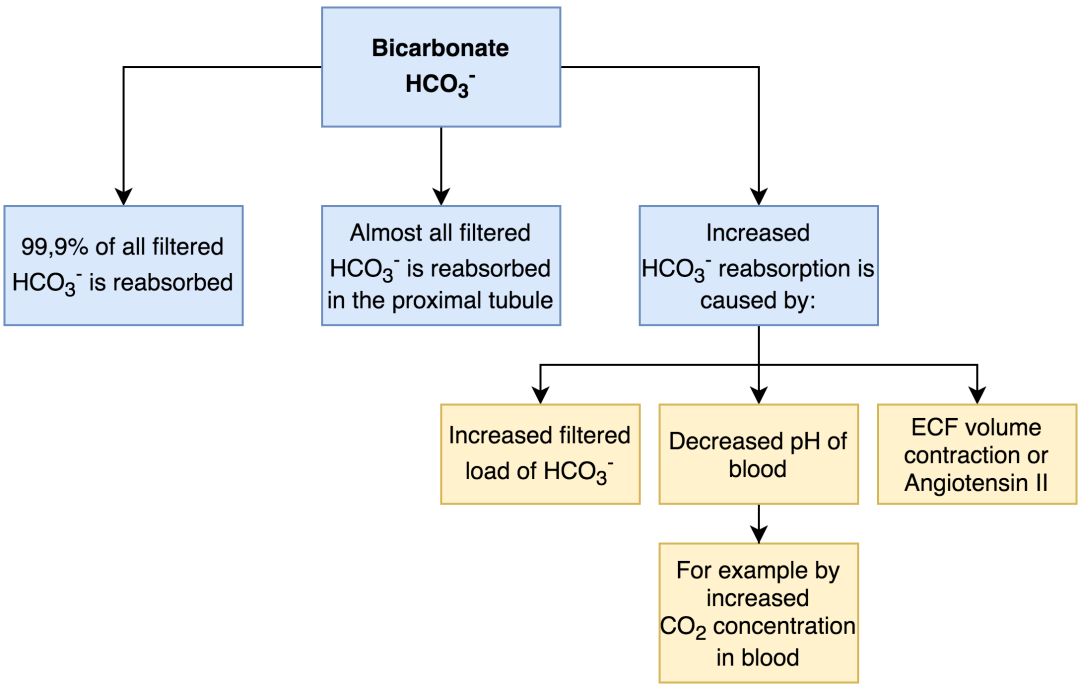
Section 13 – Renal Mechanisms in Acid-Base Balance

13.0 – Overview

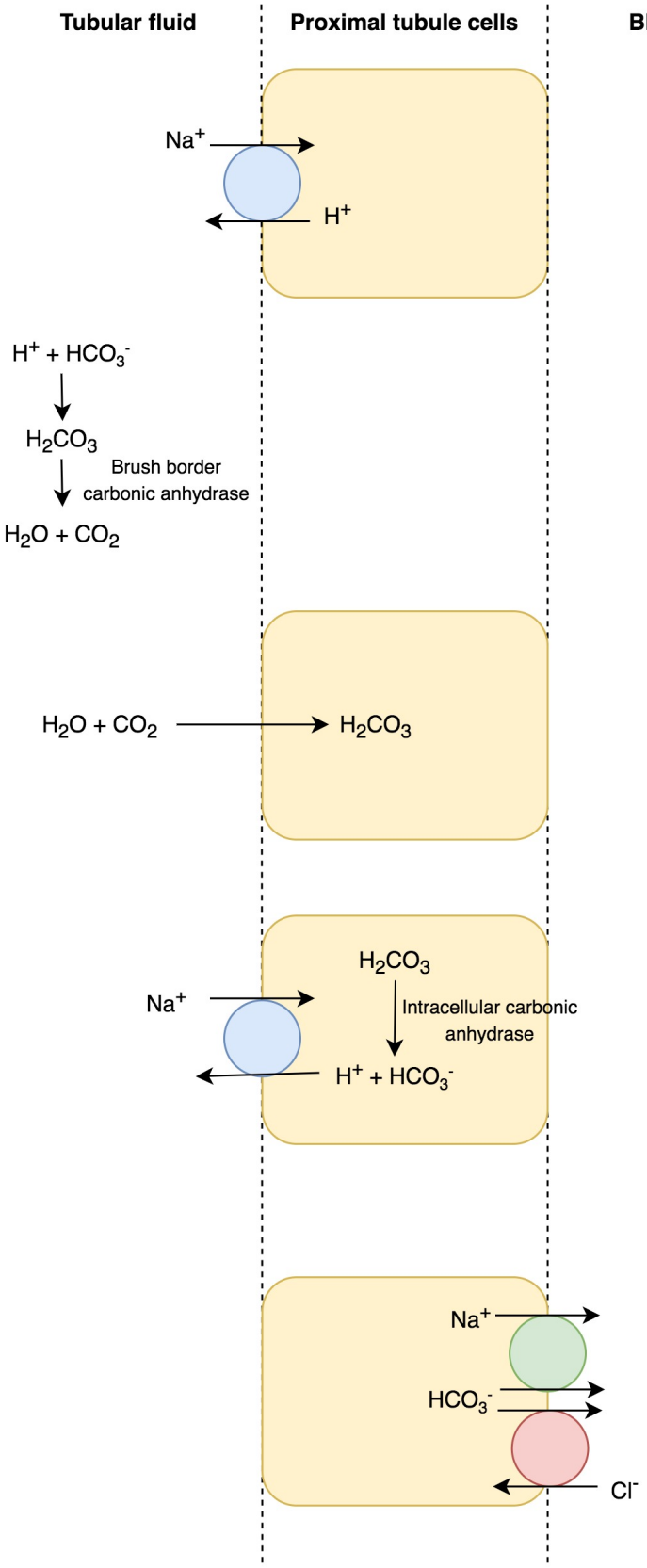


13.1 – Reabsorption of Filtered HCO_3^-

13.1.0 – Overview



13.1.1 – Mechanism of reabsorption



1. H^+ is exchanged with Na^+ across the luminal membrane. H^+goes into the lumen (tubular fluid) against gradient, while Na^+ goes into the proximal tubule cell with it's gradient.

2. In the lumen, H^+ combines with HCO_3^- to form H_2CO_3.The enzyme carbonic anhydrase, found in the brush border of the proximal tubule cells, split H_2CO_3 into CO_2 and H_2O.

3. $CO_2$and H_2O then diffuse into the proximal tubule cell. They combine to form H_2CO_2 inside the cell.

4. Intracellular carbonic anhydrase splits H_2CO_3 into H^+ and HCO_3^-. H^+ can then be recycled in exchange for Na^+ like we explained in step 1.

Because it is recycled, H^+ is continuously used to combine with HCO_3^- from the lumen into the proximal tubule cell. There is no net excretion of H^+ with little change in pH of tubular fluid.

5. HCO_3^- is brought into the cell, but it still needs to be transported into blood. It can either be co-transported with Na^+ or as counter-transport with Cl^-. In both cases, the net sum of electric charge will be 0.

Conclusion

- Net absorption of HCO_3^- and Na^+
- H^+ is recycled → No net excretion of H^+ → No change in pH of tubular fluid

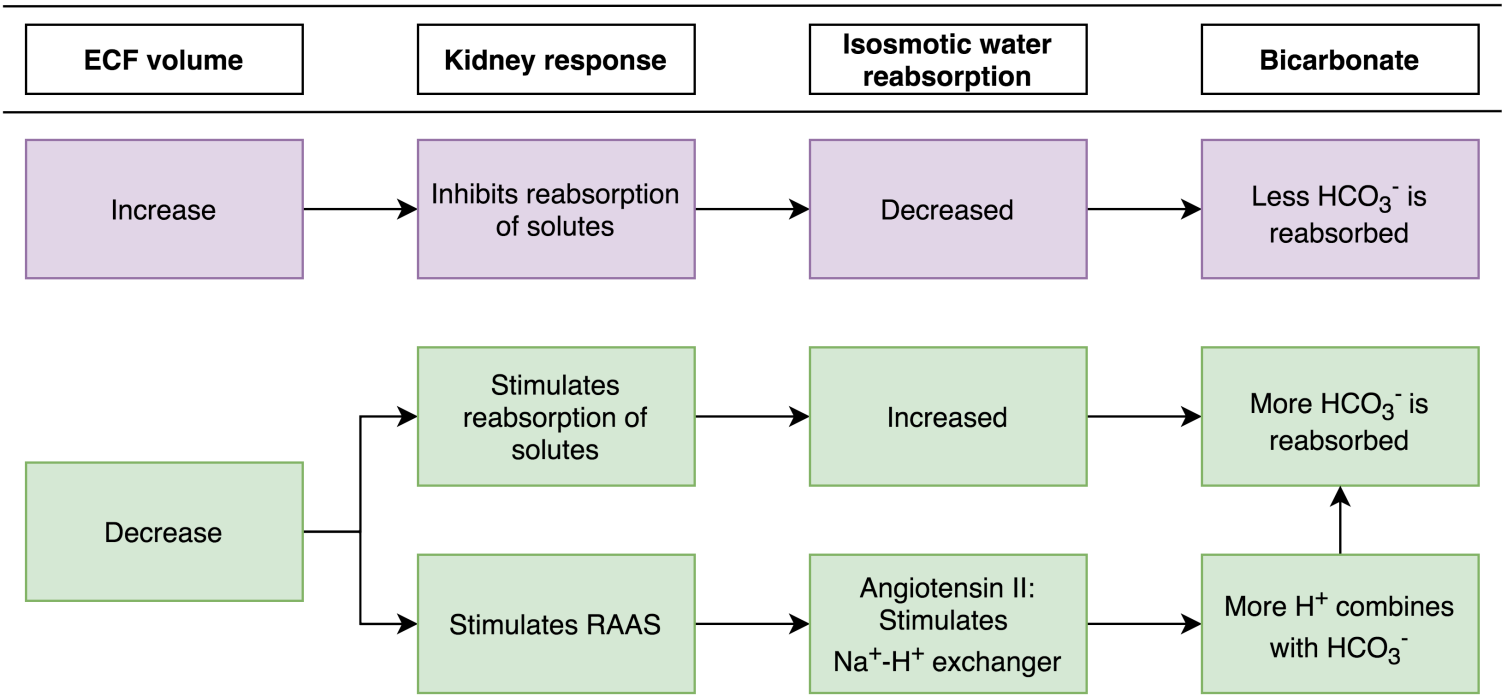
13.1.1 – Changes in HCO_3^- reabsorption

I. Saturated carriers

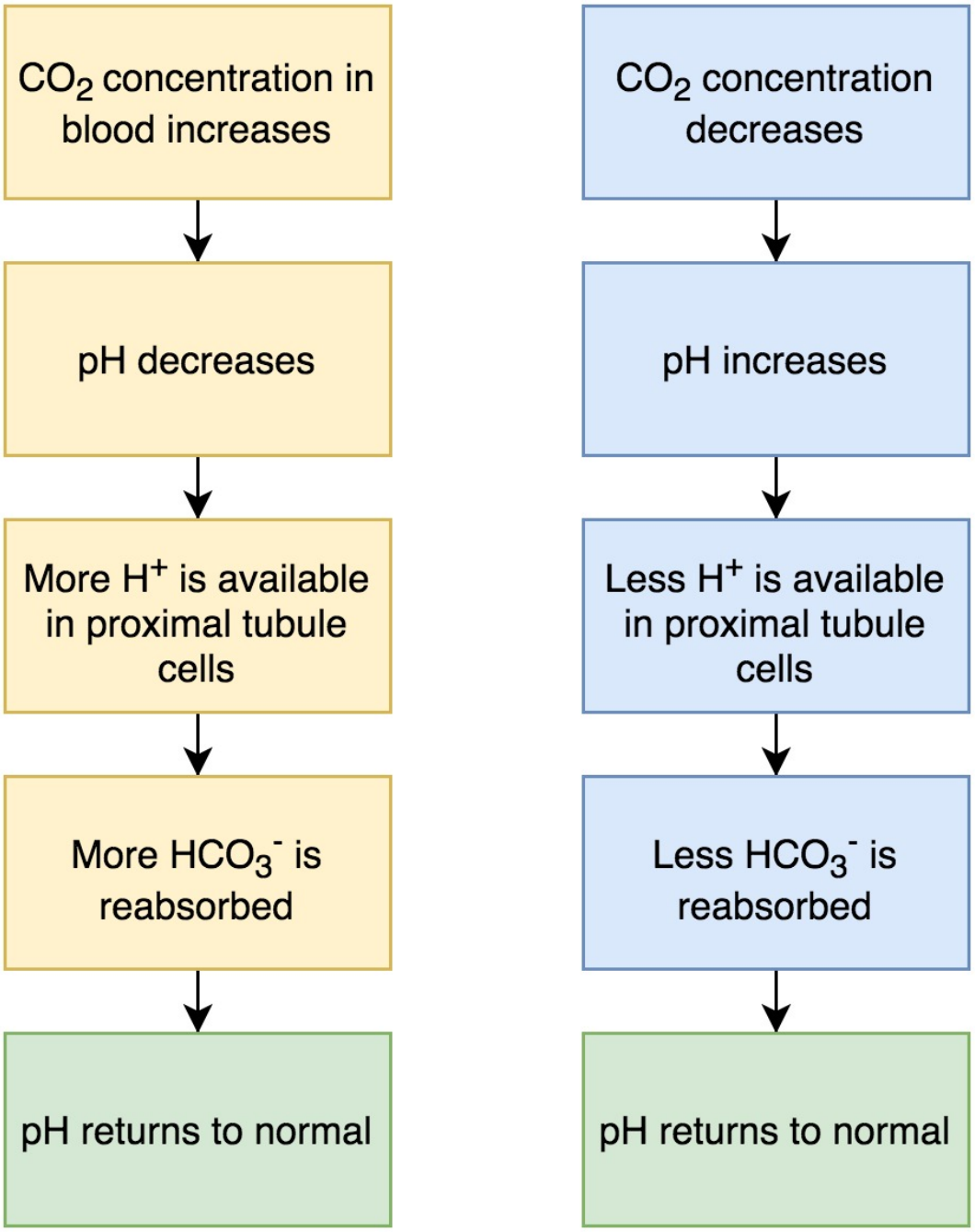
- When HCO_3^- concentration of blood is higher than 40 mEq/L, the carriers are not able to reabsorb more HCO_3^- because all the carriers are being used → The carriers are *saturated*.
- Kidneys ensure that HCO_3^- concentration is maintained within normal range by excreting the additional HCO_3^-.

II. Effect of extracellular fluid volume

- *Increased ECF volume:* Inhibits HCO_3^- reabsorption
- *Decreased ECF volume:* Stimulates HCO_3^- reabsorption which causes contraction alkalosis



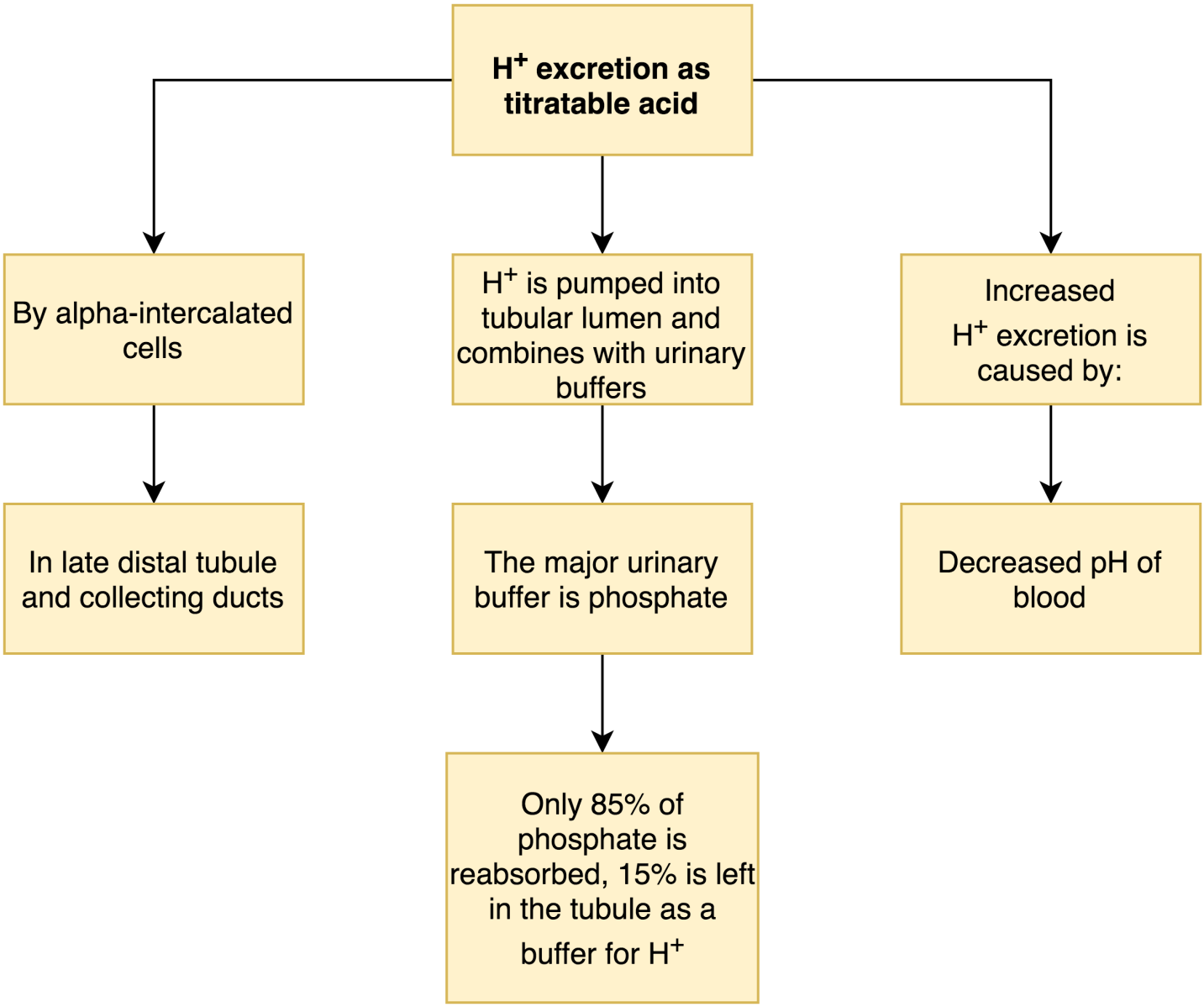
III. Effect of CO_2 concentration in blood



13.2 – Excretion of H^+ as Titratable Acid

13.2.0 – Overview

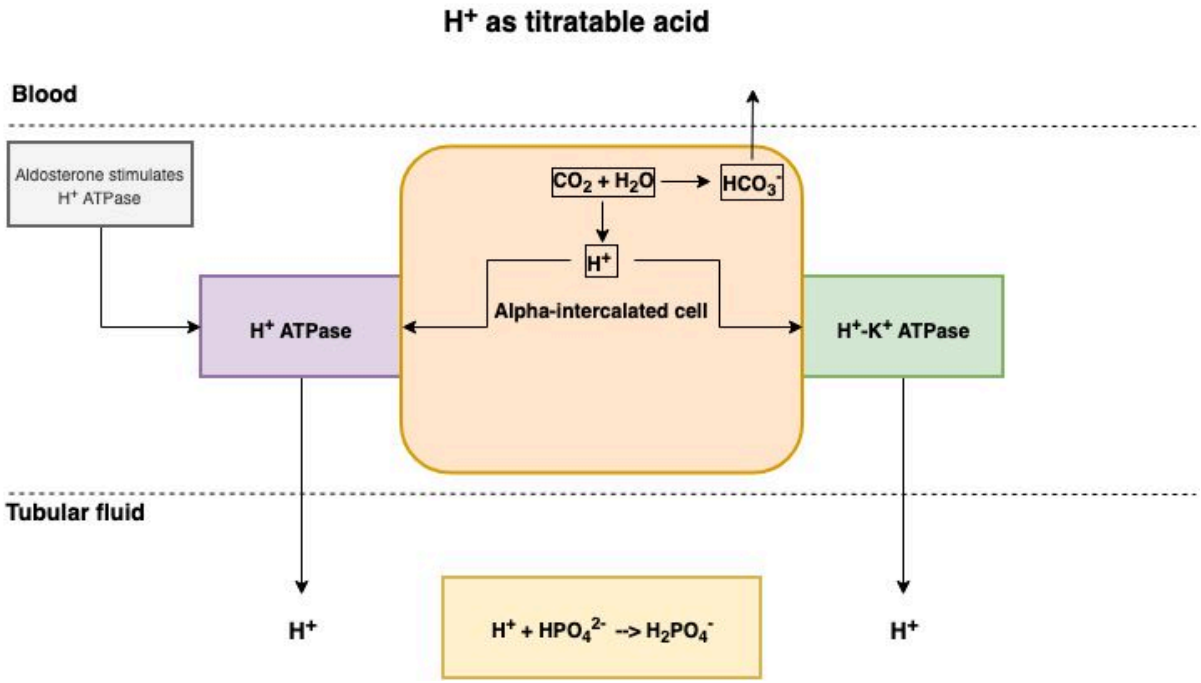
- When H^+ combines with buffers in the tubule it is called titratable acid.



13.2.1 – Buffering

I. **There are two main mechanisms for excretion of H^+ as titratable acid:**
- H^+ ATPase pump (Stimulated by Aldosterone)
- H^+-K^+ ATPase exchanger

II. **Excretion of H^+ as titratable acid:**
- Renal catabolism creates the byproducts CO_2 and H_2O. They will combine to form H_2CO_3 and then dissolve into H^+ and HCO_3^-
- H^+ is secreted into the lumen by either the H^+ ATPase or the H^+-K^+ ATPase
- H^+ combines with HPO_4^- (inorganic phosphate) to form $H_2PO_4^-$ (titratable acid) in tubular lumen
- For every H^+ secreted, HCO_3^- will be reabsorbed from the cells into blood



13.2.2 – The amount of urinary buffer

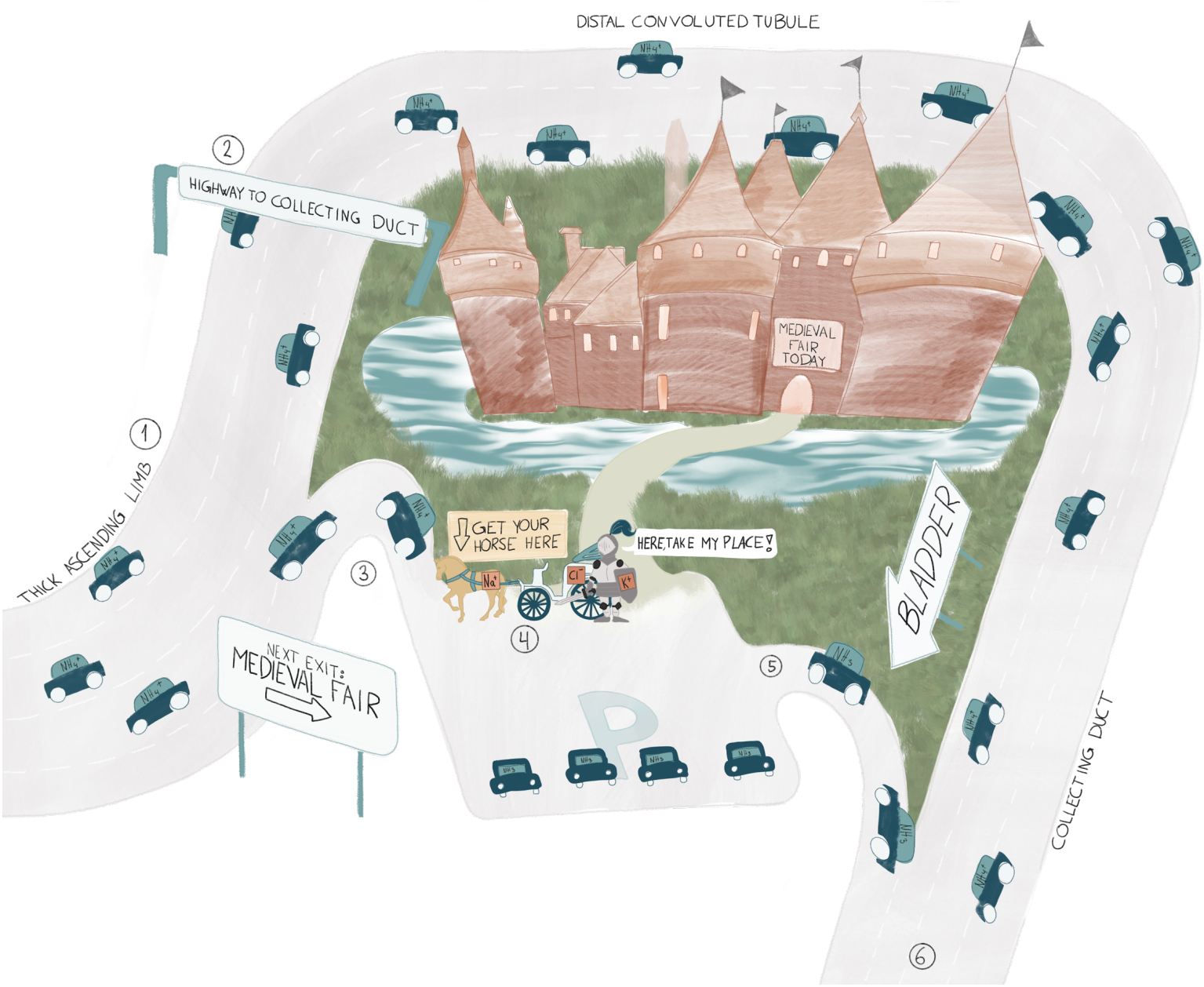
- Low urine pH → High concentration of H^+
- High concentration of H^+ → H^+ pumps work against greater electrochemical gradient
- Minimum pH of urine is 4.

13.3 – Excretion of H^+ as NH_4^+

13.3.0 – Overview

- Glutamine is the most abundant free amino acid found in blood.
- When Glutamine is metabolized – NH_4^+, H^+ and HCO_3^- will be formed.

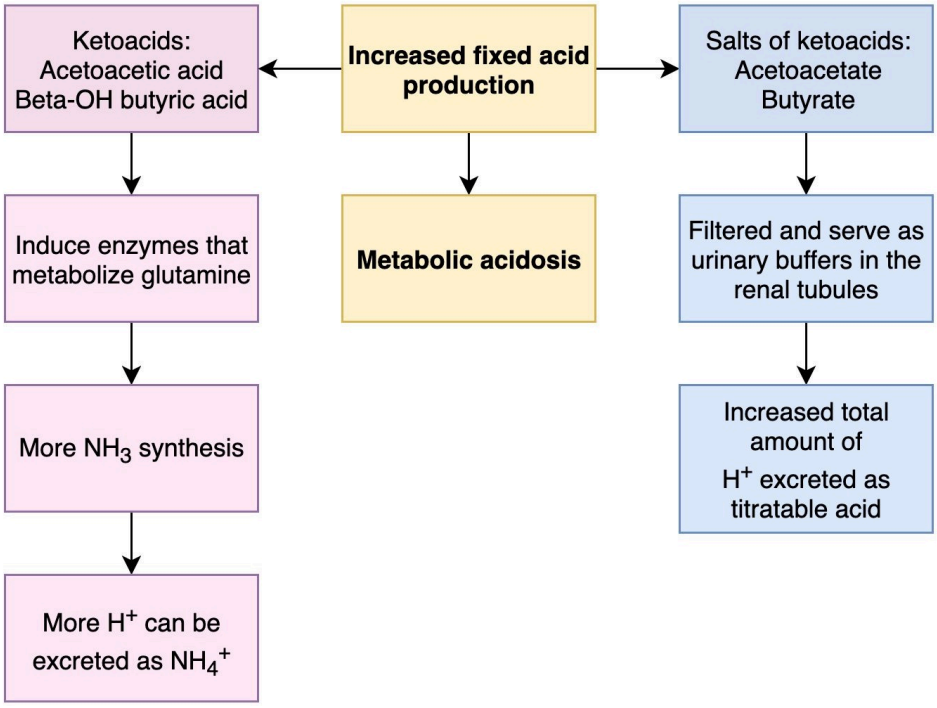
13.3.1 – Routes of excretion of NH_4^+ in the kidney



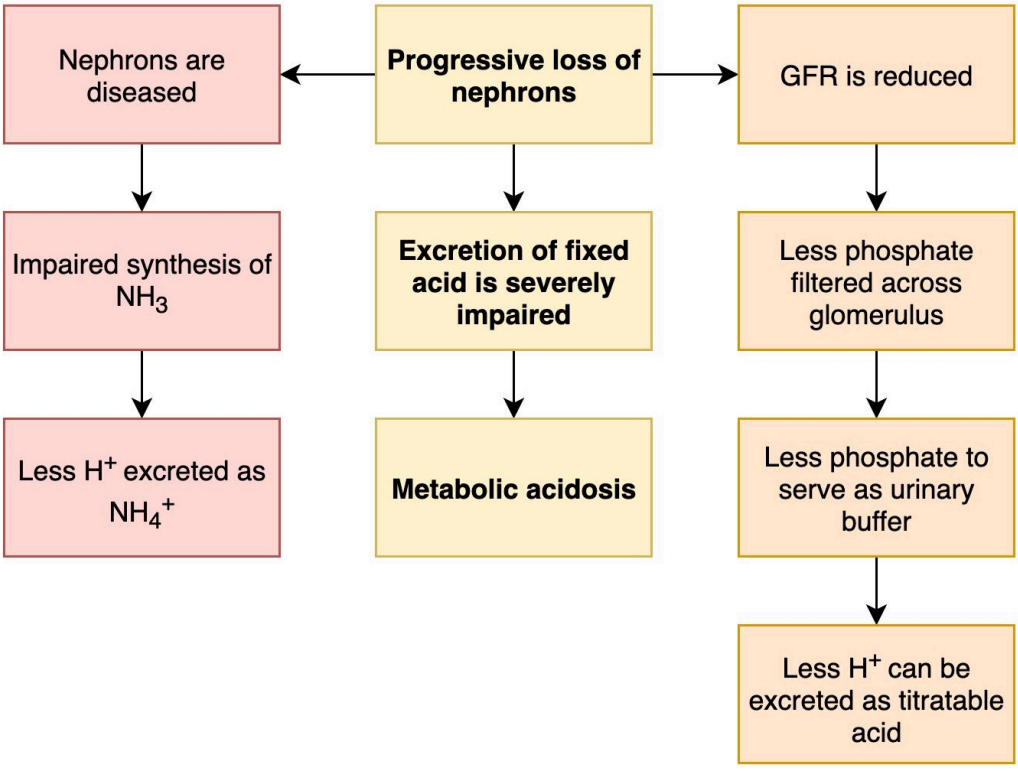
1 – Cars on the highway: NH_4^+ enters the thick ascending limb of Loop of Henle.
2 – Cars (NH_4^+) continuing on the highway: Some of the NH_4^+ will continue down the nephron to the collecting tubule via the distal convoluted tubule.
3 – Cars going to the medieval fair (medulla): While the rest of NH_4^+ will take a medullary route, via the $Na^+/K^+/2Cl^-$ cotransporter.
4 – The knight (K^+) gives up his space in the horse and carriage ($Na^+/K^+/2Cl^-$ cotransporter) to let the people in cars go to the medieval fair: NH_4^+ takes the place of K^+ on the $Na^+/K^+/2Cl^-$ cotransporter, and enters the interstitium in the medulla.
5 – Cars leaving the medieval fair: NH_3 diffuses into the collecting duct down its concentration gradient because NH_3 combines with H^+ in the lumen, creating NH_4^+. This allows more NH_3 to diffuse into the lumen.
6 – Highway to the bladder: NH_4^+ from both medullary and tubular routes is excreted in urine.

13.4 – Comparison of Titratable Acid and NH_4^+ Excretion

13.4.0 – Diabetic ketoacidosis



13.4.1 – Chronic renal failure



13.5 – Test Yourself

1) When H^+ is excreted as a titratable acid:
a) It means that it is excreted as NH_4^+
b) It is buffered by phosphate in the tubule

2) Almost all HCO_3^- entering the nephron is reabsorbed in:
a) Thick ascending limb
b) Collecting duct
c) Proximal tubule
d) Distal convoluted tubule

3) Increased HCO_3^- reabsorption is caused by:
a) Decreased pH of blood
b) Increased CO_2 in blood
c) Decreased HCO_3^- in blood
d) All the above

4) Decreased HCO_3^- reabsorption is caused by:
a) Decreased pH of blood
b) Increased ECF volume
c) Decreased CO_2 in blood
d) Activation of RAAS

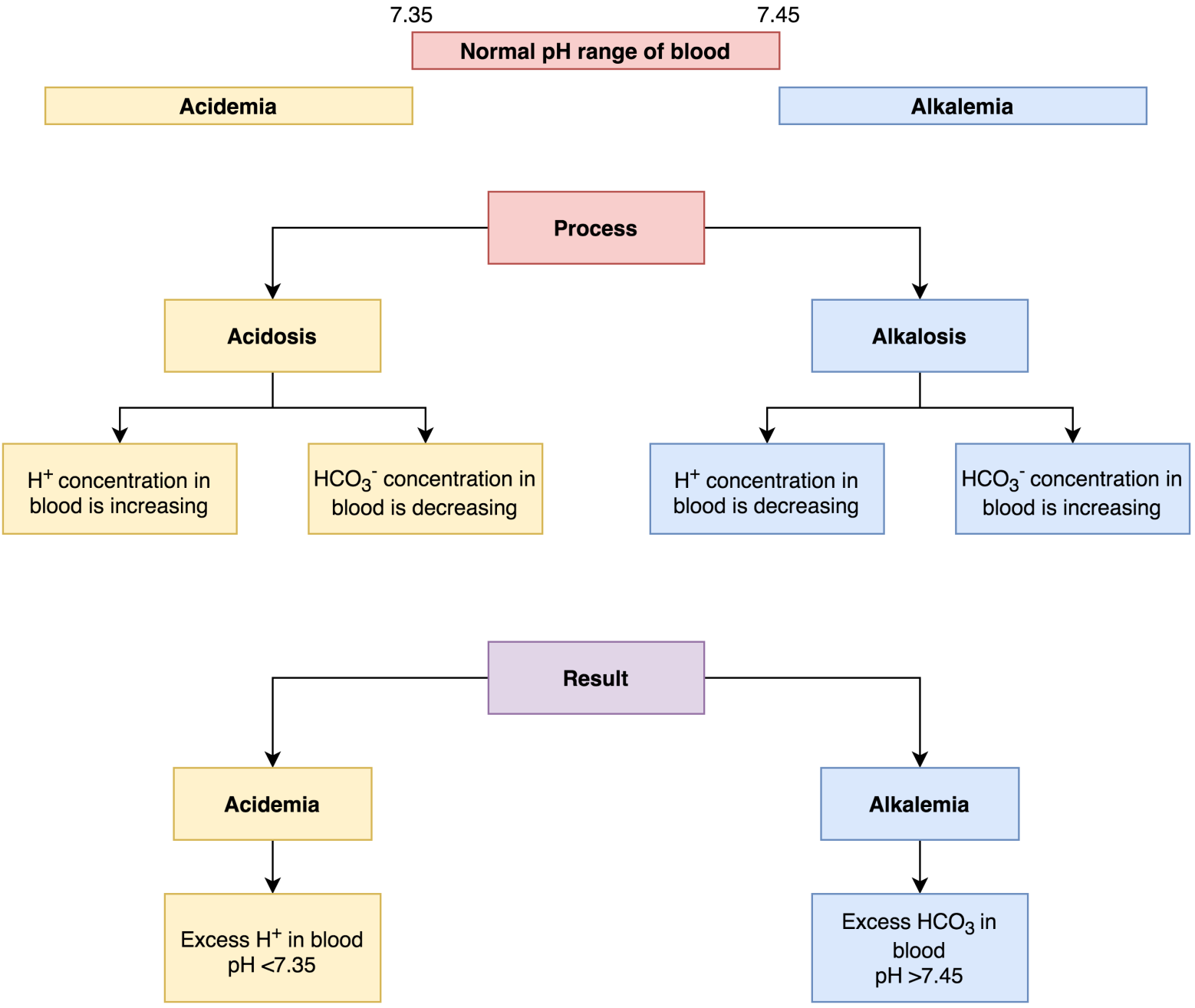
5) Increased H^+ excretion is caused by all except:
a) Increased pH of blood
b) Decreased pH of blood
c) Increased aldosterone
d) Increased renal catabolism

6) What is false about H^+ excretion as NH_4^+?
a) Some NH_4^+ is reabsorbed from the tubule in thick ascending limb
b) NH_4^+ takes the place of Na^+ on the $Na^+/K^+/2Cl^-$ cotransporter
c) Some NH_4^+ is not reabsorbed in thick ascending limb and follows the tubule to collecting duct
d) NH_3 is excreted in the collecting duct and combines with H^+ to form NH_4^+ in the tubule

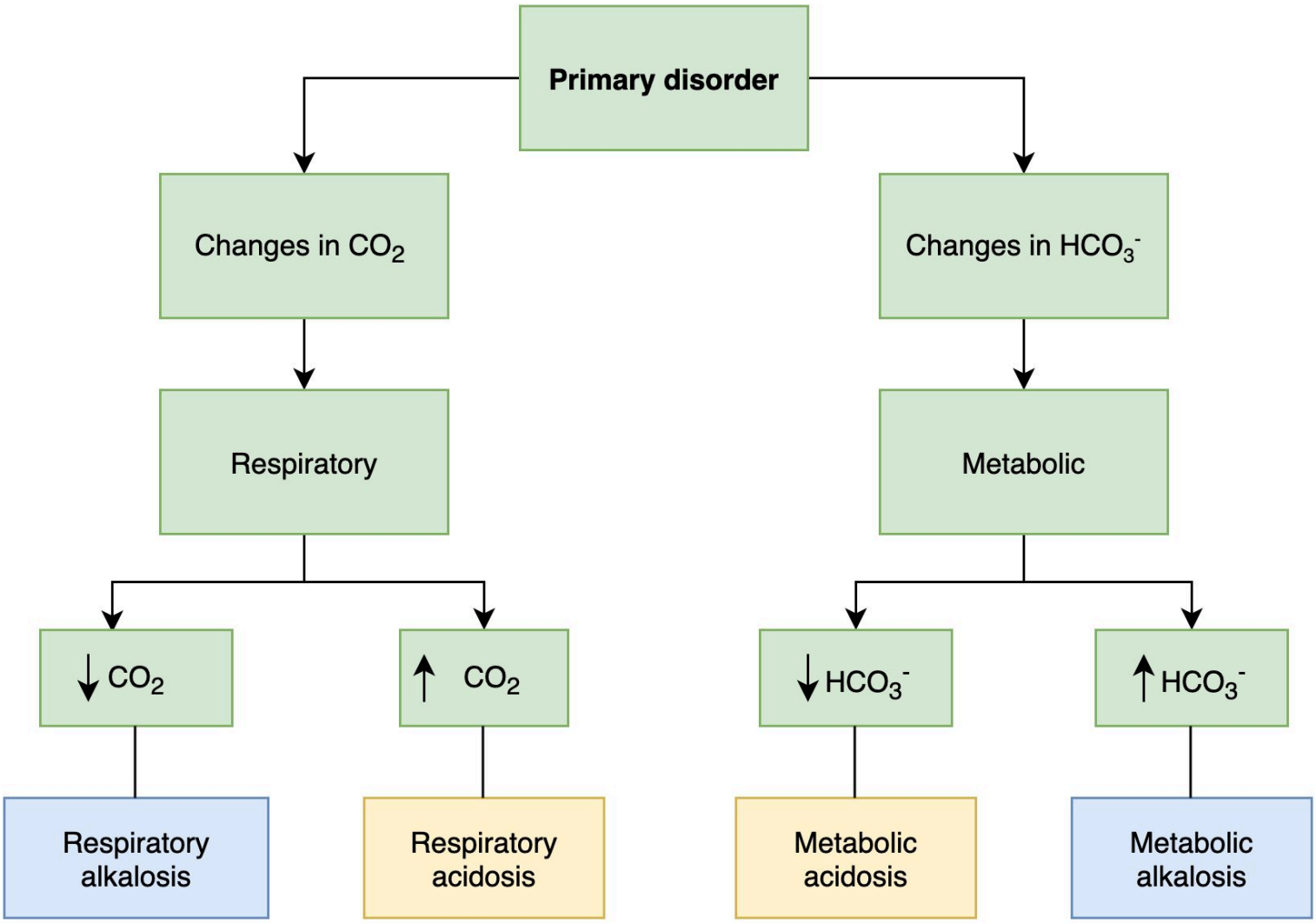
7) Diabetic ketoacidosis and chronic renal failure will cause:
a) No change in pH
b) Decreased reabsorption of HCO_3^-
c) Metabolic alkalosis
d) Metabolic acidosis

Section 14 – Acid-Base Disorders

14.0 – Overview



14.0.0 – Respiratory and metabolic changes in pH



14.0.1 – Defense against changes in pH

Time span	Response	Example
Instant response	Buffers in ICF and ECF	Plasma proteins Hemoglobin in RBCs Bicarbonate Phosphate Etc.
Within 1-3 minutes	Respiratory compensation	Hypoventilation Hyperventilation
Within hours	Renal compensation	Changes in: Excretion of H^+ Reabsorption of HCO_3^-

14.1 – Anion Gap of Plasma

14.1.0 – Overview

Plasma anion gap = Na – (HCO_3^- + Cl^-)

I. Electroneutrality

- The electrical sum of cations and anions in plasma must be equal.
- Normal anion gap = 8-16 mEq/L
- Example with normal values: Plasma anion gap = 140 – (24 + 105) = 11

II. Unmeasured anions

- Include plasma proteins, phosphate, citrate and sulfate
- The concentration of unmeasured anions is calculated by the anion gap

14.1.1 – Anion gap in metabolic acidosis

I. Overview

- Metabolic acidosis is caused by decreased HCO_3^-
- To preserve electroneutrality, the concentration of another anion must increase to replace lost HCO_3^-
- Anion gap can help us determine what is the cause of the patient's metabolic acidosis!

II. Hyperchloremic metabolic acidosis

- Cl^- concentration increases to replace HCO_3^-
- For example: Plasma anion gap = 140 – (20 + 109) = 11 → Plasma anion gap remains normal

III. Increased anion gap

- Many forms of metabolic acidosis are caused by accumulation of organic acids
- Examples are ketoacid, lactic acid, formic acid and salicylate
- Increase of unmeasured anions cause increased anion gap

14.1.2 – Osmolar gap

Estimated plasma osmolarity = 2 x Na^+ + glucose/18 + BUN/2.8

I. Overview

- Osmolar gap = Measured plasma osmolarity – Calculated/estimated plasma osmolarity
- Plasma osmolarity is the sum of the major solutes in plasma: Na^+, Cl^-, HCO_3^-, glucose and urea.

II. Methanol and ethylene glycol poisoning

- Methanol and ethylene will increase plasma osmolarity but are not accounted for in the calculation of plasma osmolarity
- The measured plasma osmolarity will therefore be higher than that estimated by the equation → Osmolar gap.

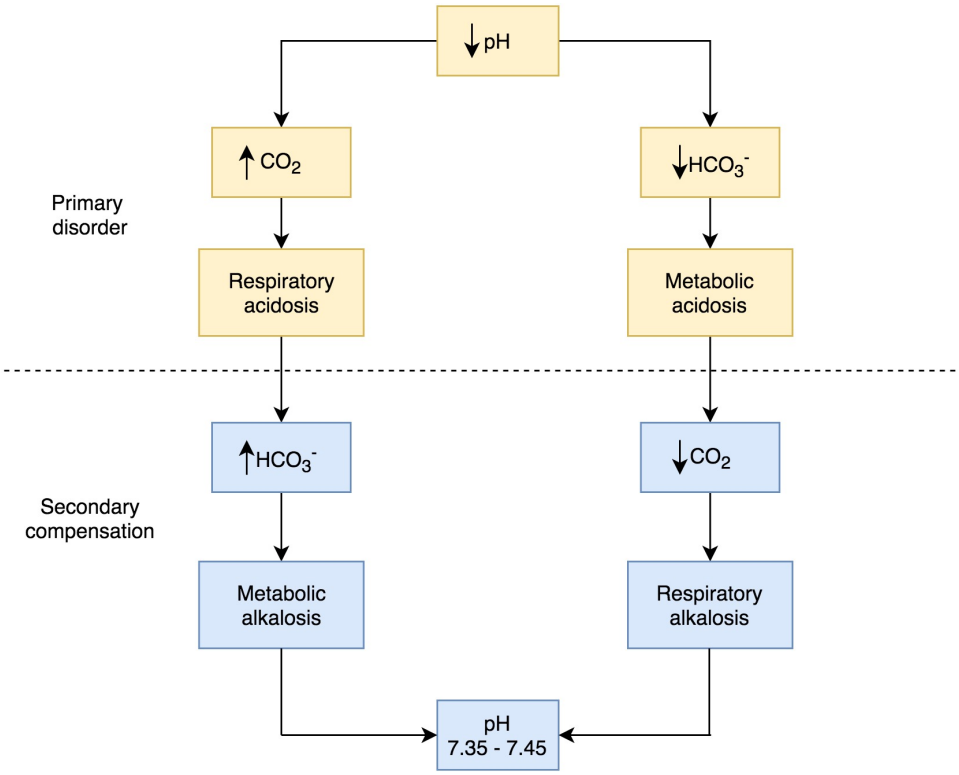
CLINICAL CORRELATION

Even as small amount as 4 mL of methanol can cause blindness!

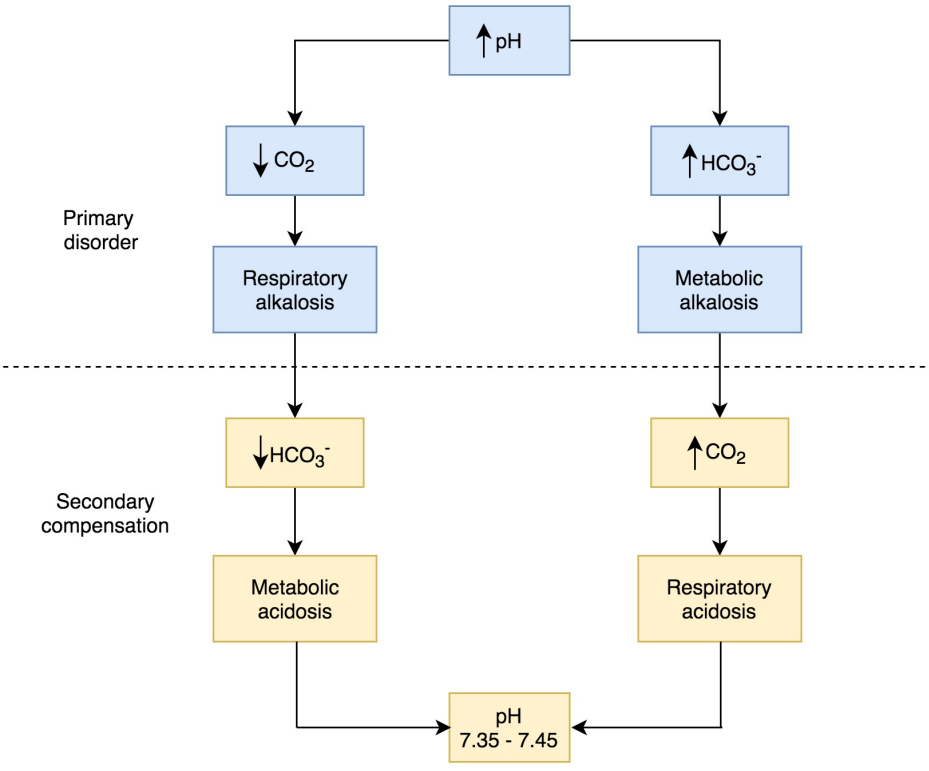
The treatment of methanol and ethylene glycol poisoning is fomepizole.
It inhibits the enzyme that converts methanol and ethylene glycol to their toxic breakdown products.
However, if fomepizole is not available, doctors can actually use ethanol!
Ethanol competes for a spot at the same enzyme and will hinder breakdown of methanol and ethylene glycol.
The acute management of methanol poisoning is actually getting drunk!

14.2 – Rules for Compensatory Responses

14.2.0 – Acidosis



14.2.1 – Alkalosis



14.2.2 – Simple vs. mixed acid-base disorder

I. Predicted compensation

- The illustrations above depict which compensatory responses we can expect.

II. Example: Respiratory acidosis

- A respiratory acidosis is caused by CO_2 levels greater than normal (>45 mmHg).
- The predicted compensatory response would be an increase in HCO_3^- (>26 mmHg).

III. Simple acid-base disorder

- If the cause of an acidosis is caused by increased CO_2 is would be a simple acid-base disorder.

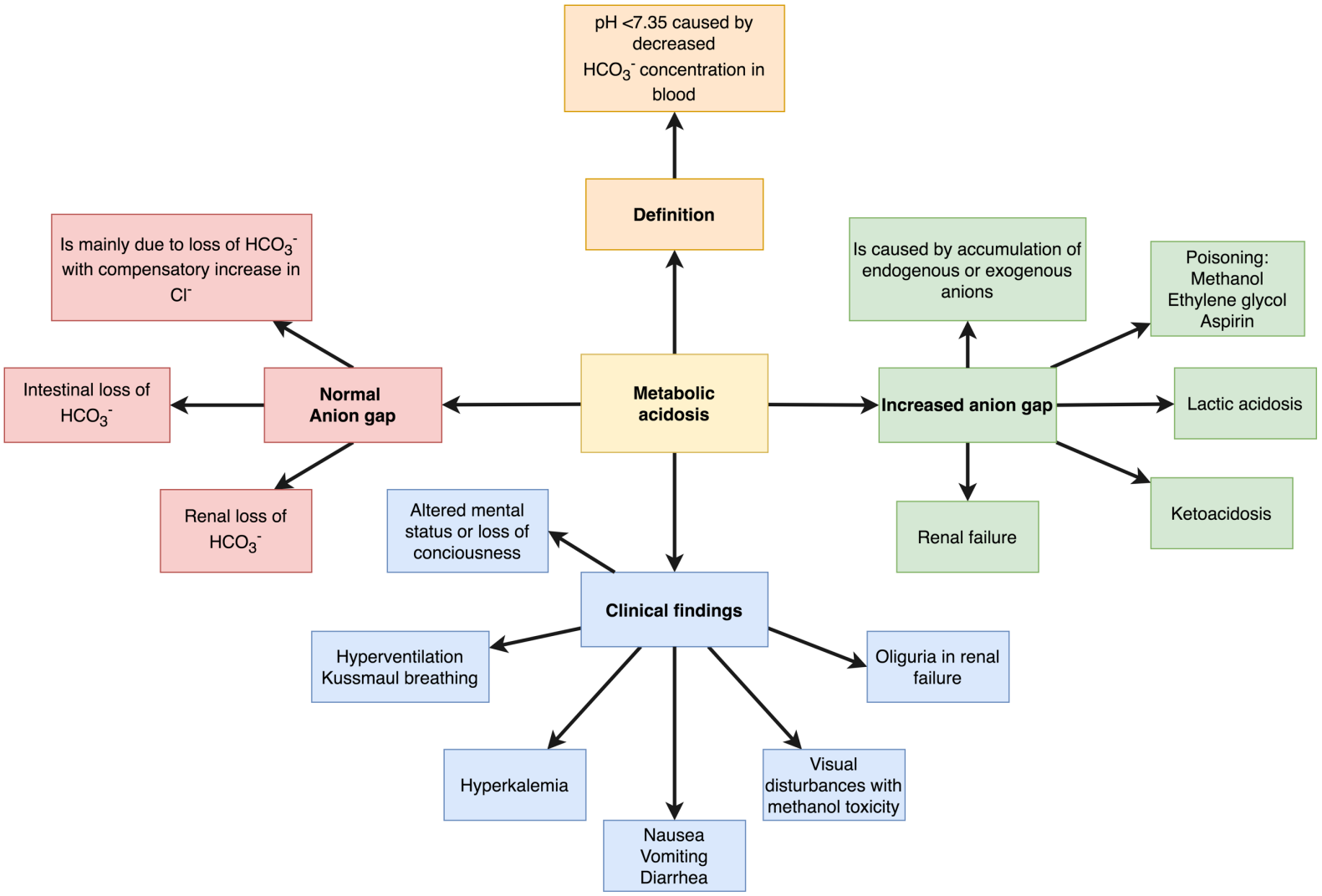
IV. Mixed acid-base disorder

- *Definition:* Combination of two primary acid-base disorders
- *Mixed acidosis:* Increased CO_2, decreased HCO_3^-
- *Mixed alkalosis:* Decreased CO_2, increased HCO_3^-

14.3 – Metabolic Disturbances: Acidosis and Alkalosis

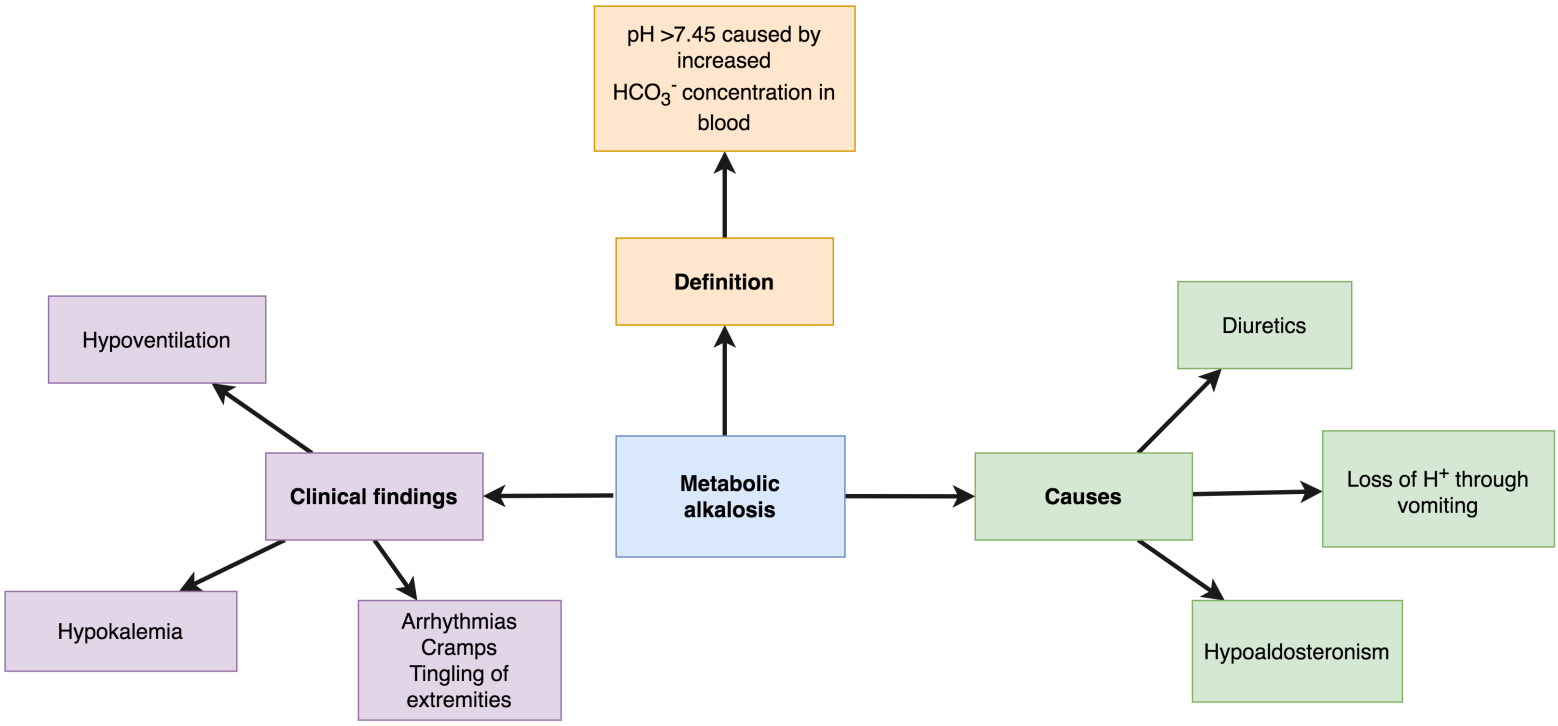
14.3.0 – Metabolic acidosis

Definition	Compensation	Arterial blood gas
pH < 7.35 caused by *decreased* HCO_3^- concentration in blood	Hyperventilation ↓ CO_2 Compensation occurs within minutes	↓ pH ↓ HCO_3^- ↓ CO_2 (compensation)



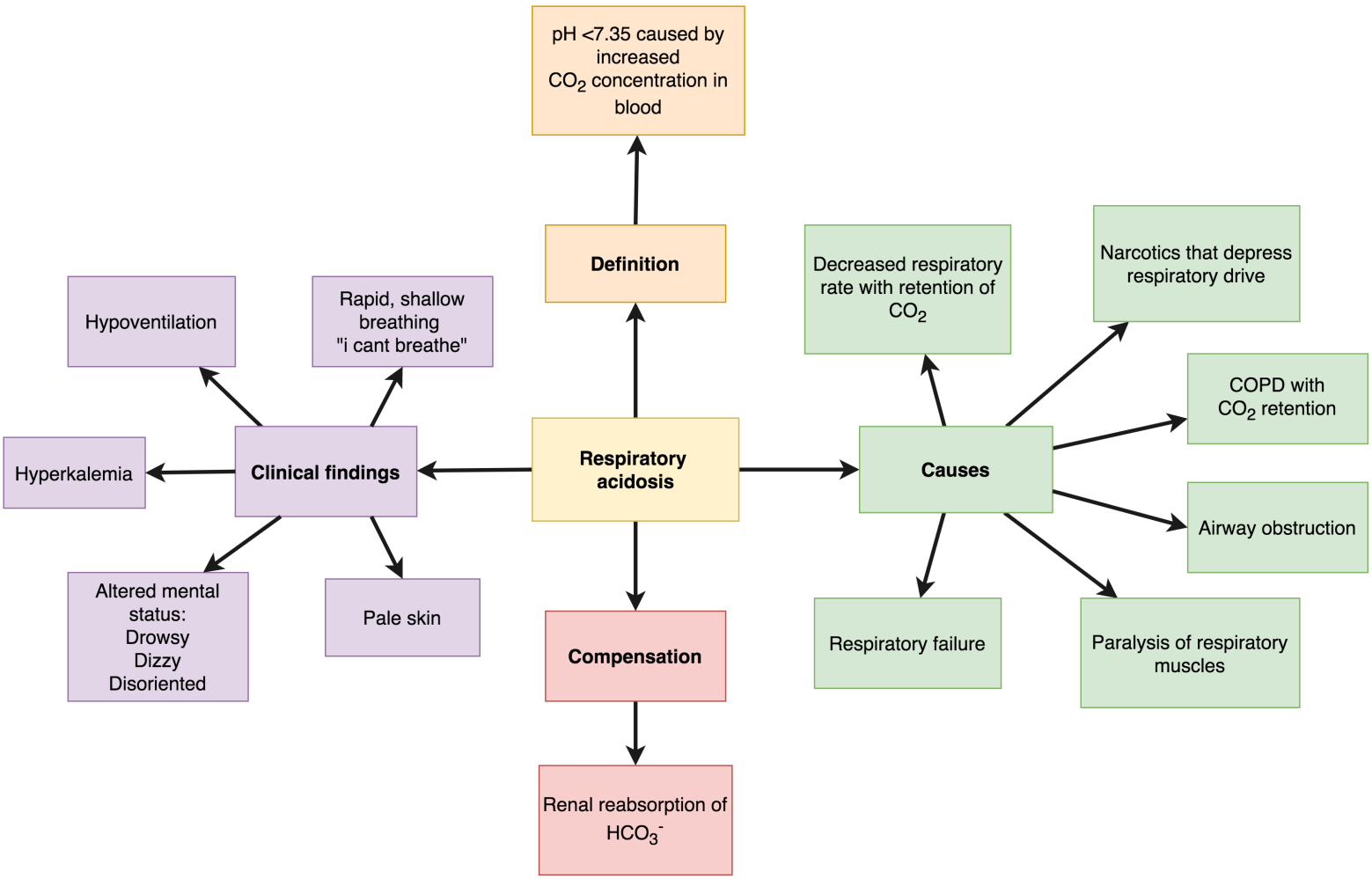
14.3.1 – Metabolic Alkalosis

Definition	Compensation	Arterial blood gas
pH >7.45 caused by *increased* HCO_3^- concentration in blood	Hypoventilation ↑ CO_2 Compensation occurs within minutes	↑ pH ↑ HCO_3^- ↑ CO_2 (compensation)



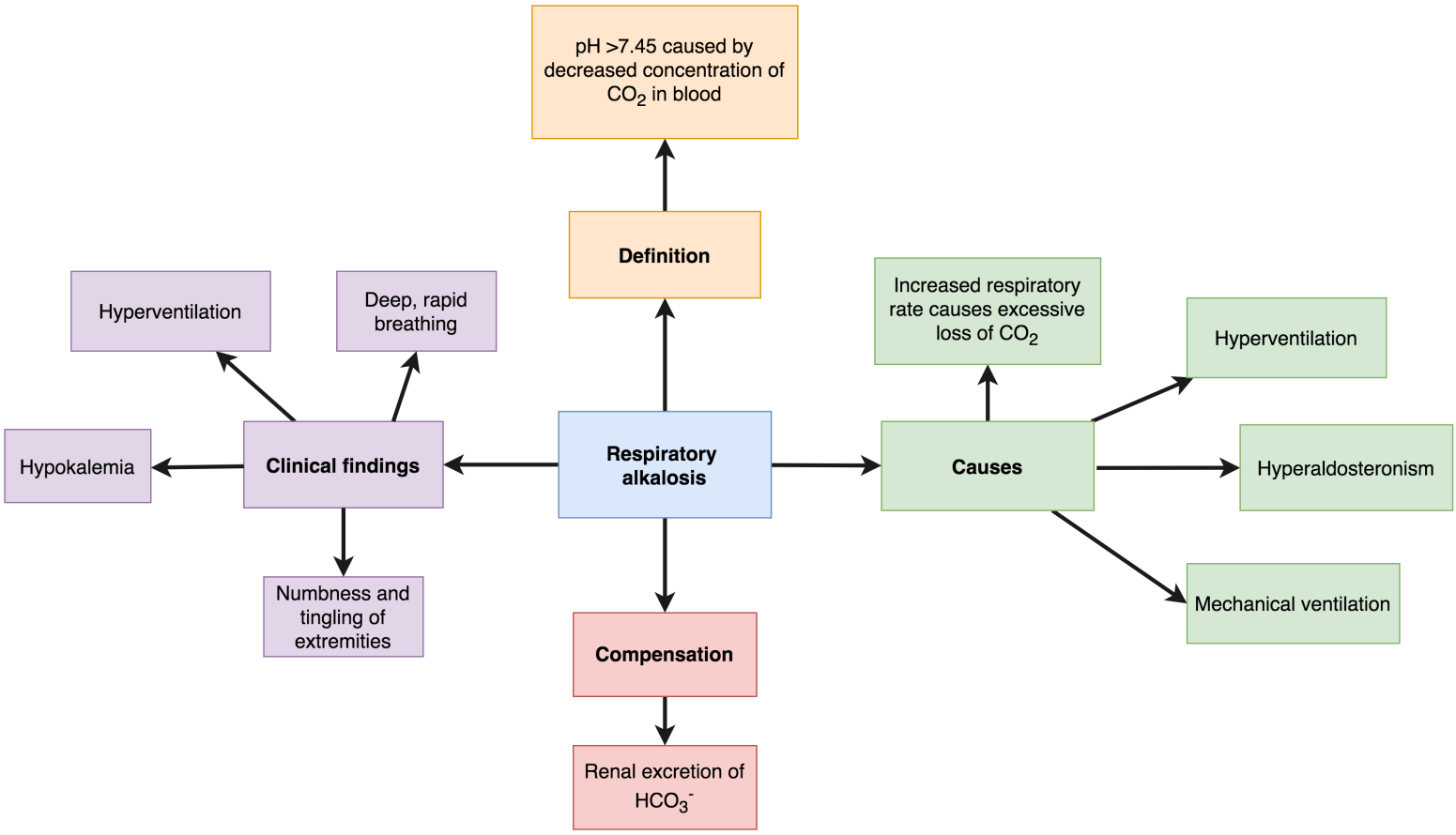
14.3.2 – Respiratory Acidosis

Definition	Compensation	Arterial blood gas
pH < 7.35 caused by *increased* CO_2 concentration in blood	Increased renal reabsorption of HCO_3^- ↑ HCO_3^- Compensation occurs within hours to days *Acute phase:* Renal compensation has not occurred yet → pH is low *Chronic phase:* Renal compensation has increased HCO_3^- → pH is normalized	↓ pH ↑ CO_2 ↑ HCO_3^- (compensation)



14.3.3 – Respiratory Alkalosis

Definition	Compensation	Arterial blood gas
pH >7.45 caused by *decreased* CO_2 concentration in blood	Decreased renal reabsorption of HCO_3^- ↓ HCO_3^- Compensation occurs within hours to days *Acute phase:* Renal compensation has not occurred → pH is high *Chronic phase:* Renal compensation → pH is normalized	↑ pH ↓ CO_2 ↓ HCO_3^- (compensation)



14.4 – Arterial Blood Gas (ABG)

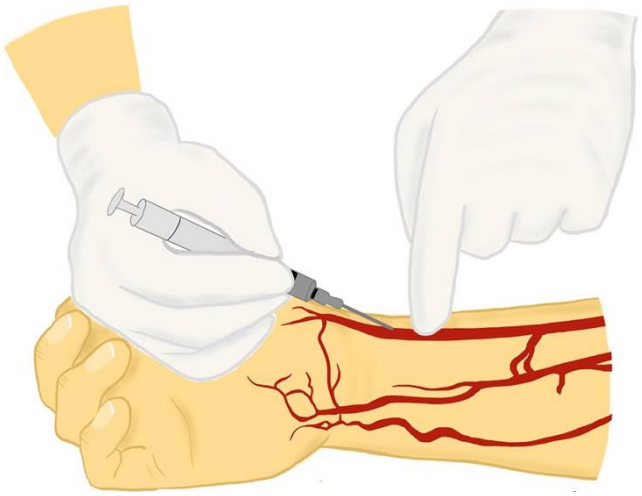
I. Overview

- Puncture site: Radial artery > Femoral artery
- Indications: Dyspnea and/or suspicion of diseases causing acid-base alterations

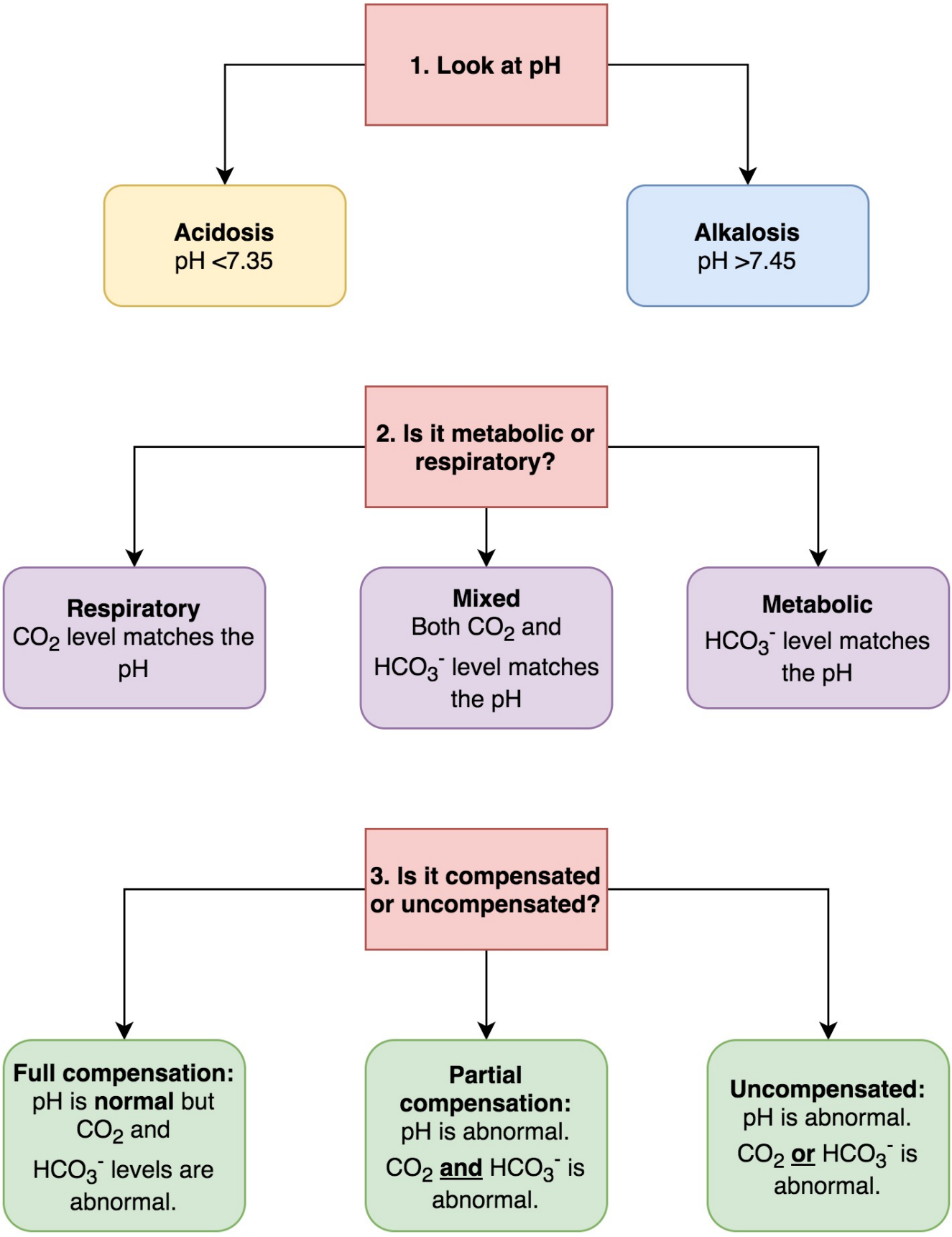
CLINICAL CORRELATION

How to take an Arterial Blood Gas sample

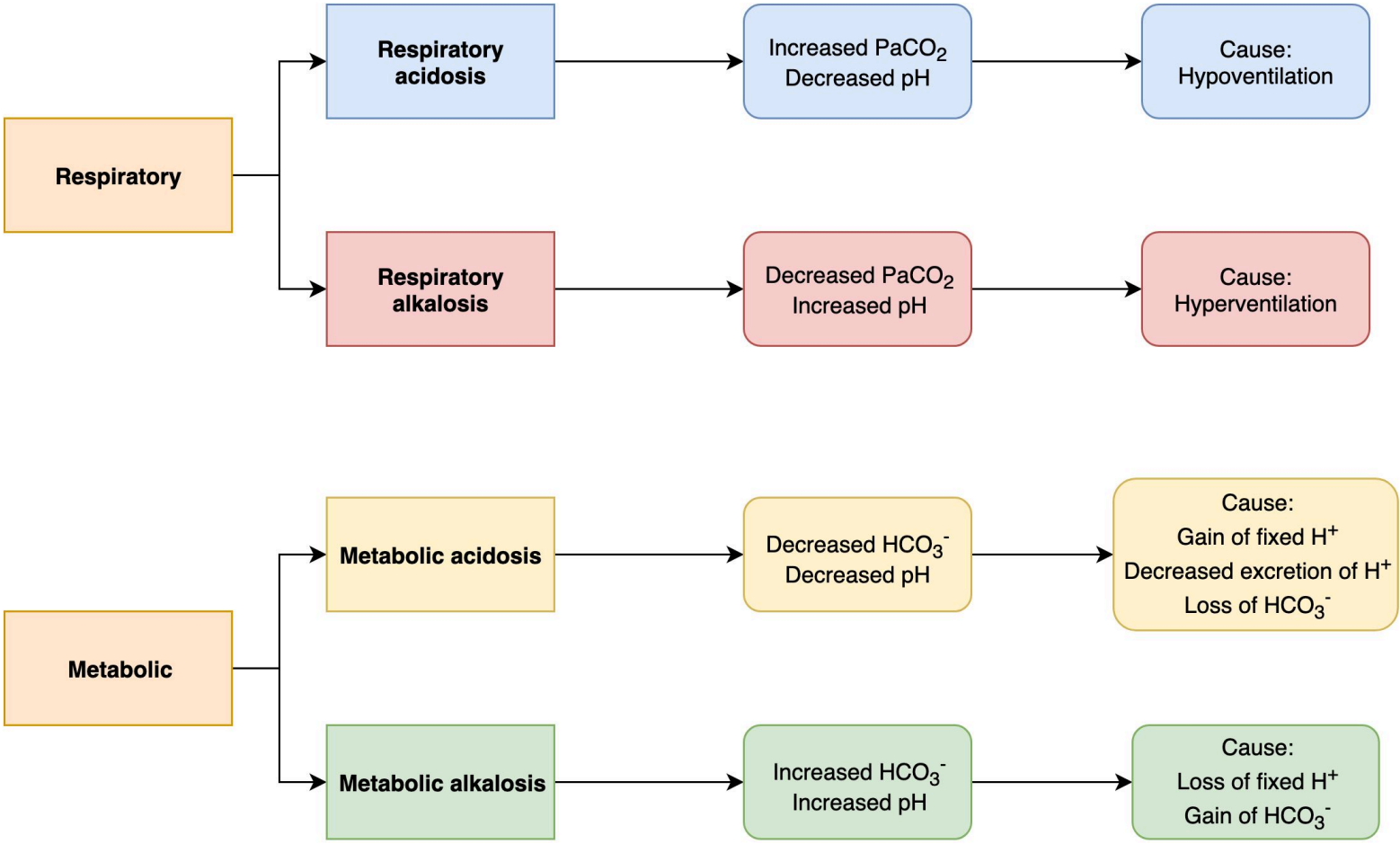
1. Prepare needle, sterile gauze and put on gloves.
2. Localize the artery by feeling the pulsations.
3. Sterilize the area with disinfectant.
4. The non-dominant hand should palpate the artery proximal to the puncture site.
5. The dominant hand inserts the needle at 45-60^0 directed towards the artery.
6. Blood fills the syringe.
7. Remove the needle and compress the puncture wound with a sterile gauze. Compress at least 5 minutes.



II. How can we interpret the results?



14.5 – Summary


Respiratory
Respiratory acidosis
Increased $PaCO_2$
Decreased pH
Cause:
Hypoventilation
Respiratory alkalosis
Decreased $PaCO_2$
Increased pH
Cause:
Hyperventilation
Metabolic
Metabolic acidosis
Decreased HCO_3^-
Decreased pH
Cause:
Gain of fixed H^+
Decreased excretion of H^+
Loss of HCO_3^-
Metabolic alkalosis
Increased HCO_3^-
Increased pH
Cause:
Loss of fixed H^+
Gain of HCO_3^-

14.6 – Test Yourself

1) A patient with metabolic acidosis will

a) Hypoventilate

b) Hyperventilate

2) A patient with metabolic alkalosis will

a) Hypoventilate

b) Hyperventilate

3) Calculating the osmotic gap is important when finding differential diagnosis for

a) Metabolic acidosis

b) Metabolic alkalosis

c) Respiratory acidosis

d) Respiratory alkalosis

4) Find two correct statements

a) Acidosis causes hyperkalemia

b) Alkalosis causes hyperkalemia

c) Acidosis causes hypokalemia

d) Alkalosis causes hypokalemia

4) Follow the diagram in section 14.4 explaining how to interpret ABG results. Establish if the disorder is acidosis or alkalosis, compensated or uncompensated, respiratory or metabolic and simple or mixed:

a) After a panic attack, ABG results are:

pH: 7.50
CO_2: 29 mmHg
HCO_3^-: 25 mmol/L

☐ Acidosis	☐ Compensated
☐ Alkalosis	☐ Uncompensated
☐ Respiratory	☐ Simple
☐ Metabolic	☐ Mixed

b) A patient presents to the ER with confusion, problems with balance and visual disturbances. His respiratory rate is 35. ABG results are:

pH: 7.26
CO_2: 30 mmHg
HCO_3^-: 15 mmol/L

☐ Acidosis	☐ Compensated
☐ Alkalosis	☐ Uncompensated
☐ Respiratory	☐ Simple
☐ Metabolic	☐ Mixed

c) Patient presents to the GP office due to several days of diarrhea. She seems very unwell. Blood pressure is 86/52, pulse 115 and respiratory rate 23. The doctor sends her to hospital where fluids are started to increase the blood pressure. ABG results are:

pH: 7.37
CO_2: 31 mmHg
HCO_3^-: 20 mmol/L

☐ Acidosis	☐ Compensated
☐ Alkalosis	☐ Uncompensated
☐ Respiratory	☐ Simple
☐ Metabolic	☐ Mixed