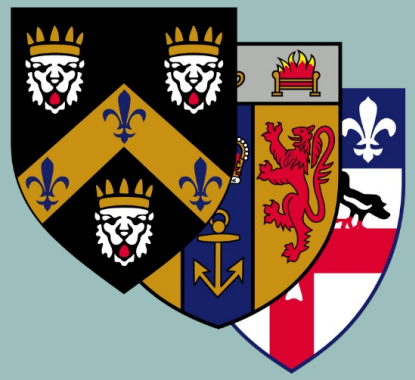


MSA Education

Physiology of Gastrointestinal and Renal Systems

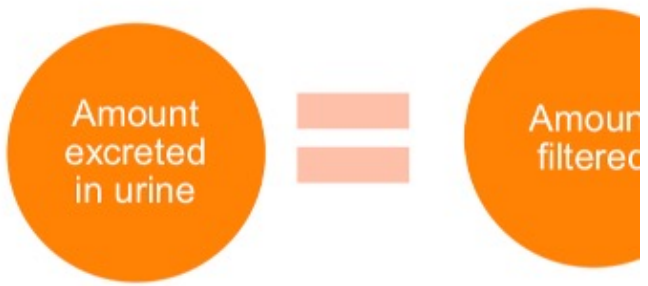
Edouard Long – Year 3 Medical Student

Friday April 19th

BASIC RENAL PROCESSES

1) Glomerular Filtration
2) Tubular Secretion
3) Tubular Reabsorption
4) Metabolism e.g. Glutamine

Glomerular filtration: the movement
plasma that enters glomerulus is filter
Tubular secretion: the secretion of so
Tubular reabsorption: the movement



Substance filtered and secreted but n
Substance filtered and some reabsorb
Substance filtered and completely rea

GLOMERULUS FILTRATION

- Most plasma constituents are
- Filtration depends on molecu

GI Physiology

GI Tract

Mouth –> oesophagus –> stomach –> small intestine – large intestine

Separated by muscular valves/sphincters with mucosal lining.

Esophagus -> Large intestine, 4 distinct histological layers:

1. Mucosa
2. Submucosa
3. Muscularis externa
4. Adventita/Serosa

Hormone	Released by	Physiological effects
Gastrin	G-cells in stomach and upper small intestine in response to products of digestion, extrinsic nerve stimulation, antral distension	↑ secretion of HCl, pepsinogen and intrinsic factor, trophic effect on gastric acid secreting mucosa
CCK	I-cells in upper small intestine in response to products of digestion, e.g. fat and protein	↑ secretion of enzyme rich fluid from pancreatic acinar cells, contraction of gall bladder and relaxation of sphincter of Oddi, ↓ gastric emptying, trophic effect on pancreatic acinar cells
Secretin	S-cells in upper small intestine in response to ↓ upper intestine pH, fatty acids upper intestine	↑ secretion of HCO_3^- rich fluid from pancreatic and hepatic duct cells
GIP	K-cells in upper small intestine in response to fat, amino acids and glucose	Releases insulin from pancreatic β cells
Proglucagon-derived peptides, enteroglucagon and GLP	L-cells in distal ileum and colon in response to glucose and fat in lumen in these regions	Enhanced intestinal glucose uptake, trophic effect on intestinal crypt cells
Somatostatin	D-cells in distal stomach in response to acid, D-cells in proximal stomach in response to CCK and ACh D-cells in intestine and panreatic islets in response to glucose, fats and bile salts in the intestinal lumen	↓ gastrin release ↓ gastric acid, histamine and pepsin secretion, inhibits trophic actions of gastrin ↓ pancreatic enzyme secretion and insulin and glucagon release

Salivary glands

Three paired glands

Salivary gland	Proportion of total saliva secreted
Submandibular	70%
Parotid	25%
Sublingual	5%

Secretion of Saliva

2 Stage process:

1. Isotonic primary fluid formed by acinar cells
2. Modified in duct system by reabsorption of NaCl and secretion of K+/HCO3-

Cells lining the stomach

Surface of stomach: simple columnar epithelium of surface mucous cells

Within the gastric pits, a number of key cells.

Parietal cells: Secrete HCl and IF
Chief cells: Secrete pepsinogens
ECL cells: secrete histamine

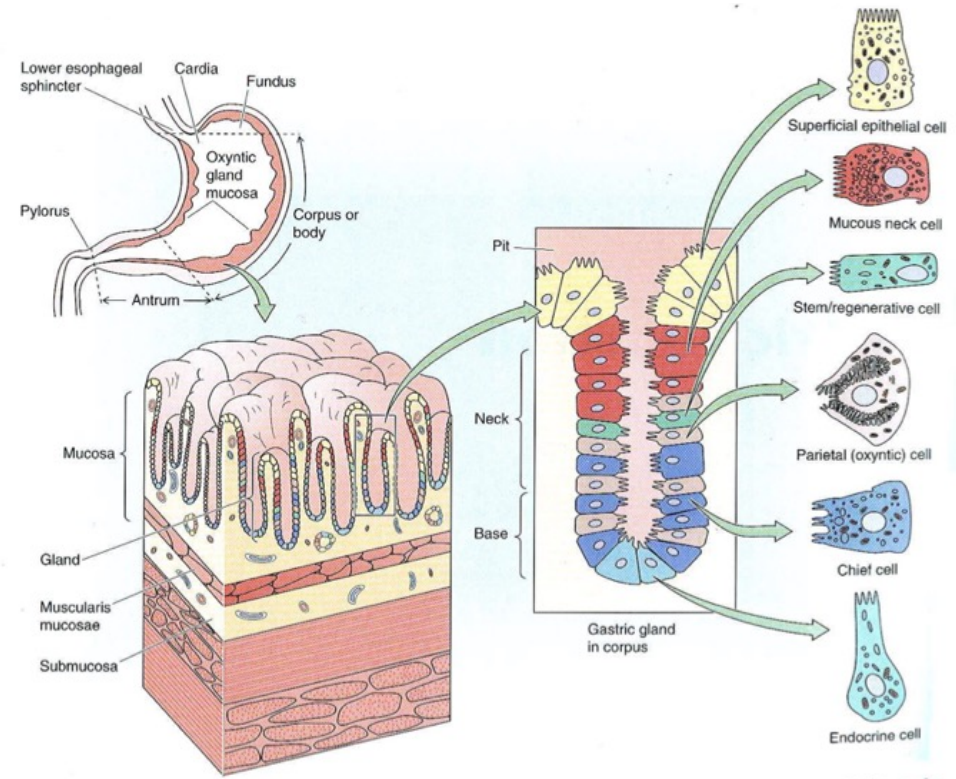
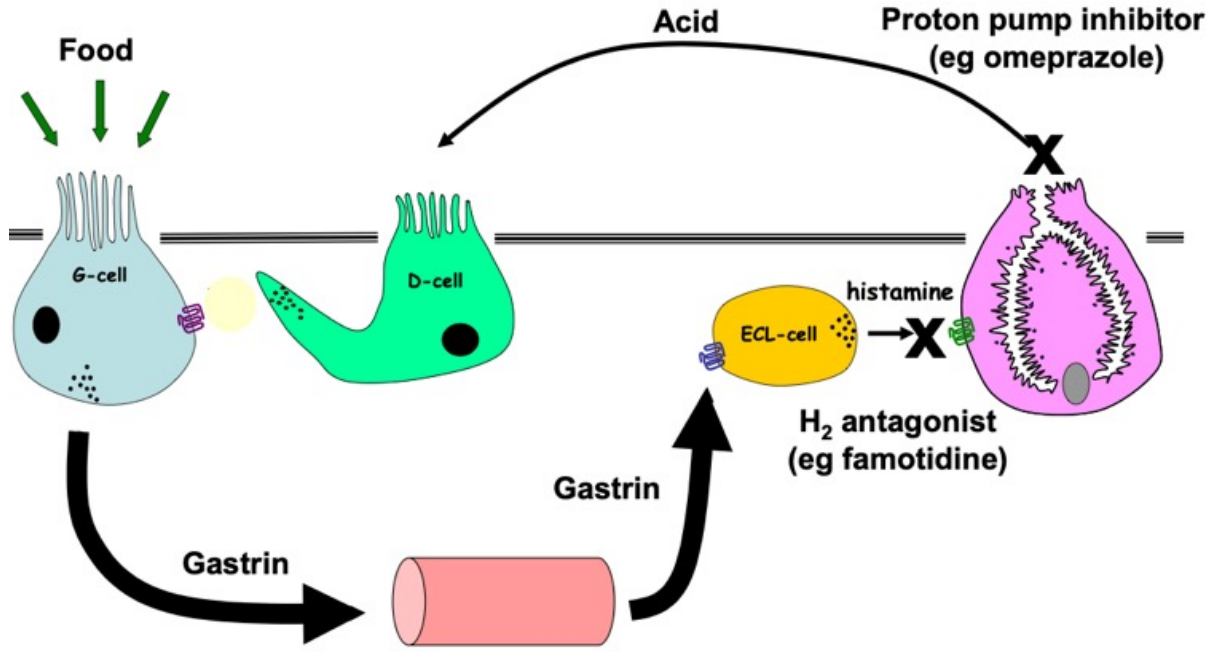


FIGURE 41–1. Anatomy of the stomach. Shown are the macroscopic divisions of the stomach, as well as two progressively magnified views of a section through the wall of the body of the stomach.

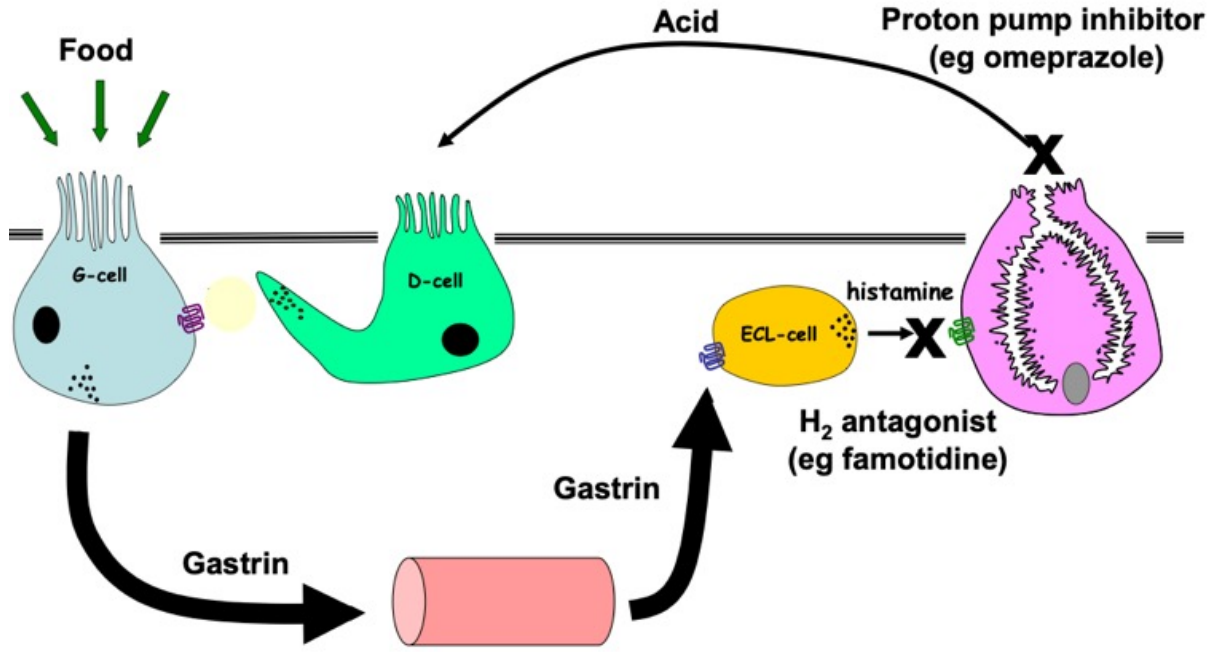
Gastric acid secretion:

- Release of gastrin from G cell
- Travels into the bloodstream and binds to ECF-cell in stomach epithelium



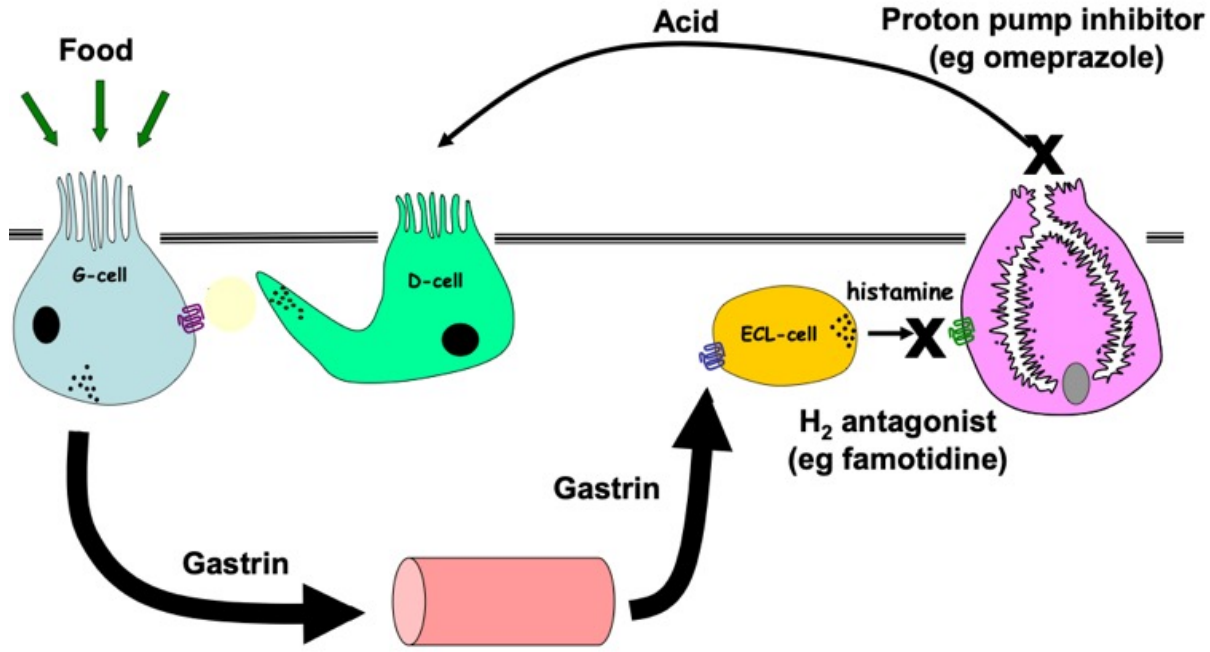
Gastric acid secretion:

- This leads to exocytosis of histamine granules which bind to H2 receptor on parietal cell



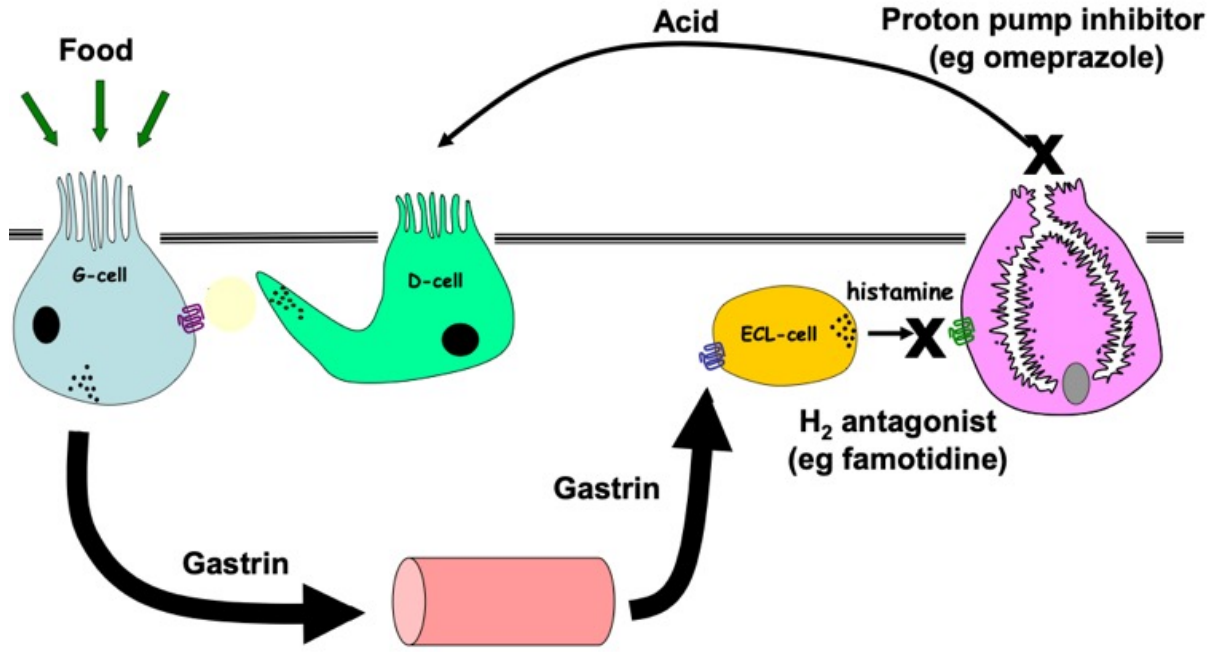
Gastric acid secretion:

- This triggers morphological changes in the intracellular canaliculi which then express K+/H+ATPase
- This leads to secretion of HCl into the lumen of the stomach



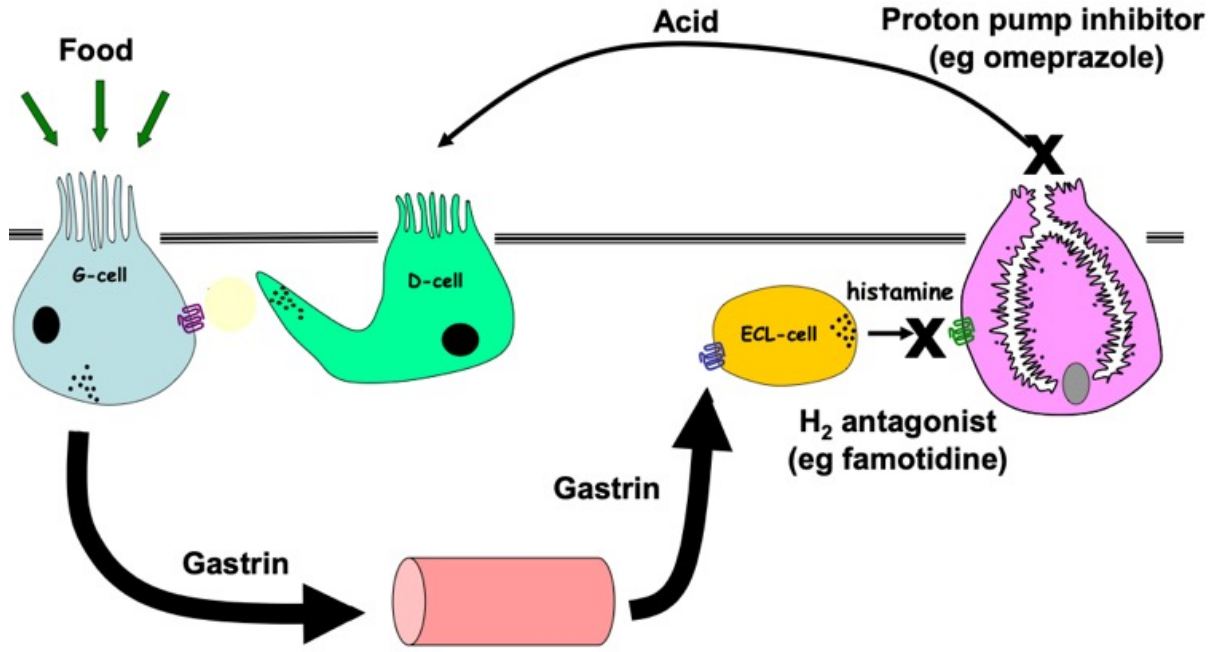
Gastric acid secretion:

- Negative feedback loop: Gastric acid activates the D cell which secretes somatostatin inhibiting gastrin release



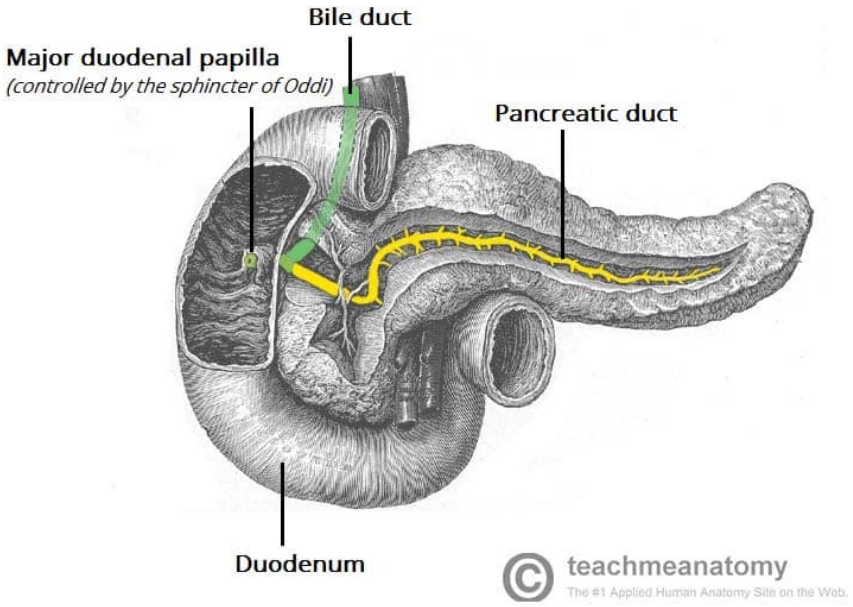
Gastric acid secretion:

- Therefore if you have gastric ulcers:
  - H+/k+ATPase inhibitor (PPI) [eg omeprazole]
  - H2 antagonist [eg famotidine]



Pancreatic secretions

Anatomically, the main pancreatic duct merges with the bile duct, which leads to the Ampulla of Vater. It is here that these secretions pour into the duodenum and help neutralise and digest chyme [contents expelled from stomach]



Pancreatic secretions

- Acinar cells produce digestive enzymes on the RER
- Moved to golgi body where they form condensing vacuoles
- Concentrated into inactive zymogen granules in the acinar cells
- These are stored for secretion / secreted into the main pancreatic duct

Pancreatic secretions

Proteases:
- Chymotrypsinogen and Trypsinogen: Digest proteins and peptides to single amino acids
- Pancreatic lipase: Digests triglycerides, monoglyceride and free fatty acids

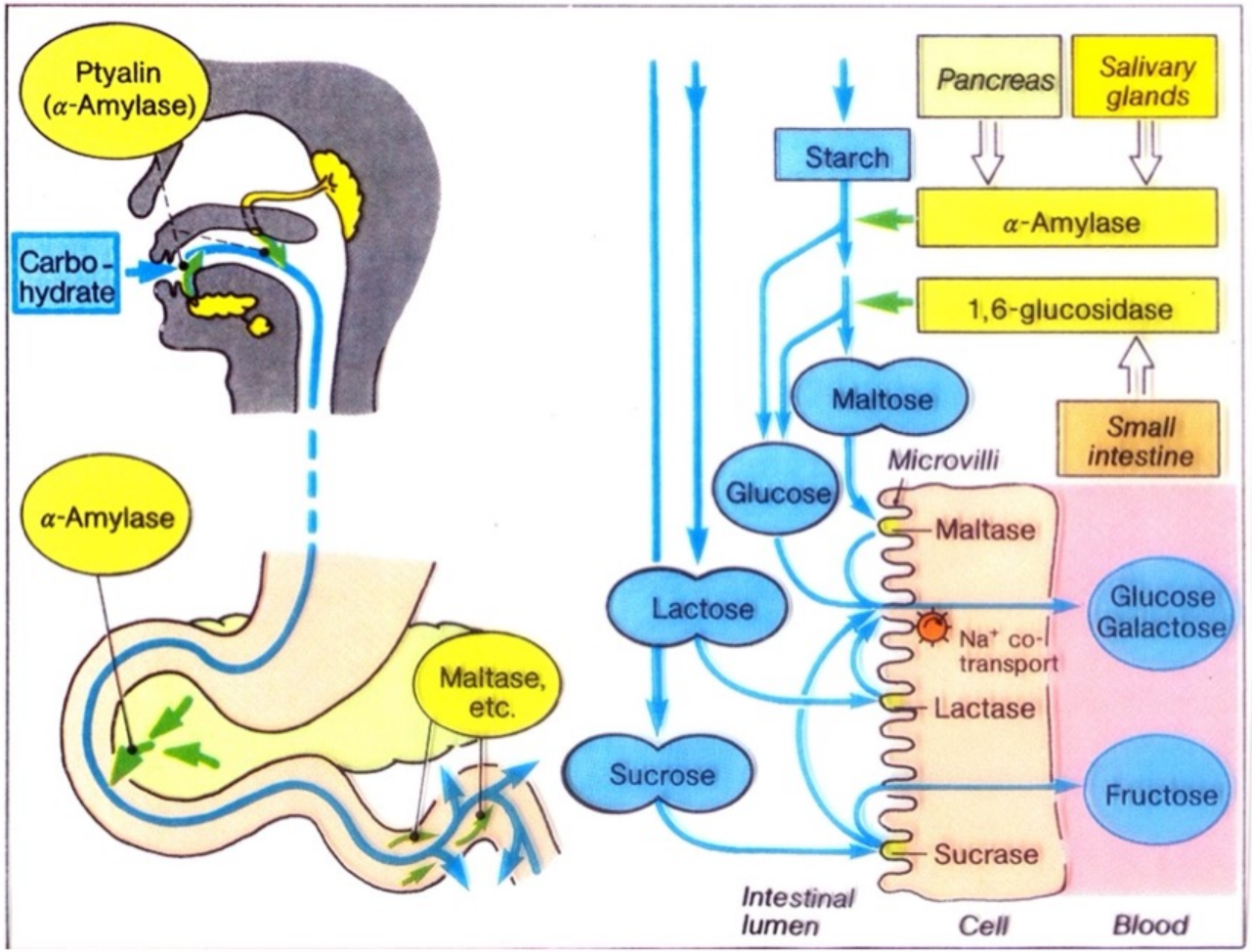
Amylase: Starch and maltose/glycogen (disaccharides)

Other enzymes include ribonuclease, gelatinase, elastase etc.

Carbohydrate digestion

Three carbohydrate products absorbed by the small intestine:
- Glucose
- Galactose
- Fructose

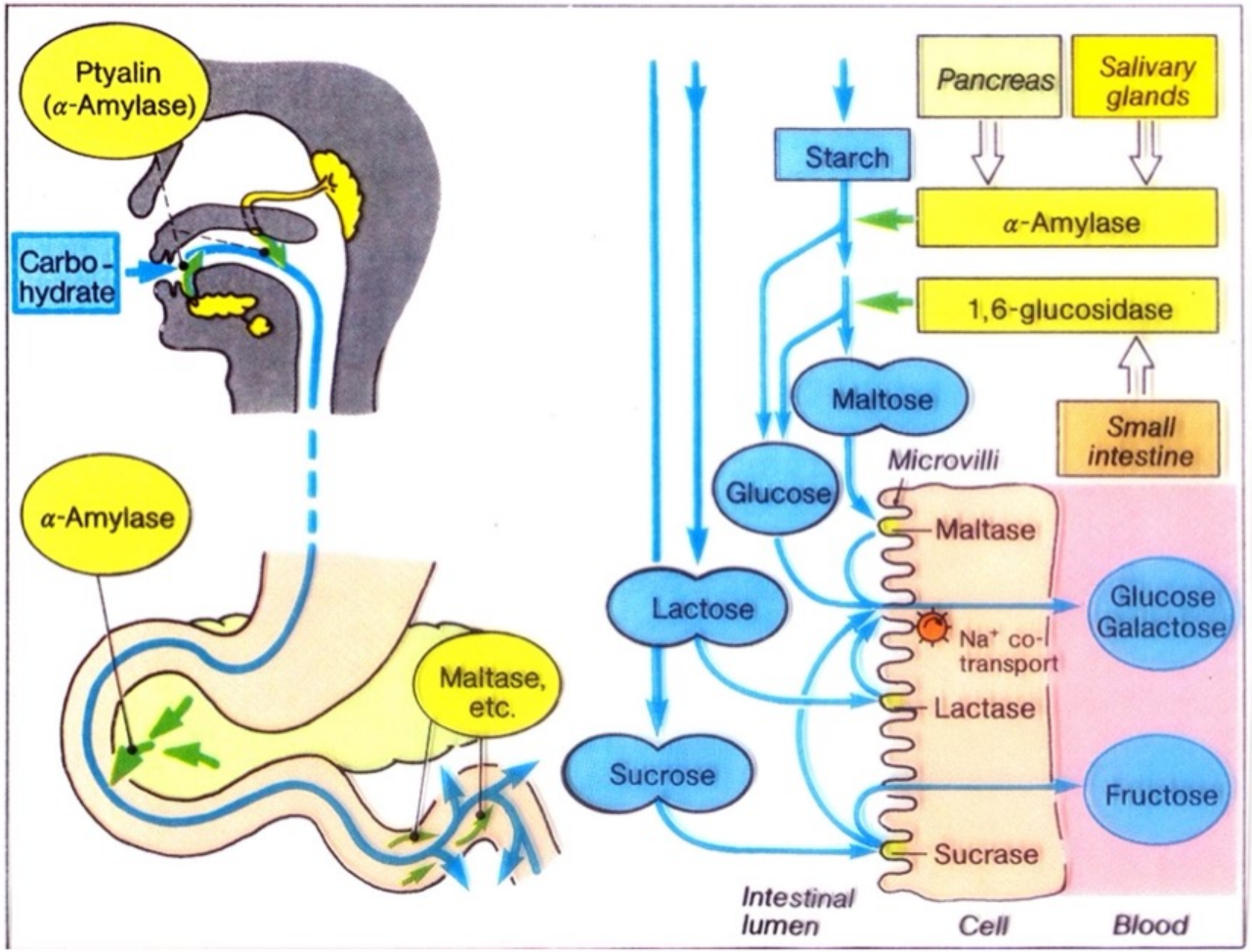
- For starch, digestion in the mouth by salivary amylase, majority is in small intestine by pancreatic amylase



Carbohydrate digestion

Disaccharides produced by amylase [from starch] are converted to glucose by brush border enzymes

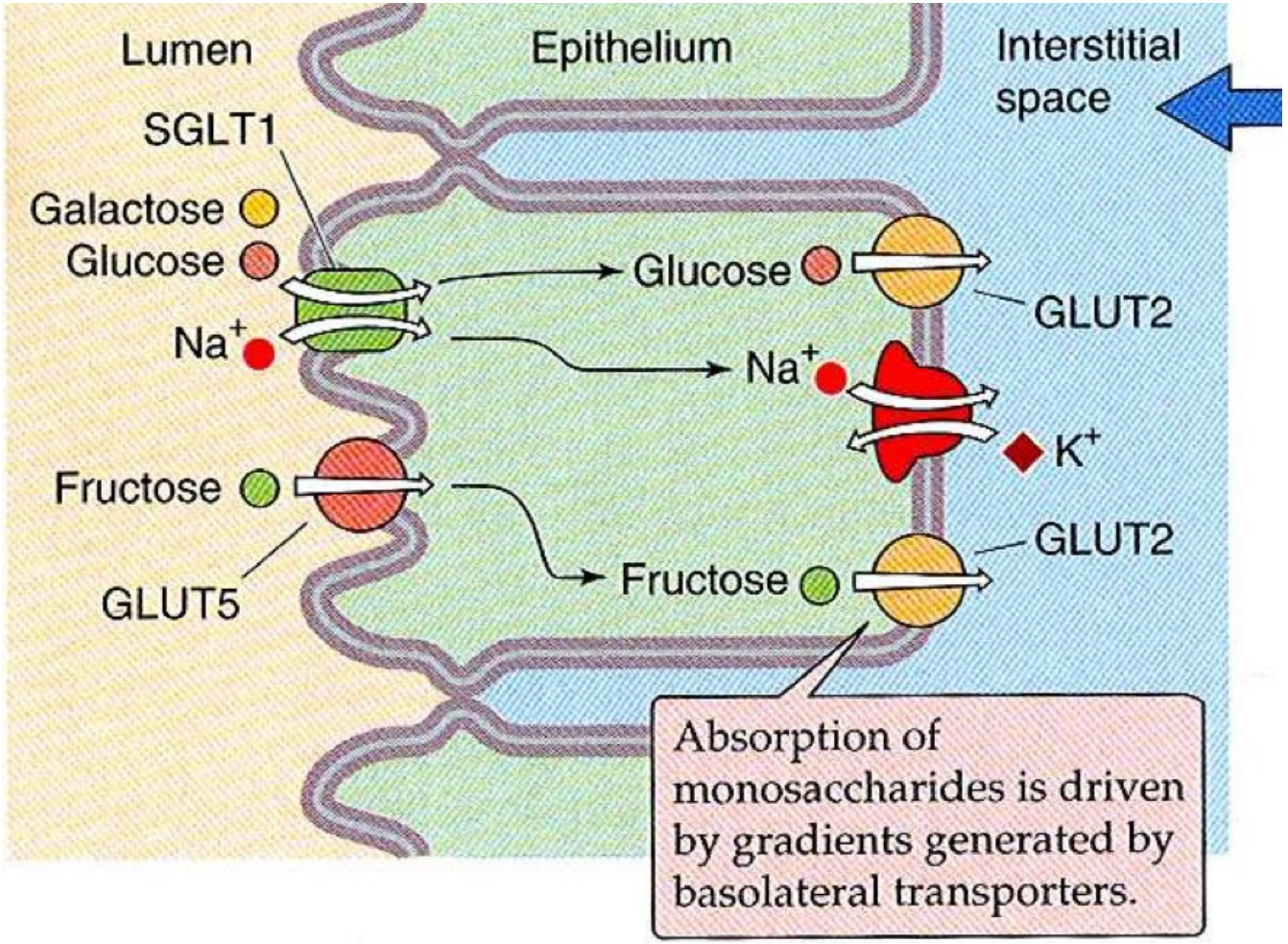
Disaccharides occurring naturally in food do not require amylase to break them down. Brush border enzymes hydrolyze these into glucose, galactose and fructose



Carbohydrate absorption

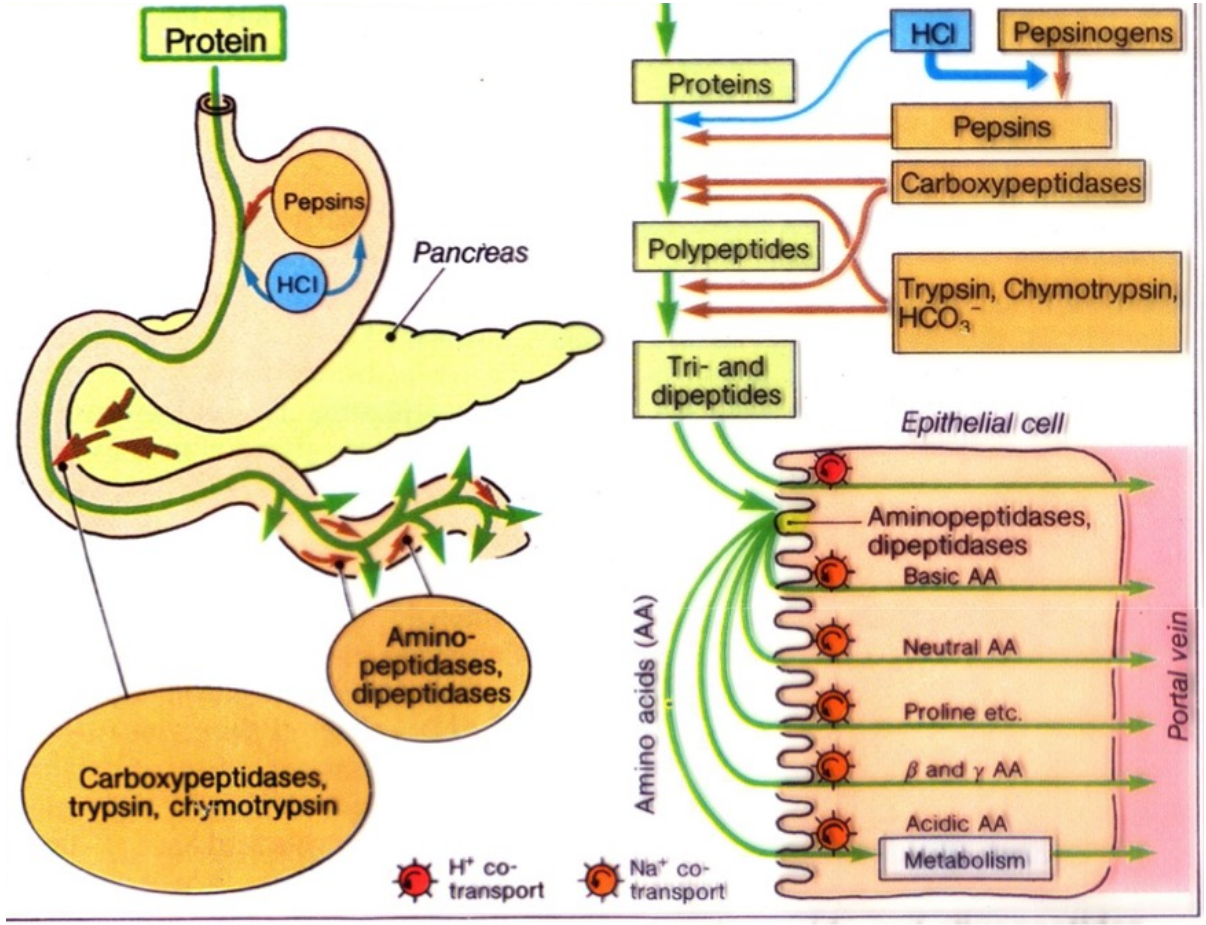
- Glucose and galactose are absorbed by secondary active transport using SGLT1 transporter
- Fructose enters the cell by facilitated diffusion with the GLUT5 transporter

- Both exit cell by GLUT2 receptors



Protein digestion

- Begins in the stomach with pepsin which breaks proteins into oligopeptides
- In small intestine, pancreatic enzymes break oligopeptides into amino acids, di-peptides and tri-peptides

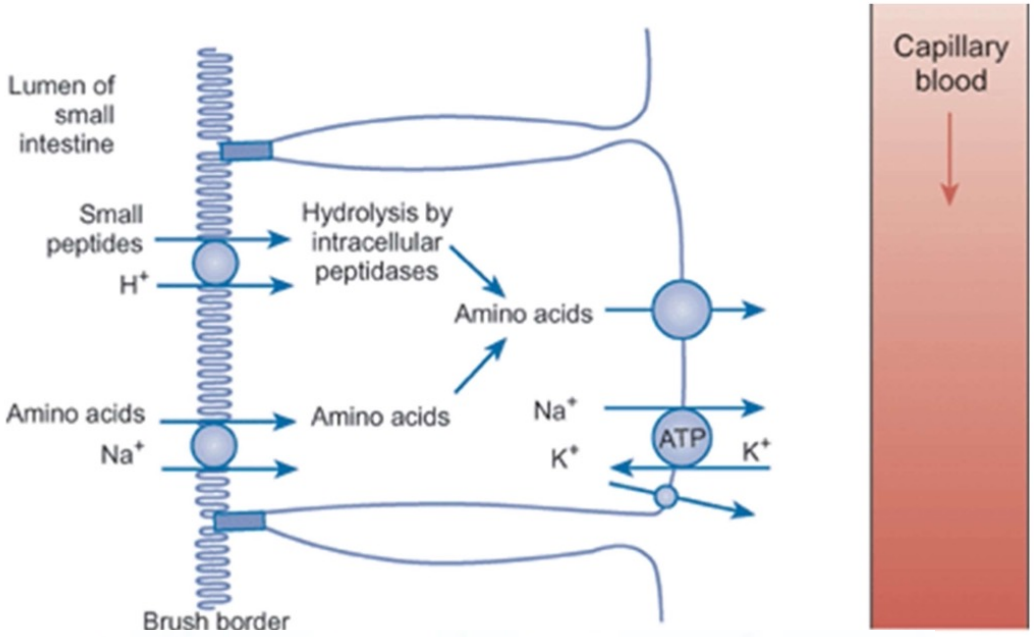


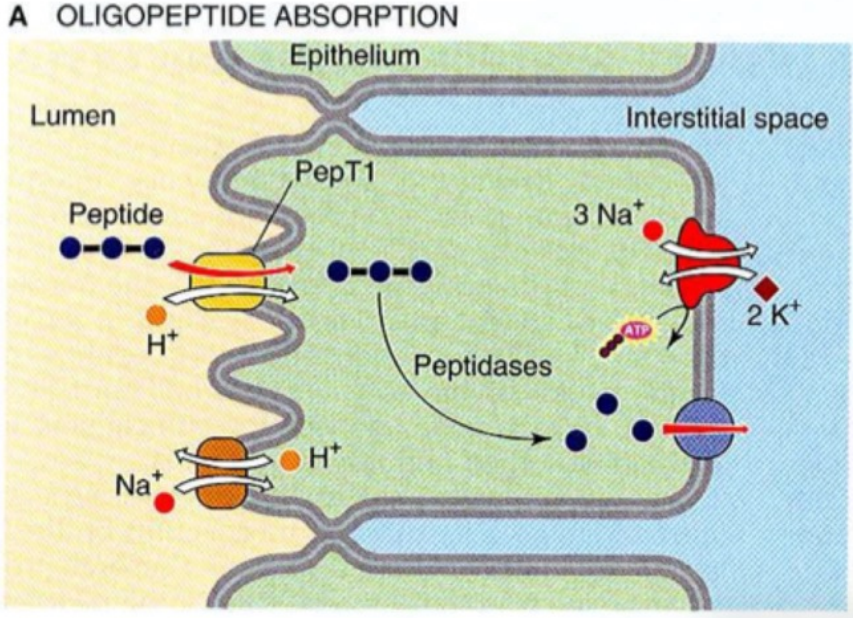
Protein absorption

- Amino acids are absorbed via a sodium co-transporter, these then exit via facilitated diffusion

- Di & tri-peptides are absorbed via H+ dependent co-transporters
- Once in the cell they are hydrolyzed to amino acids and exit via facilitated diffusion

Absorption of peptides and amino acids across intestinal villi





GI Tract Motility

Factors influencing GI motility:

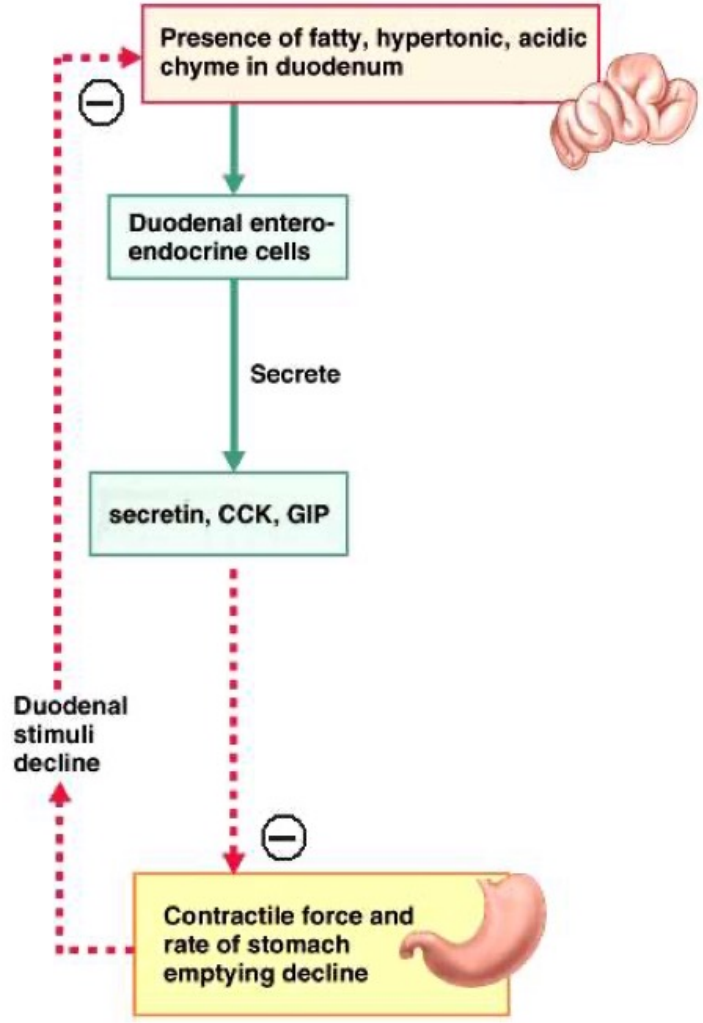
1. Smooth muscle
   - Muscle cells have electrical activity which moves in slow waves [interstitial cells of Cajal]

2. Neuronal control
- Parasympathetic (vagus nerve) has excitatory fibers and inhibitory fibers
- Sympathetic NS has primary inhibitory effects

3. Hormonal control
- Endocrine (gastrin, cholecystokinin) and local (paracrine, neurocrine)

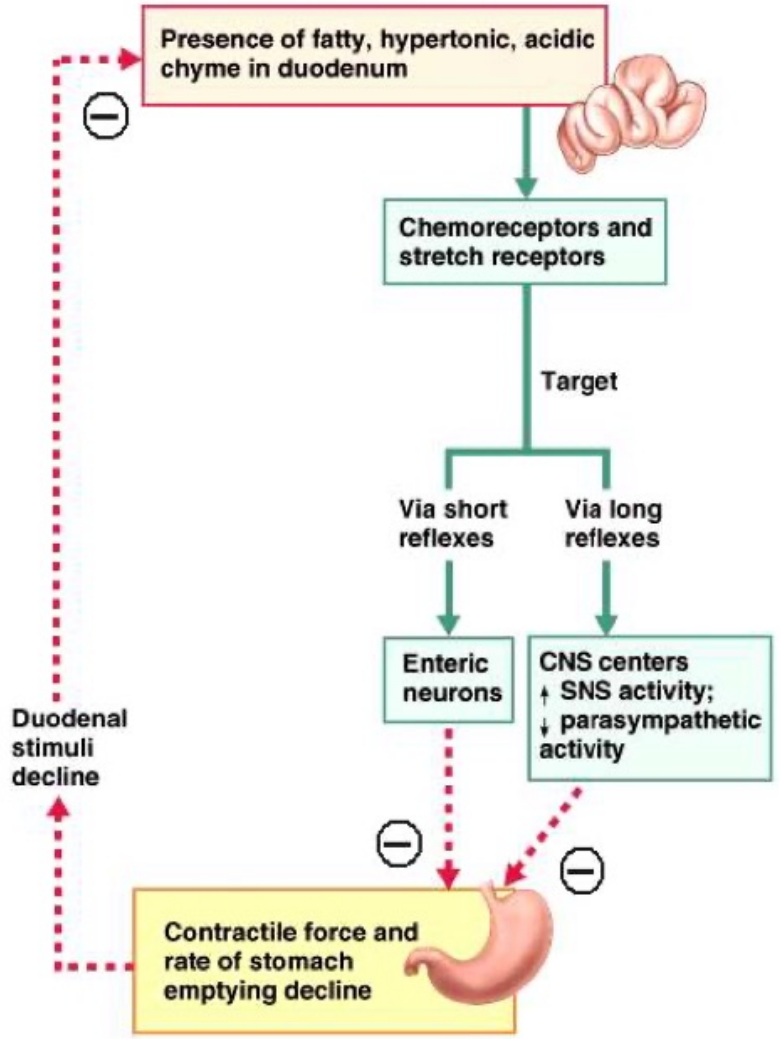
Regulation of gastric activity: Hormonal

- Chyme in the duodenum causes entero-endocrine cells to secrete inhibitory hormones:
  - Secretin
  - Cholecystokinin (CCK)
  - Gastric inhibitory polypeptide (GIP)



Regulation of gastric activity: Chemo & stretch receptors

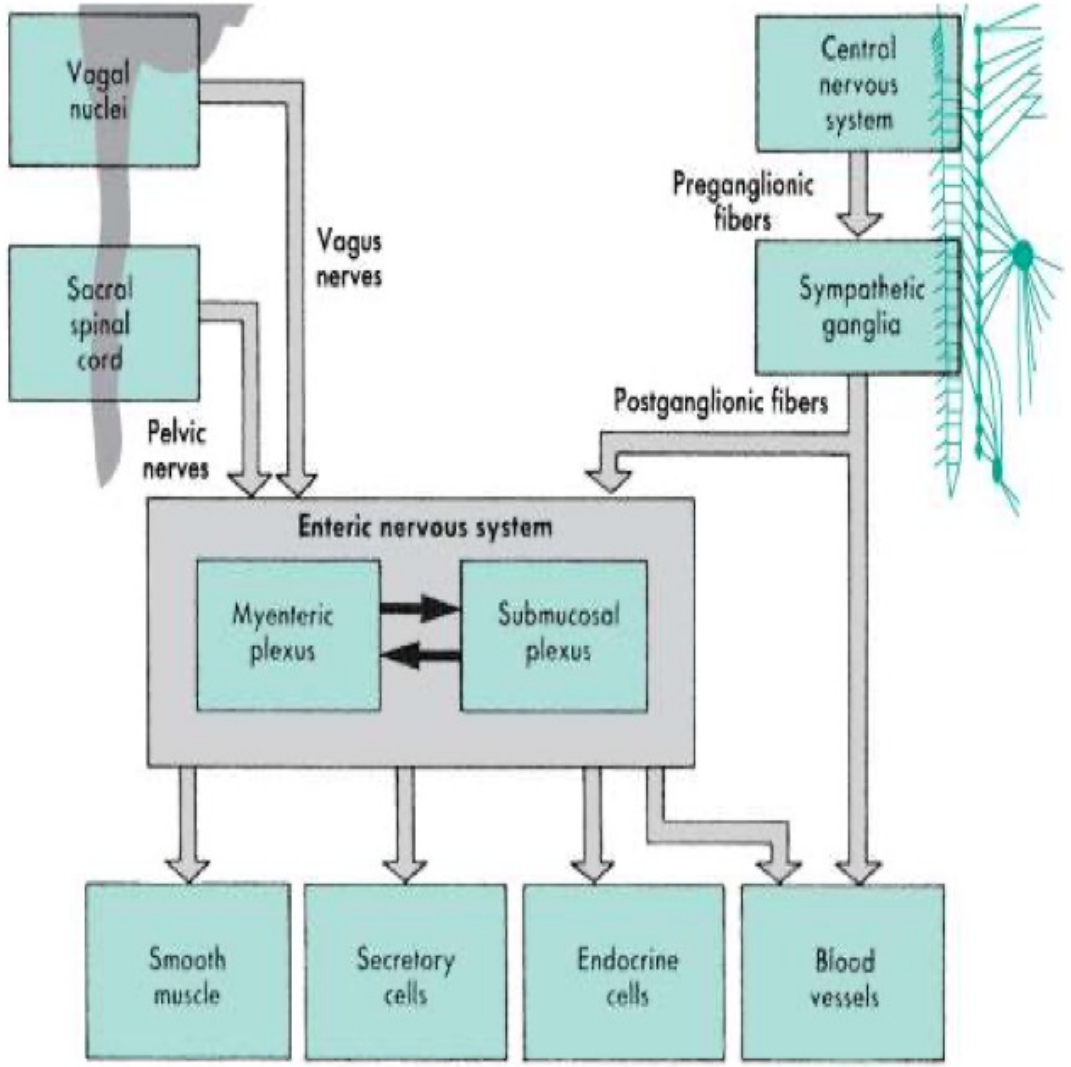
- Chyme in the duodenum activates chemo and stretch receptors
- This activates short reflexes (via enteric nervous system) and long reflexes (via CNS)
- This inhibits gastric contraction
- As pyloric sphincter closes, chyme is no longer entering duodenum -> negative feedback loop



Regulation of gastric activity: Neuronal

Parasympathetic:
- Vagus and pelvic nerves interact w/ submucosal and myenteric plexuses

(also sympathetic)



Biliary system

- Bile acids are synthesized in the liver, secreted into the biliary system and stored in the gall bladder
- Gall bladder contracts in response to CCK released from the small intestine when food enters the duodenum
- Secretin secreted by small intestine in the bloodstream also stimulates liver ductal secretion

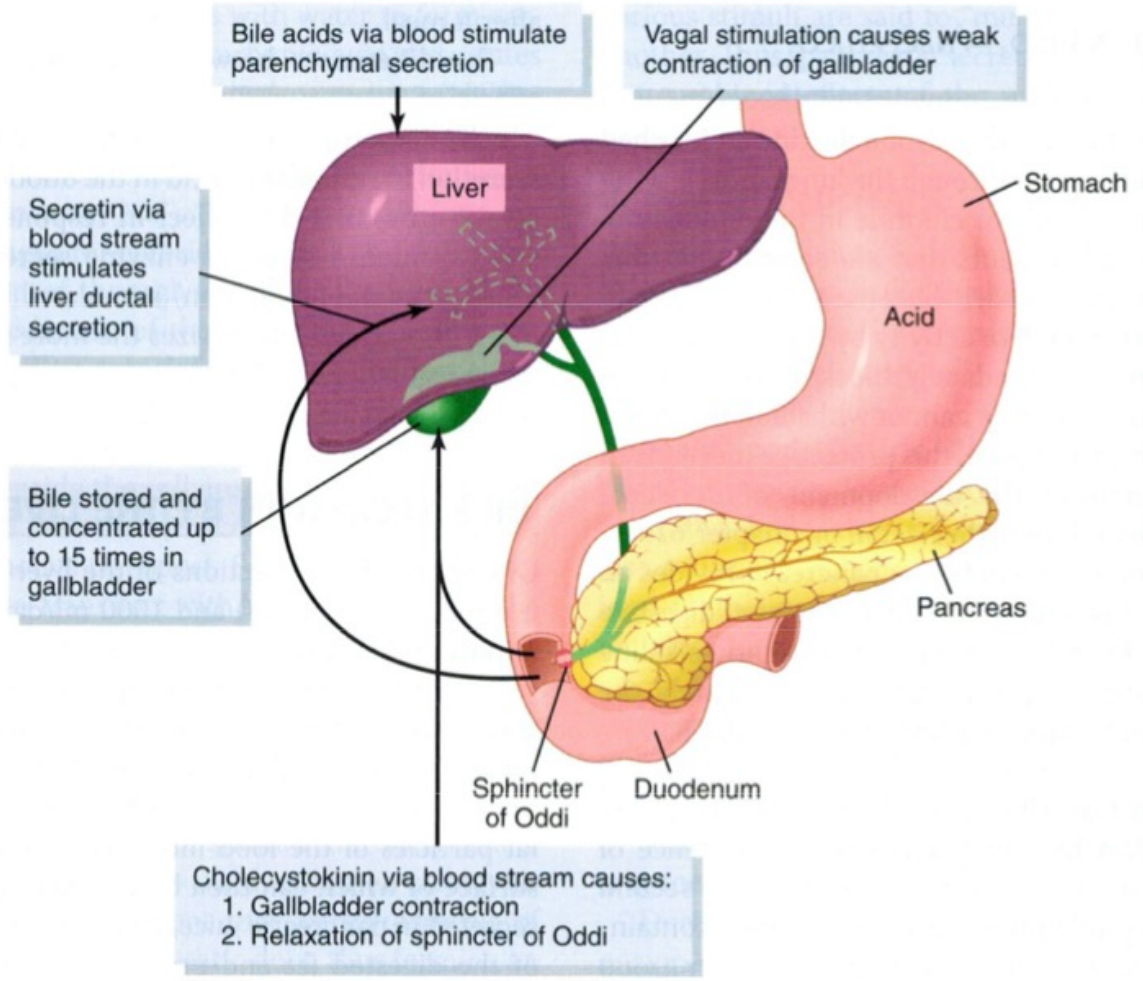


Figure 65-11. Liver secretion and gallbladder emptying.

TABLE 45–3

COMPOSITION OF BILE

PARAMETER	HEPATIC BILE
pH	7.5
Na^+ (mM)	141–165
K^+ (mM)	2.7–6.7
Ca^{2+} (mM)	1.2–3.2
Cl^- (mM)	77–117
HCO_3^- (mM)	12–55
Total phosphorus (g/liter)	0.15
Bile acids (g/liter)	3–45
Total fatty acids (g/liter)	2.7
Bilirubin (g/liter)	1–2
Phospholipids (g/liter)	1.4–8.1
Cholesterol (g/liter)	1–3.2
Proteins (g/liter)	2–20

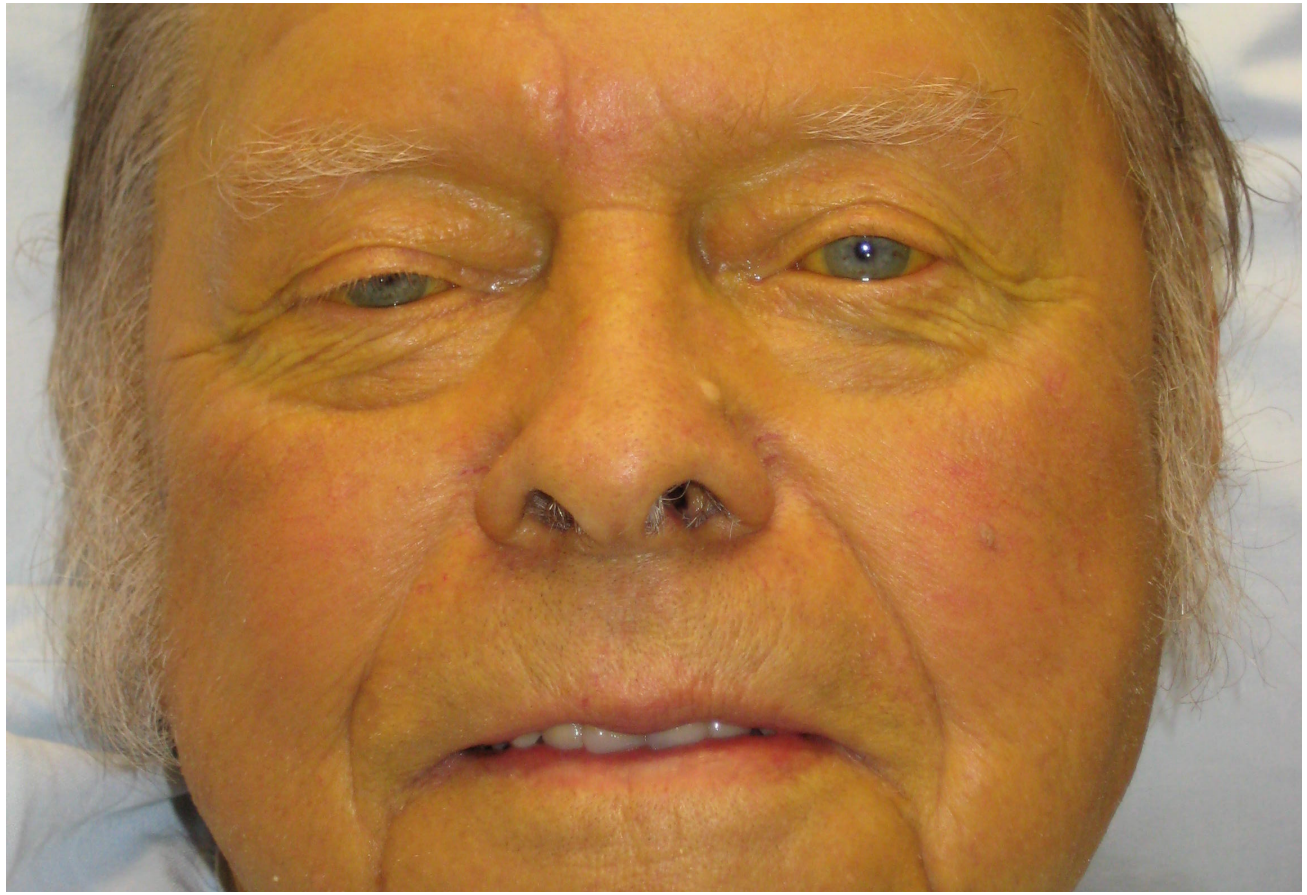
Jaundice

Yellowing of the skin due to buildup of billirubin, can usually be separated into:

Prehepatic: Increase in RBC haemolysis

Hepatic: Damage of parenchymal liver cells

Posthepatic: Obstruction / decreased bilirubin excretion



Gallstones (biliary calculi)

Occurs due to:
- Too much absorption of water from bile
- Too much absorption of bile acids from bile
- Too much cholesterol in bile
- Inflammation of the epithelium

- If lodges in ampulla of vater, can cause acute pancreatitis

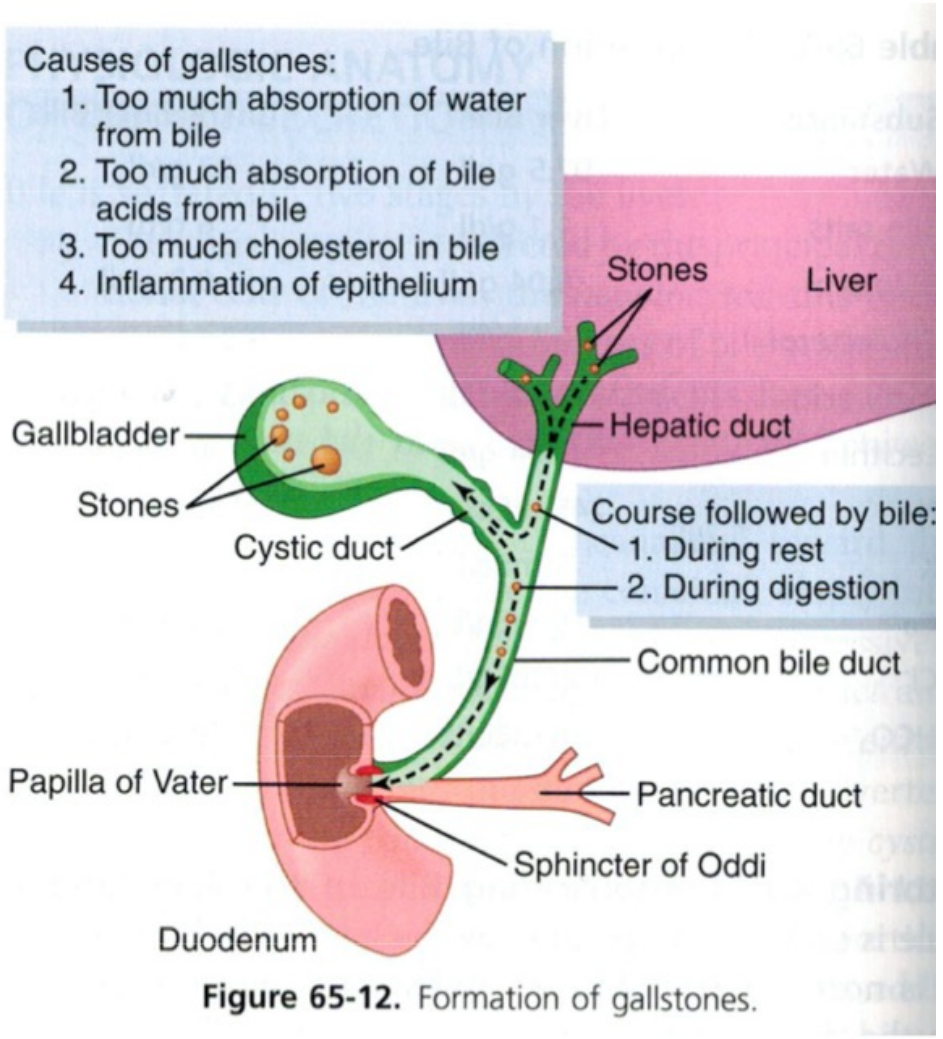


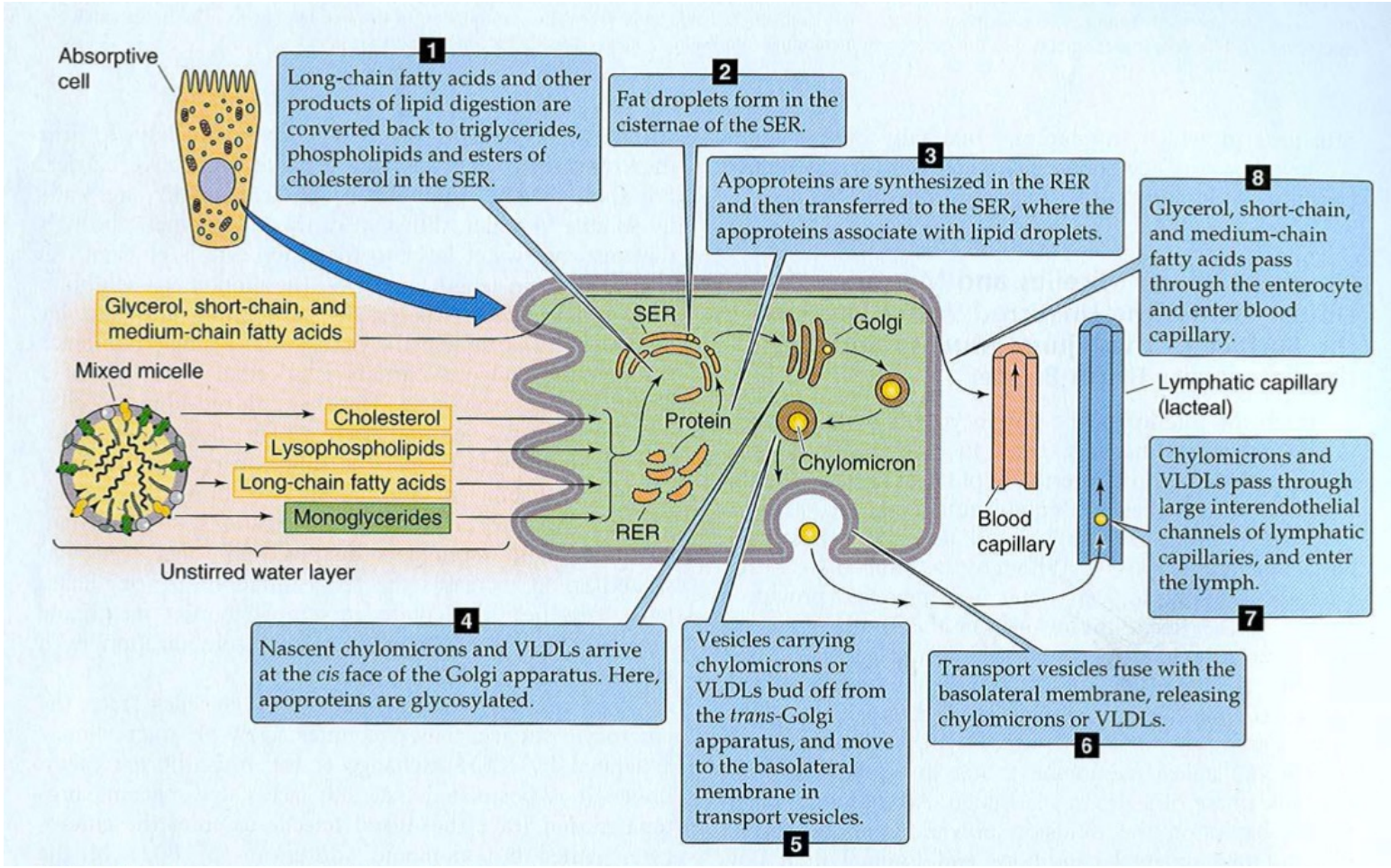
Figure 65-12. Formation of gallstones.

Intestinal handing of lipids

- Glycerol & short chain fatty acids can move through the intestinal membrane and directly into blood capillaries due to their small size

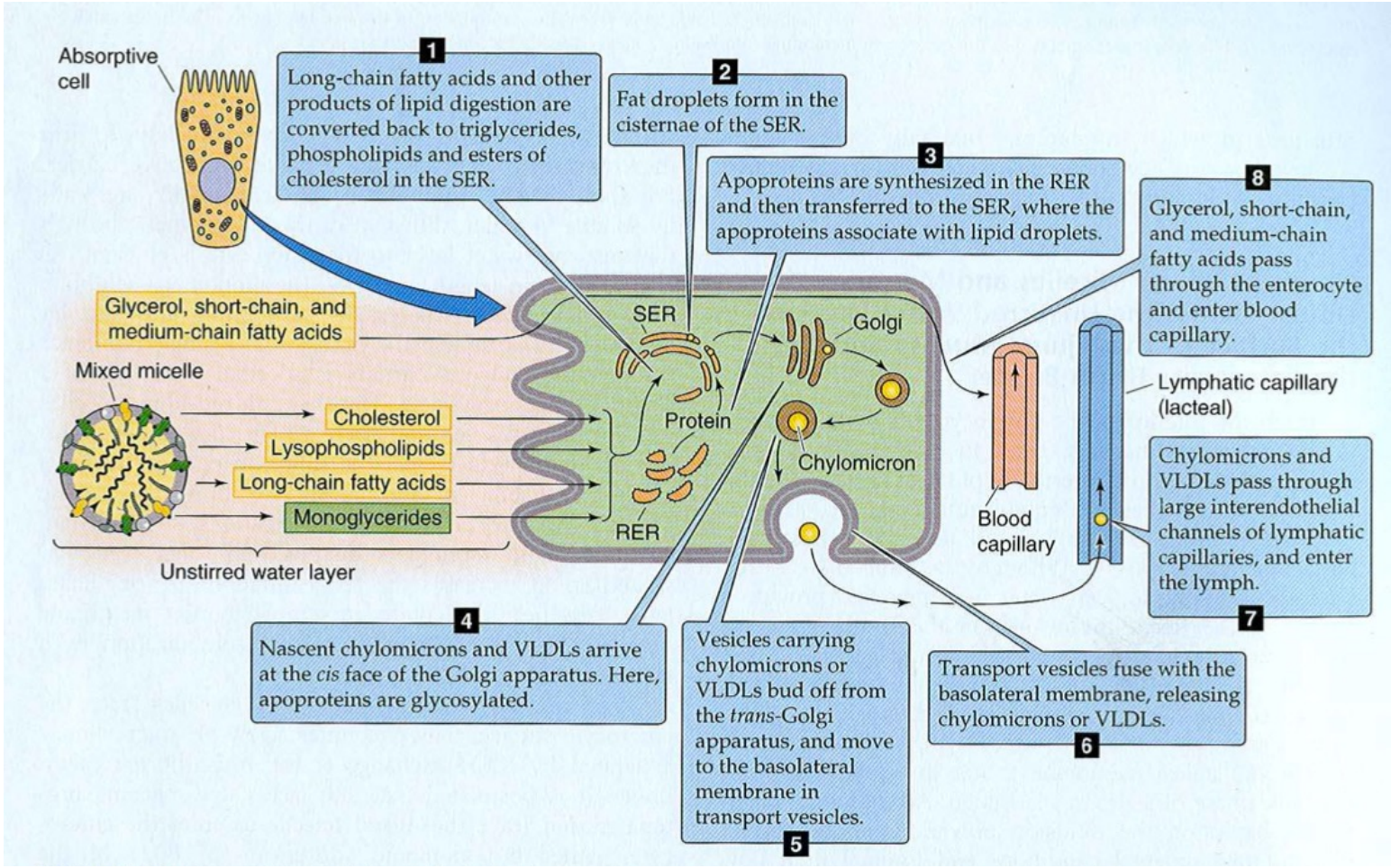
Intestinal handing of lipids

- Cholesterol, long chain fatty acids and lysophospholids cannot undergo the same process



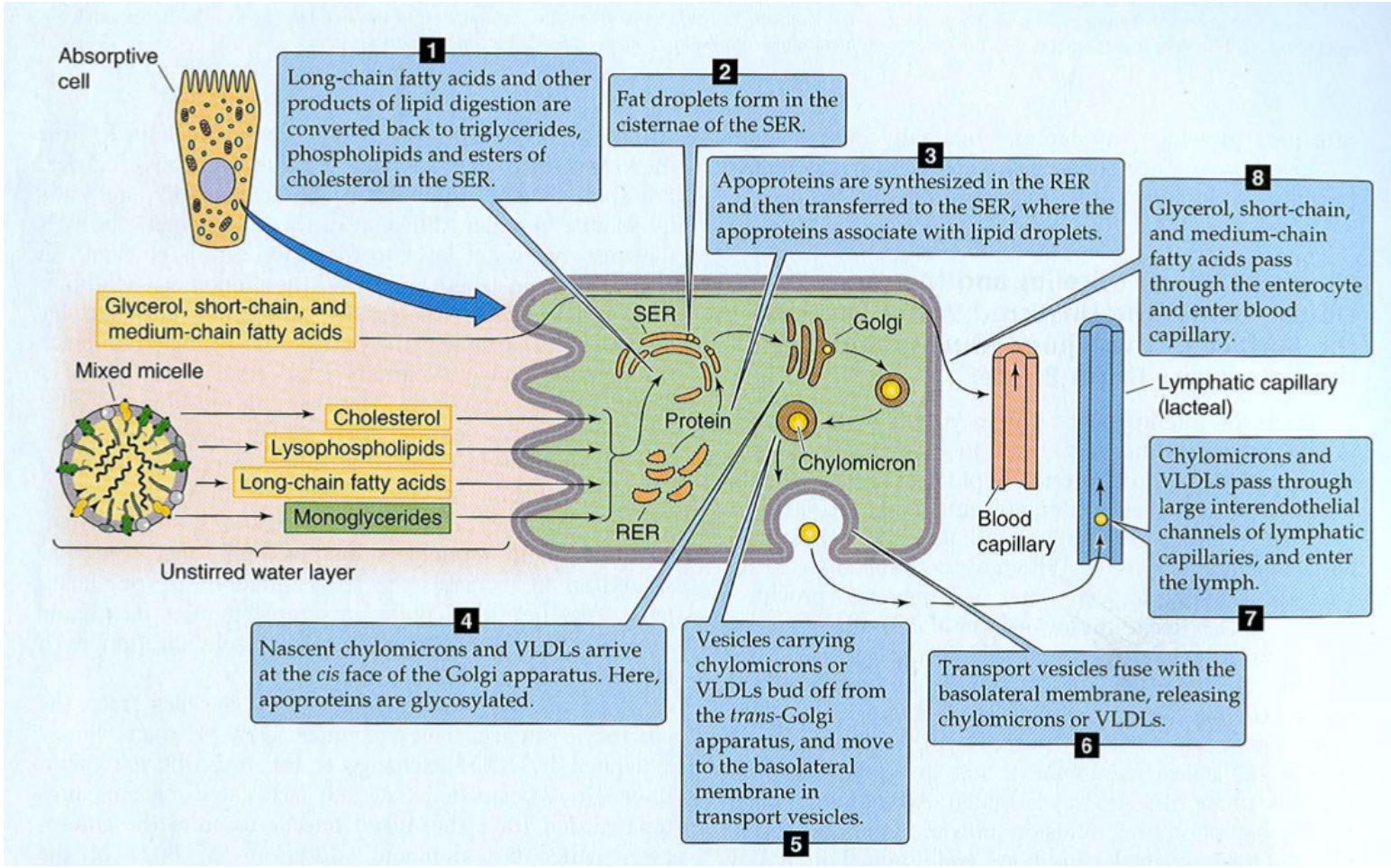
Intestinal handing of lipids

- Bile salts form a ring around these molecules and allow the molecules to move close to the microvilli
- When they get close, the pH becomes acidic and the micelles open up allowing the long chain substances to enter the cell via diffusion



Intestinal handing of lipids

- In the cell they are packages into chylomicrons
- These then fuse w/ the basolateral membrane releasing the chylomicrons
- They then enter the lactile vessels which form the lymphatics that drain into the thoracic duct



MCQ

How is glucose primarily absorbed across the brush-border of the intestine into the circulation?

A) In chylomicrons

B) In micelles

C) Via GLUT 4

D) Via SGLT

E) Via PEPT1

MCQ

Which cells in the GI tract synthesise and release cholecystokinin?

A) Acinar cells

B) Enterochromaffin-like cells

C) I cells in the duodenum and jejunum

D) S cells in the duodenum and jejunum

E) Striated ductal cells

MCQ

What do salivary gland acinar cells secrete?

A) Chymotrypsinogen

B) Fluid isotonic to plasma

C) Proteolytic enzymes

D) Secretin

E) Vasoactive intestinal polypeptide

PGRS Guide:

Renal Physiology

Pt 1: Objectives

- Define the key functions and anatomy of the kidney/nephron.
- Understand the nature of the glomerular filter and the dynamics of ultrafiltration.
- Describe the processes of tubular reabsorption of glucose and amino acids.
- Describe the processes of tubular secretion of organic acids and bases.

What are the functions of the kidneys?

- Excretion
- Volume regulation
- Osmoregulation
- pH regulation
- Endocrine functions

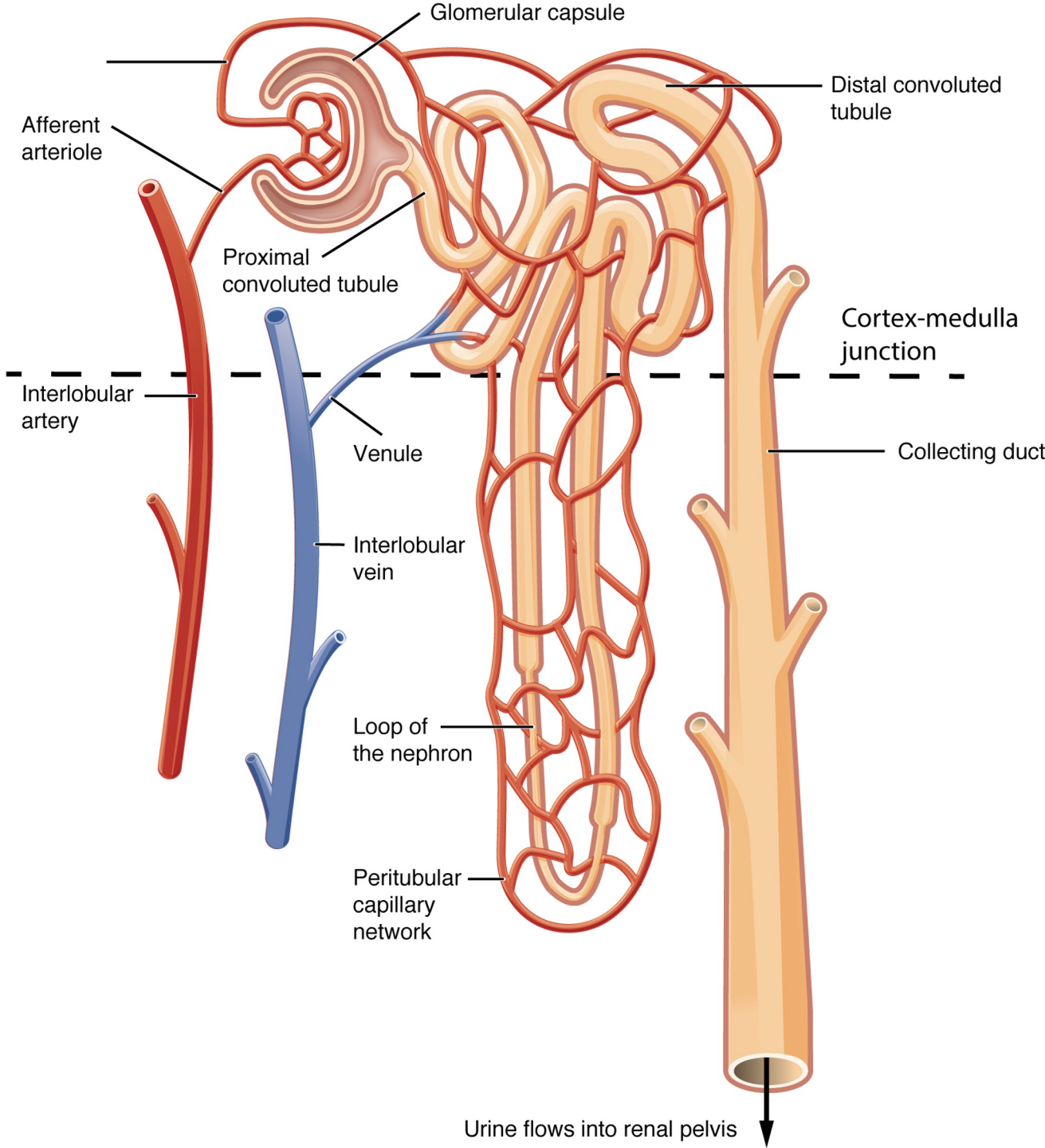
Hormones produced by the kidney:

- Renin
  - This is a protein released by the juxtaglomerular apparatus; it results in the formation of angiotensin II. Angiotensin II acts directly on the proximal tubules and via aldosterone on the distal tubules to promote sodium retention and is also a potent vasoconstrictor.
- Vitamin D3 (calcitriol)
  - Promotes absorption of calcium and phosphorus
- Erythropoietin (EPO)
  - Promotes RBC formation in bone marrow
- Prostaglandins
  - Various effects, especially on renal vessel tone (NSAID)

Hormones that act on the kidney:

- ADH
  - Peptide released by the posterior pituitary & promotes water reabsorption in collecting duct
- Aldosterone
  - This is a steroid hormone produced by the adrenal cortex; it promotes sodium reabsorption in the collecting ducts
- Natriuretic peptides (BNP/ANP)
  - These are produced by cardiac cells and promote sodium excretion in the collecting ducts.
- Parathyroid hormone
  - This is a protein produced by the parathyroid gland; it promotes renal phosphate excretion, calcium reabsorption and vitamin D production
  - Phosphate trashing hormone
- FGF23
  - This is produced by bone osteocytes and promotes renal phosphate excretion and inhibits vitamin D production.

- What are the 2 types of nephrons?
  - Cortical (85%)
  - Juxtaglomerular (15%) -> concentrated urine, long loop of Henle



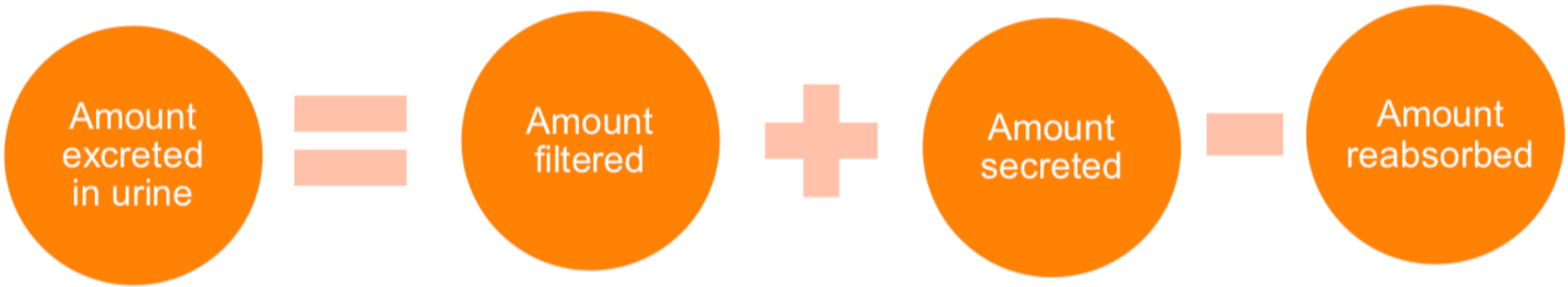
What are the 3 basic excretory processes?

- Glomerular filtration
- Tubular reabsorption
- Tubular secretion

Glomerular filtration: the movement of fluid and solutes from glomerular capillaries into Bowman's space, 20% of plasma that enters glomerulus is filtered and enters the Bowman's space.

Tubular secretion: the secretion of solutes from the peritubular capillaries into the tubules

Tubular reabsorption: the movement of materials from the filtrate in the tubules into the peritubular capillaries


Amount excreted in urine
=
Amount filtered
+
Amount secreted
-
Amount reabsorbed

- What substance is filtered and secreted but not reabsorbed?
  - PAH [para-aminohippuric acid] [used in medical tests]
- What substance is filtered and some of it is reabsorbed?
  - Water and most electrolytes
- What substance is filtered, completely reabsorbed and not secreted?
  - Glucose
- What substance is freely filtered, not reabsorbed or secreted?
  - Inulin -> not practical so we use creatinine to measure GFR
  - Creatinine is slightly secreted

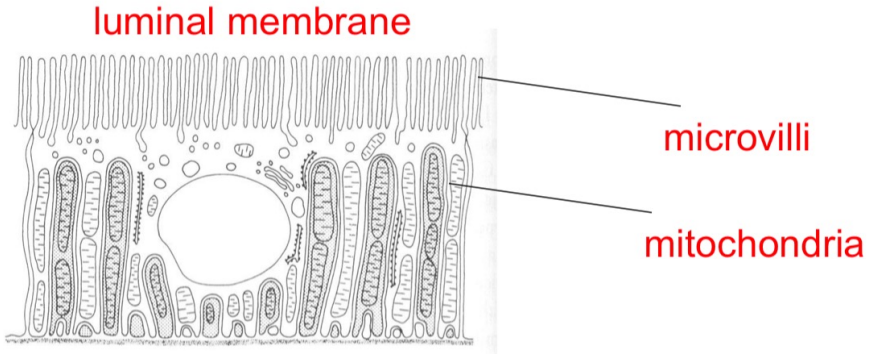
Renal Corpuscle

= Bowman’s capsule + glomerulus

- What are the 3 layers of the filtration barrier?
  - Endothelial cells of glomerular capillaries
  - Glomerular basement membrane
  - Epithelial cells of Bowman’s Capsule (podocytes)

- What is glomerular filtration rate (GFR)?
  - Volume of fluid filtered from the glomeruli per minute (ml/min) -> 125-180ml/min
  - Net filtration pressure
  - Permeability of capsular membranes
  - Surface area available for filtration

Reabsorption

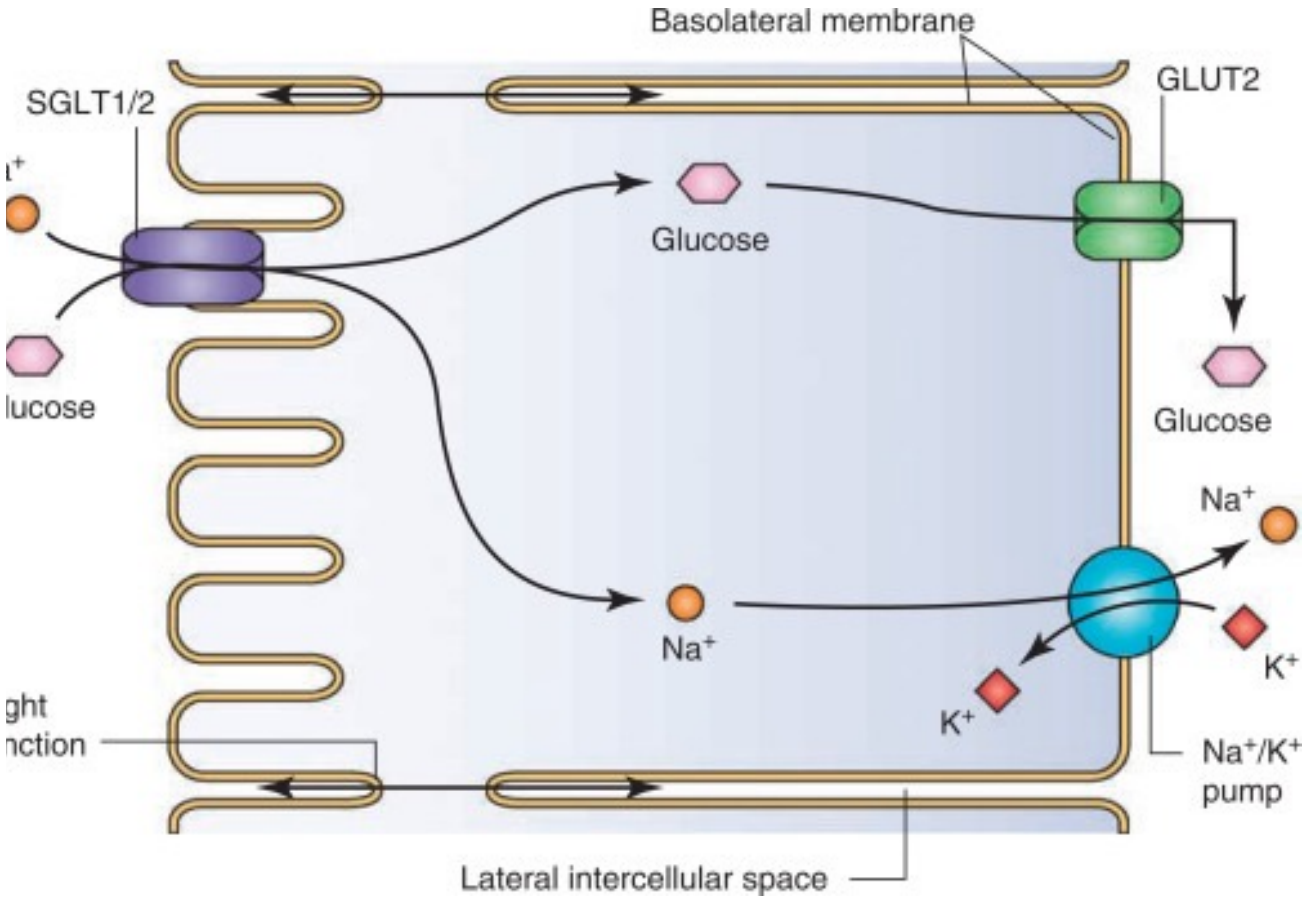


- PCT adaptations
  - Increased number of microvilli and mitochondria

- **REMEMBER luminal membrane faces lumen i.e., PCT and basolateral membrane faces outside i.e., peritubular capillaries**

Reabsorption

- Glucose:
  - Freely filtered
  - SGLT -> luminal membrane
  - GLUT (facilitated diffusion) -> basolateral membrane
  - Na+/K+/ATPase -> basolateral membrane



Reabsorption

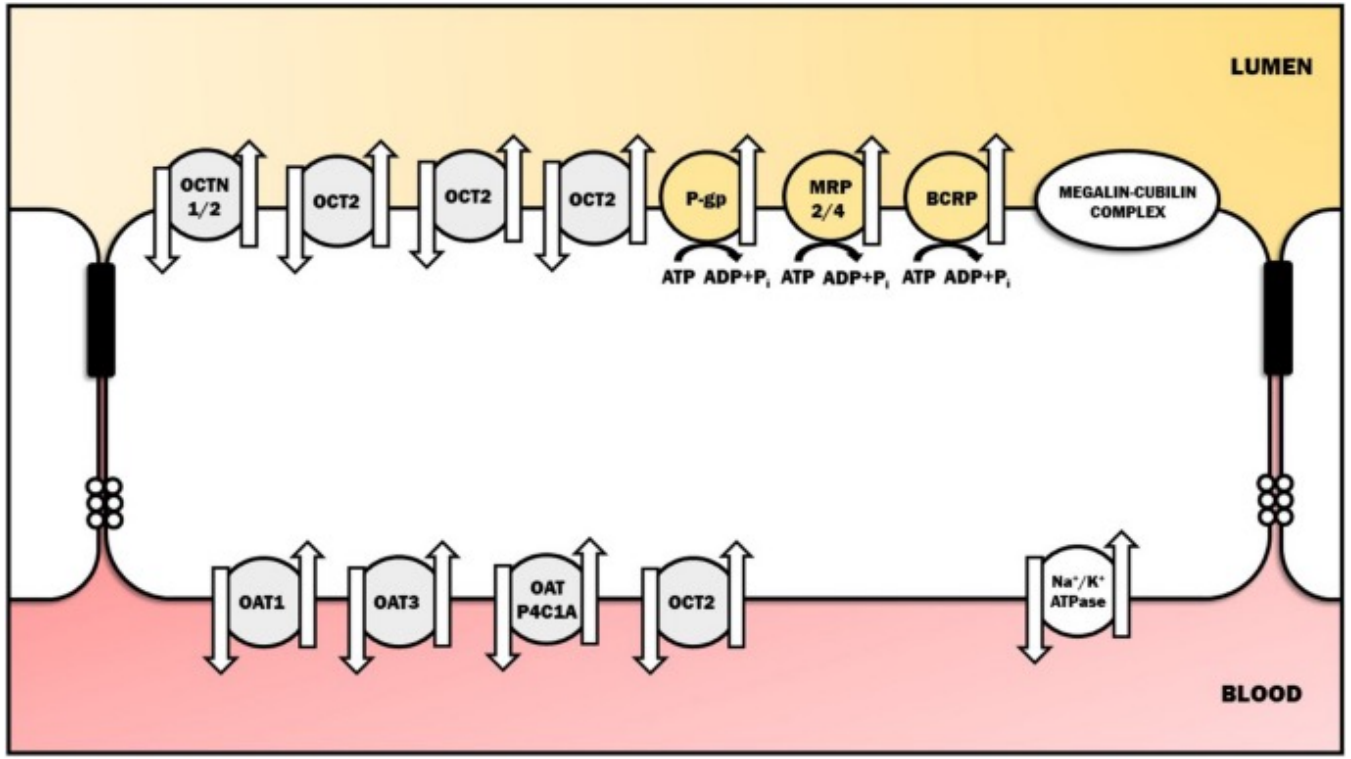
- Amino Acids:
  - At least 8 amino acid transporters, 6 are Na dependent
  - Overlapping amino acid specificity
  - Vast majority of filtered protein reabsorbed in PCT by endocytosis and degraded to amino acids

- Na coupled transporters for:
  - Glucose, amino acids, phosphate, sulphate

- Passive reabsorption:
  - Urea, chloride, potassium, calcium

Tubular Secretion

- Peritubular capillaries -> tubular lumen (2 stage process)
- Basolateral + luminal membrane transporters
- Transporters are broadly selective – organic anions or cations



Tubular Secretion

- **Organic acids (anions)**
- Endogenous molecules (bile salts, fatty acids, prostaglandins)
- Drugs (furosemide, penicillin and acetazolamide)
- Diagnostic agent (PAH)
- **Organic bases (cations)**
- Endogenous molecules (choline, creatinine, dopamine, guanidine, histamine, serotonin)
- Drugs (atropine, cimetidine, morphine)

MCQ

The renal corpuscles:

A. Are located in the renal medulla

B. Are the site of specialised epithelial cells called podocytes

C. Do not filter the exogenous polysaccharide, inulin

D. Include the proximal convoluted tubule

E. Process protein bound molecules and allow them to freely enter the ultrafiltrate

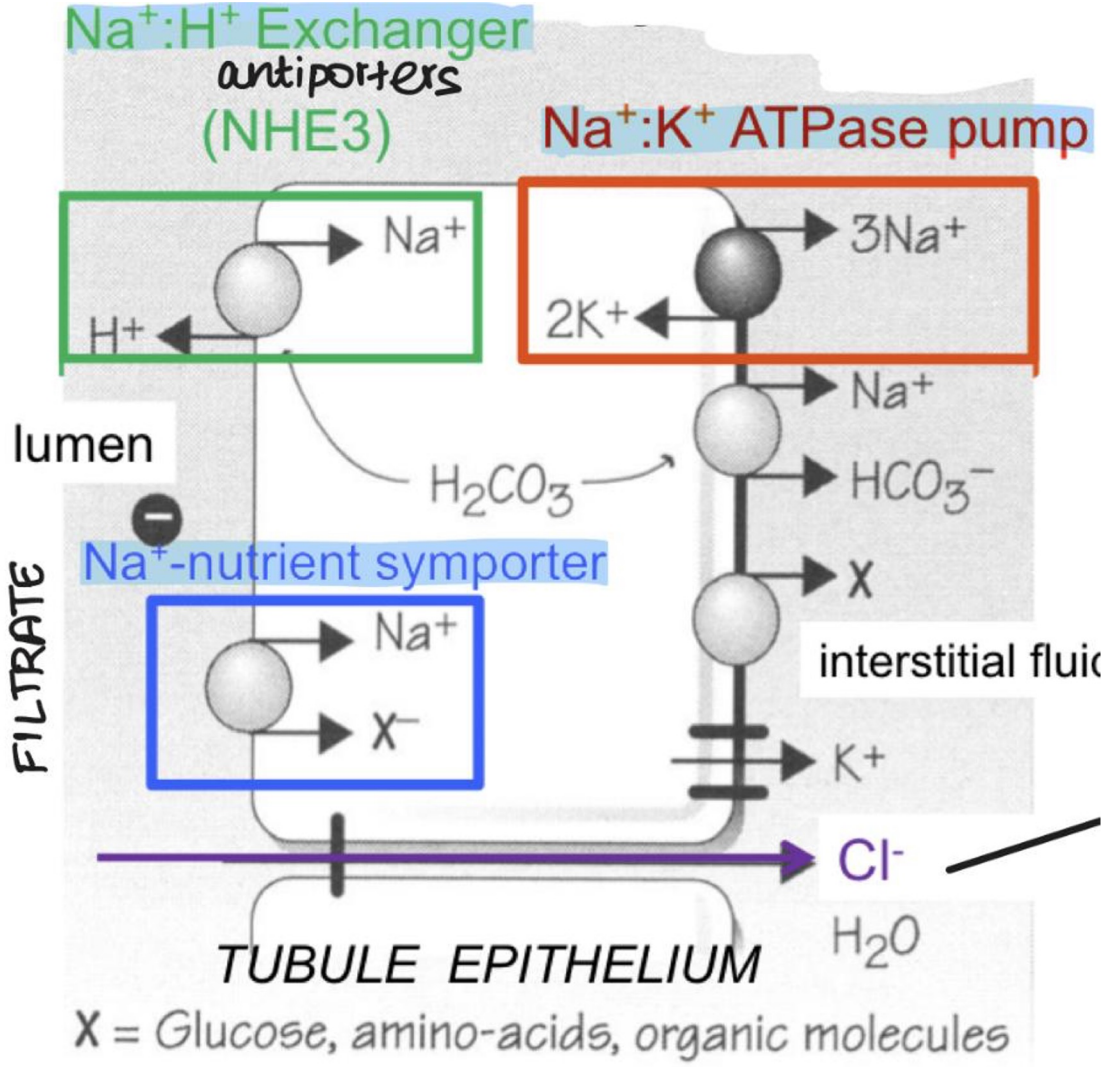
Pt 2: Objectives

- Define clearance and its use in the study of renal physiology.
- Explain how GFR and effective renal plasma flow are measured.
- Define osmolality and its importance to renal function.
- Describe the processes of salt and water reabsorption throughout the nephron.
- Describe the mechanisms of production of concentrated urine.
- Describe the counter-current mechanism.
- Describe the recycling of urea.
- Explain the role of ADH at the collecting duct.

Definitions

- What is clearance?
  - Volume of plasma that is cleared of a substance per unit time
  - Renal clearance = concentration in urine x volume in urine / concentration in plasma
- Clearance of PAH is a measure of effective renal plasma flow
- Normal renal plasma flow ~1100ml/min (>20% of cardiac output)
- What is osmolality?
  - A measure of water concentration, independent of temperature.
- What is the main osmotically active solute in plasma?
  - Sodium

Sodium Reabsorption – PCT [65%]



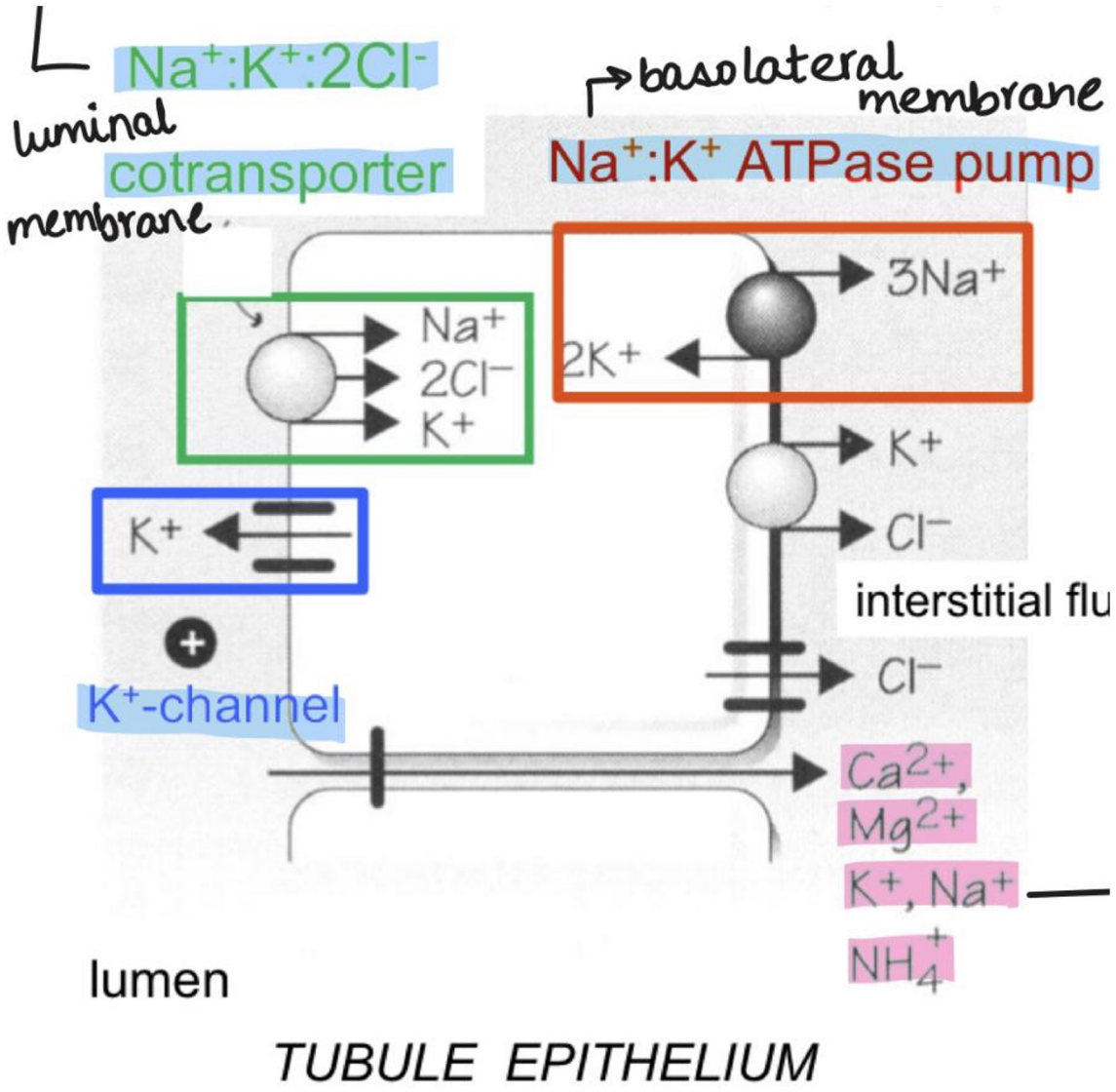
Water:

- AQP-1 channels
- Transcellular movement

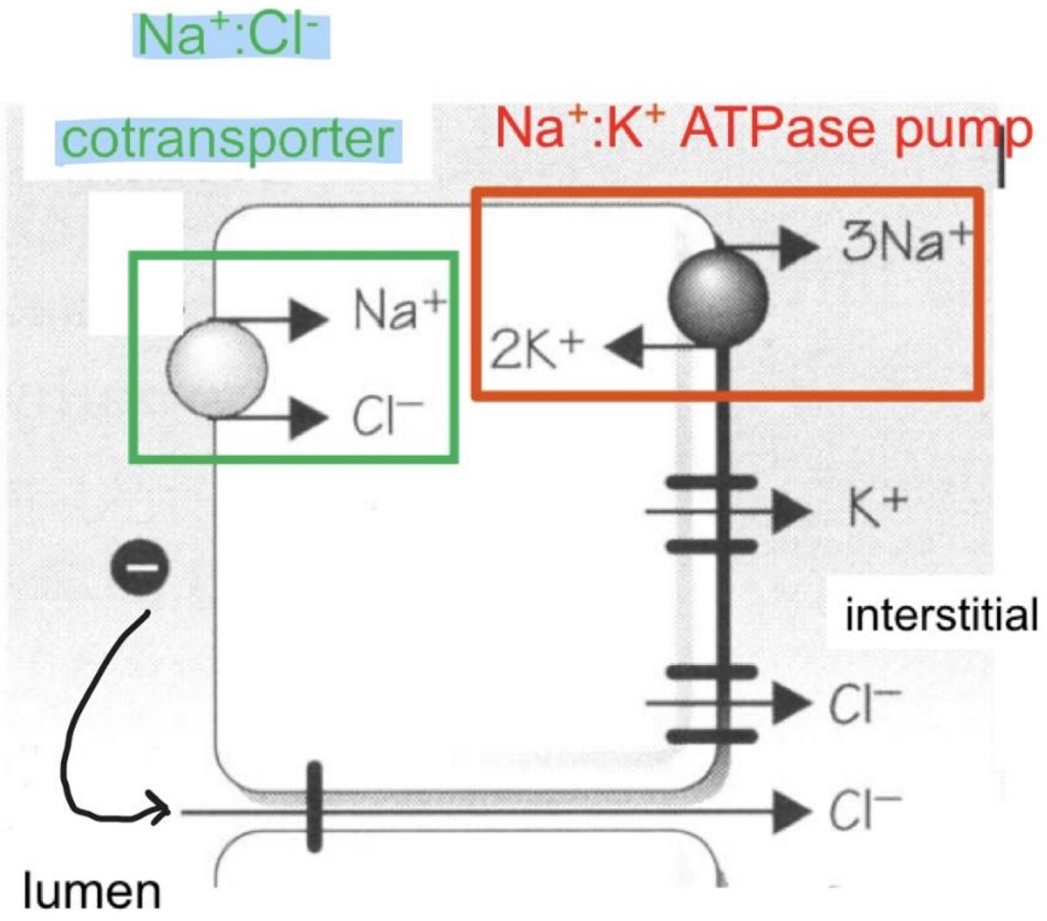
Sodium Reabsorption – Thick Ascending Limb [25%]

No H2O reabsorption in the thick ascending limb

No AQP channels



Sodium Reabsorption – DCT [2-5%]

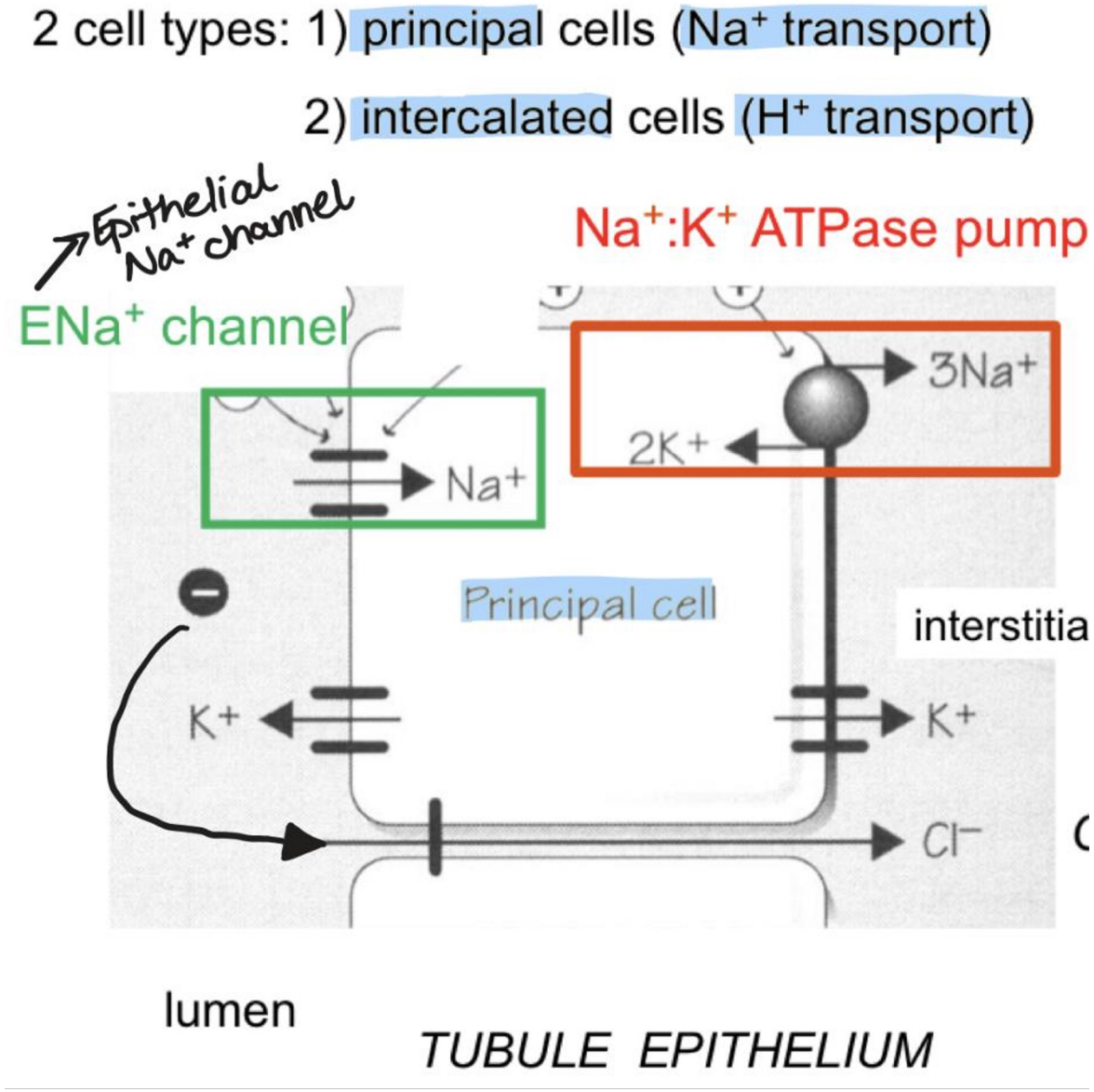


TUBULE EPITHELIUM

Sodium Reabsorption – Collecting Duct [5%]

Principal cells -> AQP2 channels

Respond to ADH



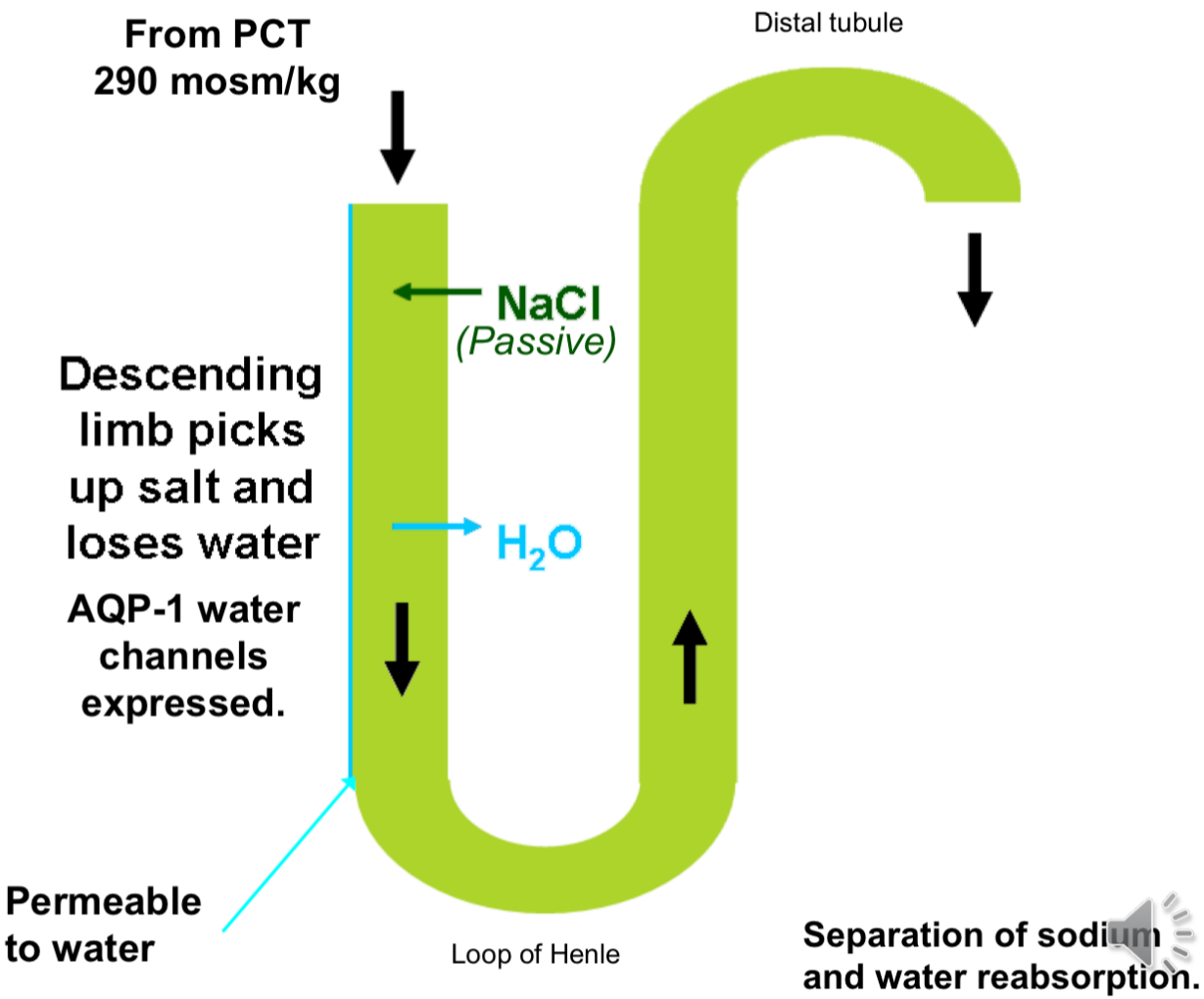
Production of concentrated urine

Concentrated urine > 300mosm/kg

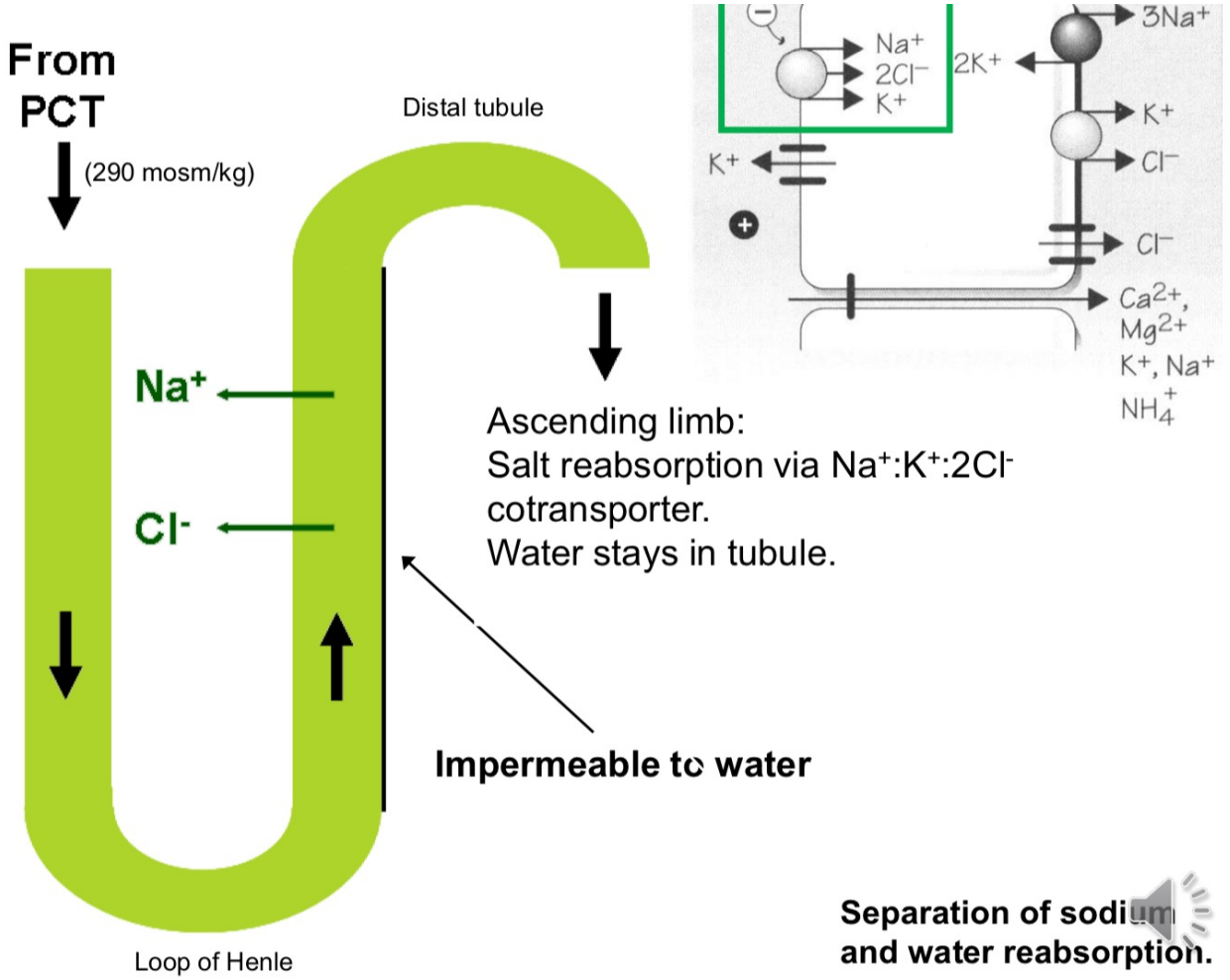
Two key factors which contribute:

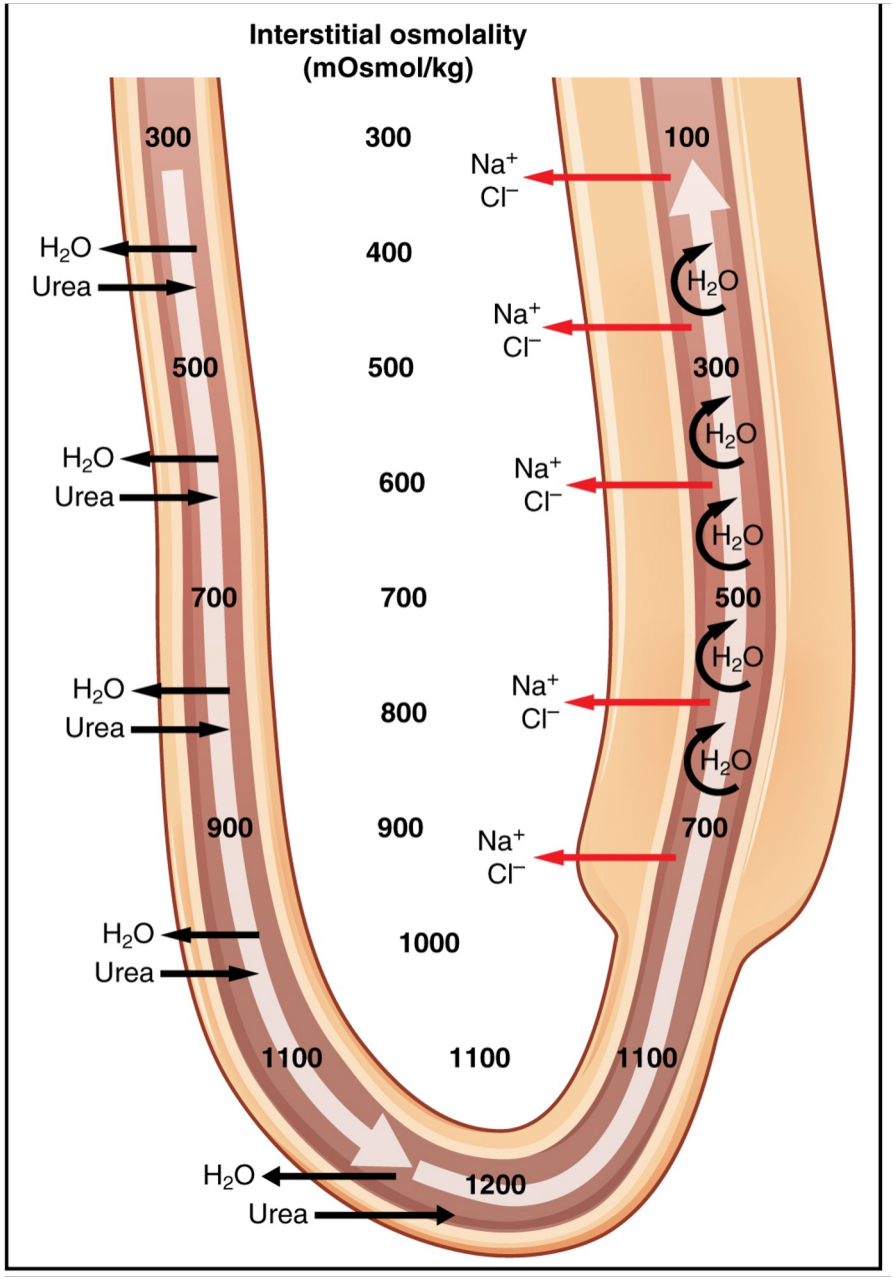
1. Separating Na+ and water reabsorption
2. Creating a renal medulla interstitial fluid with high osmolarity to drive water reabsorption

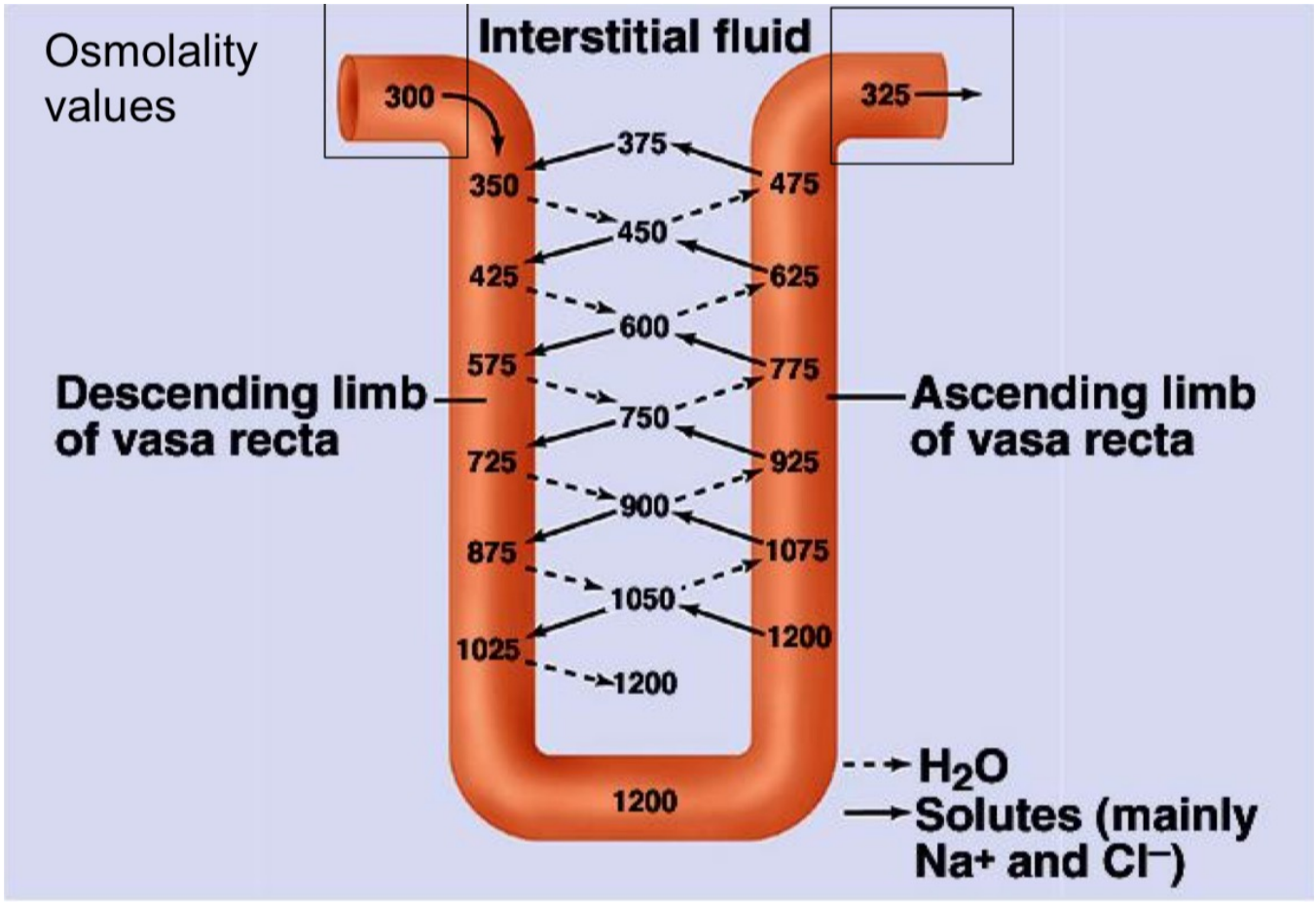
Descending loop of Henle



Thick ascending limb







Vasa recta supplies blood without washing the gradient away

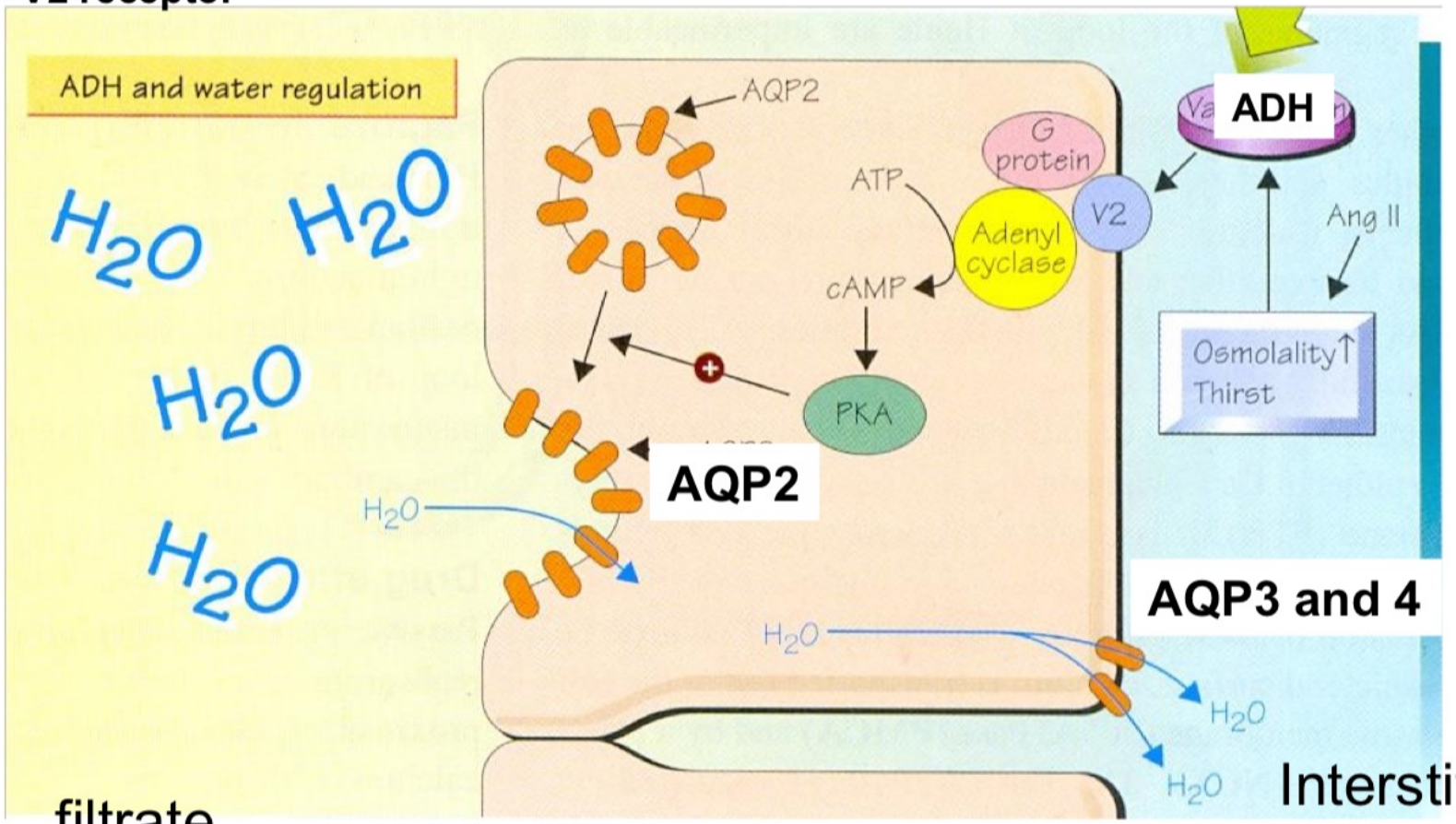
Urea Recycling

- PCT: 50% of initial ultrafiltrate concentration is reabsorbed
- Loop of Henle: 60% secreted via urea transporters (UT) [ie enters loop of henle]
- Inner medullary collecting duct: 70% reabsorbed (UTA1/UTA3) [ie leaves urine]
- Ultimately, 40% excreted

- Why?
  - Recycling contributes to high osmolality in the medulla

ADH

= water channel
= V2 receptor



Questions

- What apical mechanism is responsible for developing the positive charge in the lumen of the thick ascending loop of Henle?
  a) K+ efflux via ROMK
  b) Na+ entry via ENaC
  c) Na+/K+ ATPase
  d) The excess concentration of Na+
  e) The Na+/K+/2Cl- symport (cotransporter)

Pt 3: Objectives

- Describe diuresis, polyuria and oliguria.
- Define water clearance and osmolar clearance.
- Describe the control of ADH secretion from the pituitary gland and its effects on the kidney.
- Describe diabetes insipidus and osmotic diuresis.
- Describe the renal handling of potassium.

Pt 3: Objectives cont.

- Describe the main fluid compartments of the body and factors that affect movement of water between them.
- Explain the relationship between osmolality and volume and their multiple regulatory pathways, sensors and effectors.
- Understand the role of the juxtaglomerular apparatus in renin release.
- Understand the roles of the renin-angiotensin-aldosterone and sympathetic nervous system and atrial stretch receptors in the regulation of ECF volume.

Osmolarity

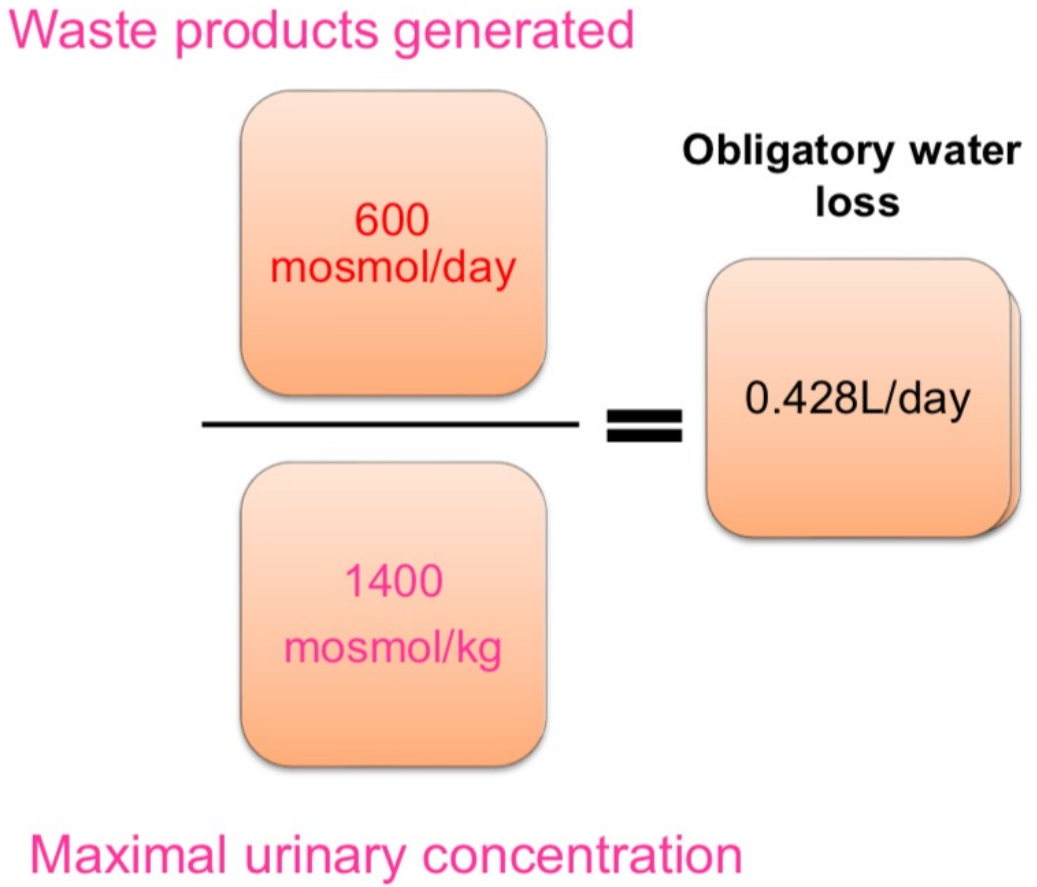
- Osmolality is the concentration of dissolved particles in the blood
- High osmolarity = v. concentrated

Usual plasma osmolarity = 275-295 mosmol/kg

How is osmolality maintained?

1) Urine formation
2) Thirst

Required to eliminate ~ 600mosmol of waste products per day



Output below this level is termed oliguria.

Normal urine output ~1/2L per day

Osmolar clearance (Cosm; ml/min): The clearance of all osmotically active particles can be calculated in a manner similar to the clearance of individual substances.

$$C_{Osm} = \frac{U_{Osm}\,\dot{V}}{P_{Osm}}, \text{ml/min}$$

V: urine flow rate (ml/min)
Uosm: urine osmolarity (mosm/ml)
Posm: plasma osmolarity (mosm/ml)

Free water clearance (CH2O): used to assess renal function

$$C_{H2O} = \dot{V} \quad (1 - \frac{U_{Osm}}{P_{Osm}})$$

V: urine flow rate (ml/min)
Uosm: urine osmolarity (mosm/ml)
Posm: plasma osmolarity (mosm/ml)

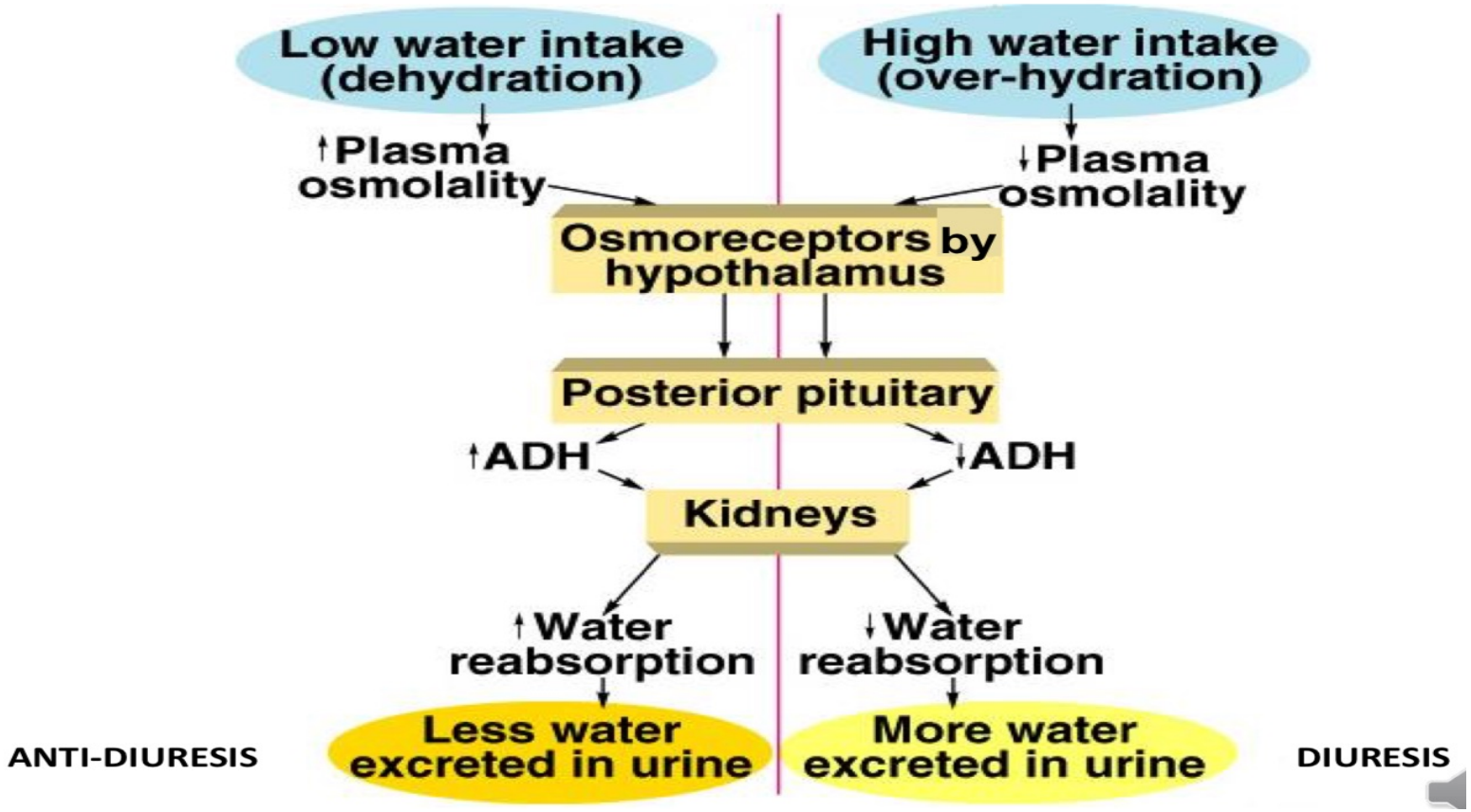
C_{H20} reflects the ability of the kidneys to excrete dilute or concentrated urine.

$C_{H20} > 0$ indicates a hypo-osmotic urine i.e. dilute urine.

$C_{H20} = 0$ indicates an iso-osmotic urine with respect to plasma.

$C_{H20} < 0$ indicates a hyper-osmotic urine i.e. concentrated urine.

Regulation of thirst



What is the juxtaglomerular apparatus?

Juxtaglomerular cells + macula densa + extraglomerular mesangial cells

Function = BP regulation

- Juxtaglomerular cells – manufacture, store and release **renin** into the blood
- Macula densa – in response to elevated Na, these cells trigger contraction of the afferent arteriole reducing blood flow to the glomerulus and reducing GFR

When is renin released?

- Reduced Na delivery to the DCT, detected by macula densa cells
- Reduced perfusion pressure in the kidney, detected by baroreceptors in the afferent arteriole
- Sympathetic stimulation of JGA via beta-1 adrenoreceptors

- INHIBITED by atrial natriuretic peptide (released by stretched atria in response to increased BP)

RAAS System

- Angiotensin -> Angiotensin I (via renin)
- Angiotensin I -> Angiotensin II (via ACE - lungs and renal endothelium)
- Angiotensin II -> AT1 and AT2 receptors (GPCRs)

Site	Main Action
Arterioles	Vasoconstriction
Kidney	Stimulates Na+ reabsorption
Sympathetic nervous system	Increased release of noradrenaline (NA)
Adrenal cortex	Stimulates release of aldosterone
Hypothalamus	Increases thirst sensation and stimulates anti-diuretic hormone (ADH) release

Increased TPR -> increase in BP

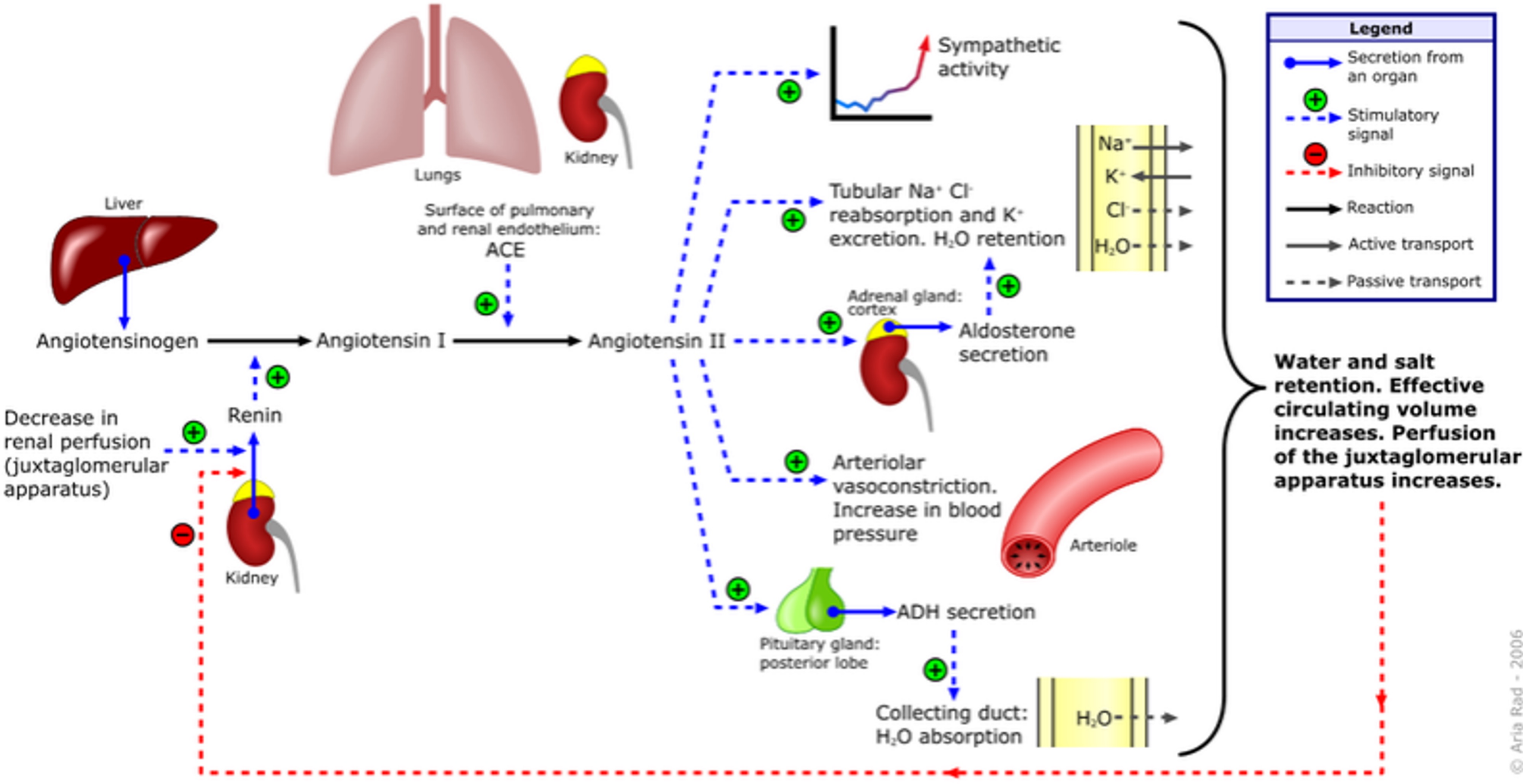
Increases cardiac output, vasoconstriction of arterioles and further release of renin.

Target	Action	Mechanism
Renal artery and afferent arteriole	Vasoconstriction	Voltage-gated calcium channels open and allow an influx of calcium ions
Efferent arteriole	Vasoconstriction (greater than the afferent arteriole)	Activation of AT1 receptor
Mesangial cells	Contraction, leading to a decreased filtration area	Activation of Gq receptors and opening of voltage-gated calcium channels
Proximal convoluted tubule	Increased Na+ reabsorption	Increased Na+/H+ antiporter activity and adjustment of the Starling forces in peritubular capillaries to increase paracellular reabsorption

Aldosterone

- Released by zona glomerulosa in response to angiotensin II
- Acts on principal cells -> increases expression of ENaC
- Increased activity of Na/K/ATPase
  - More Na reabsorbed
  - More K excreted
- Increased levels of aldosterone can cause hypokalaemia

Renin-angiotensin-aldosterone system



Diabetes Insipidus

- **Characteristics:**

1) urination (polyuria ie urine >2l/day),
2) Polydipsia
3) Nocturia

Types:

1. **Neurogenic** (no ADH secreted)
   - congenital
   - trauma e.g., head injury or brain tumour
2. **Nephrogenic** (ADH present, but kidneys do not respond to it)
   - inherited (mutated V2 receptor or aquaporin 2 channel)
   - acquired (infection or side effect of drug e.g., lithium)

(also Gestational and psychogenic)

Aldosterone

- Released by zona glomerulosa in response to angiotensin II
- Acts on principal cells -> increases expression of ENaC
- Increased activity of Na/K/ATPase
  - More Na reabsorbed
  - More K excreted
- Increased levels of aldosterone can cause hypokalaemia

Sodium in Urine

= sodium filtered – sodium reabsorbed

- Sodium filtration depends on
  - GFR
  - Neural control
  - Hormonal control
  - Intrinsic control
- A reduction in GFR -> Na and H2O retention -> BP rises
- Reabsorption of Na depends on regulation via:
  - Sensors
  - Effector pathways

Potassium

Maintenance of K+ involves three elements:

1. Renal excretion
2. GI losses
3. Cellular shifts

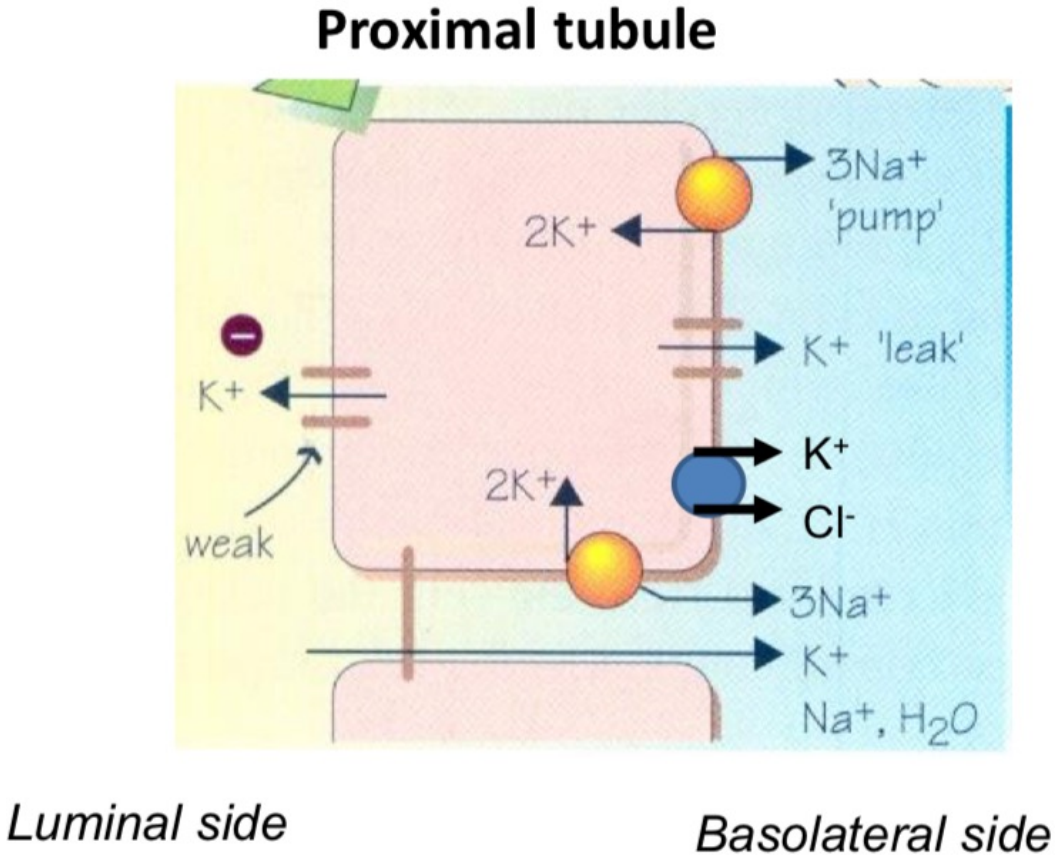
Potassium

Renal excretion of potassium: involves filtration, reabsorption and secretion

Filtration: kidney filters ~800mmoles/day

Reabsorption: ~95% of this is reabsorbed, ~65% reabsorbed passively at proximal tubule

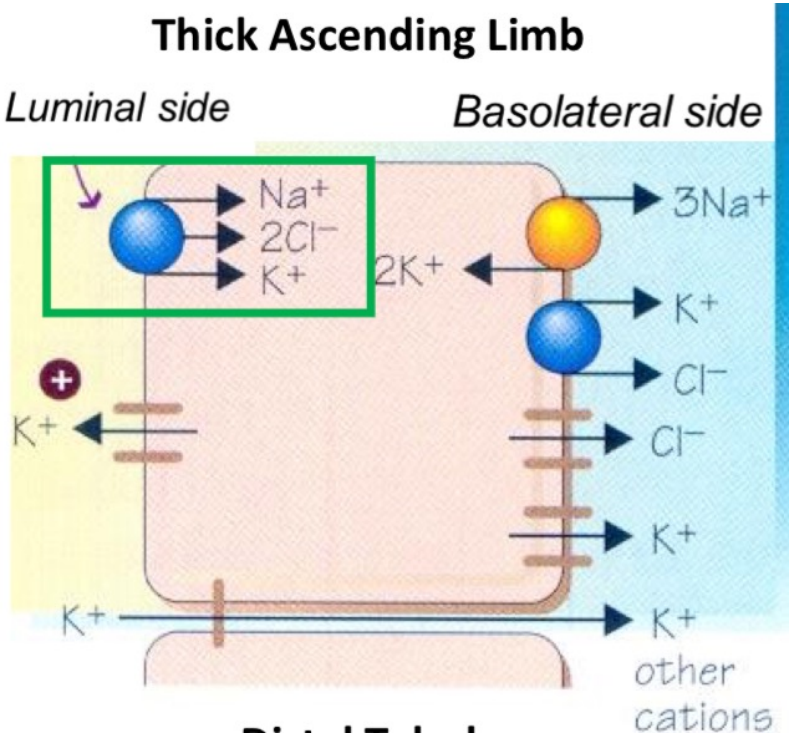
Potassium: PCT (~65% Passively reabsorbed)



Potassium: Thick ascending limb

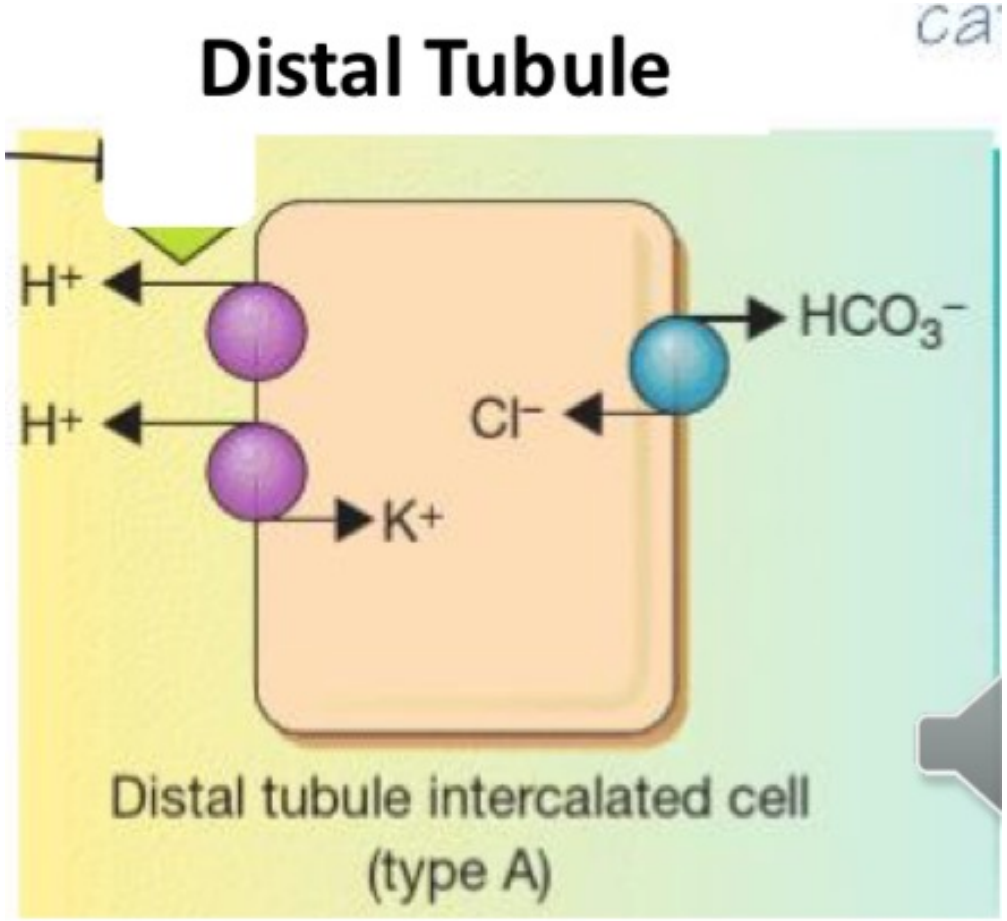
~30% of this is reabsorbed at thick ascending limb

Na+:K+:2Cl- cotransporter (NKCC2 transporter)



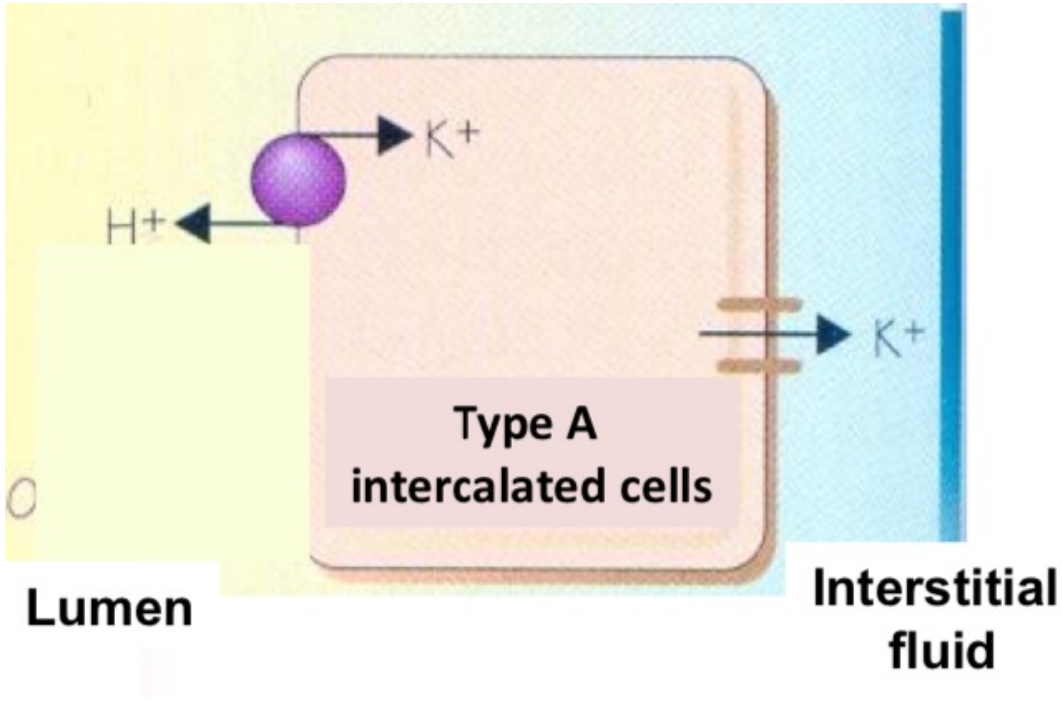
Potassium: DCT

5% is reabsorbed in the distal tubule via K+H+ exchanger



Potassium: Collecting duct

K+ is absorbed by intercalated cells and distal cells (in exchange for H+)



Potassium: Collecting duct cont.

But outweighed by:

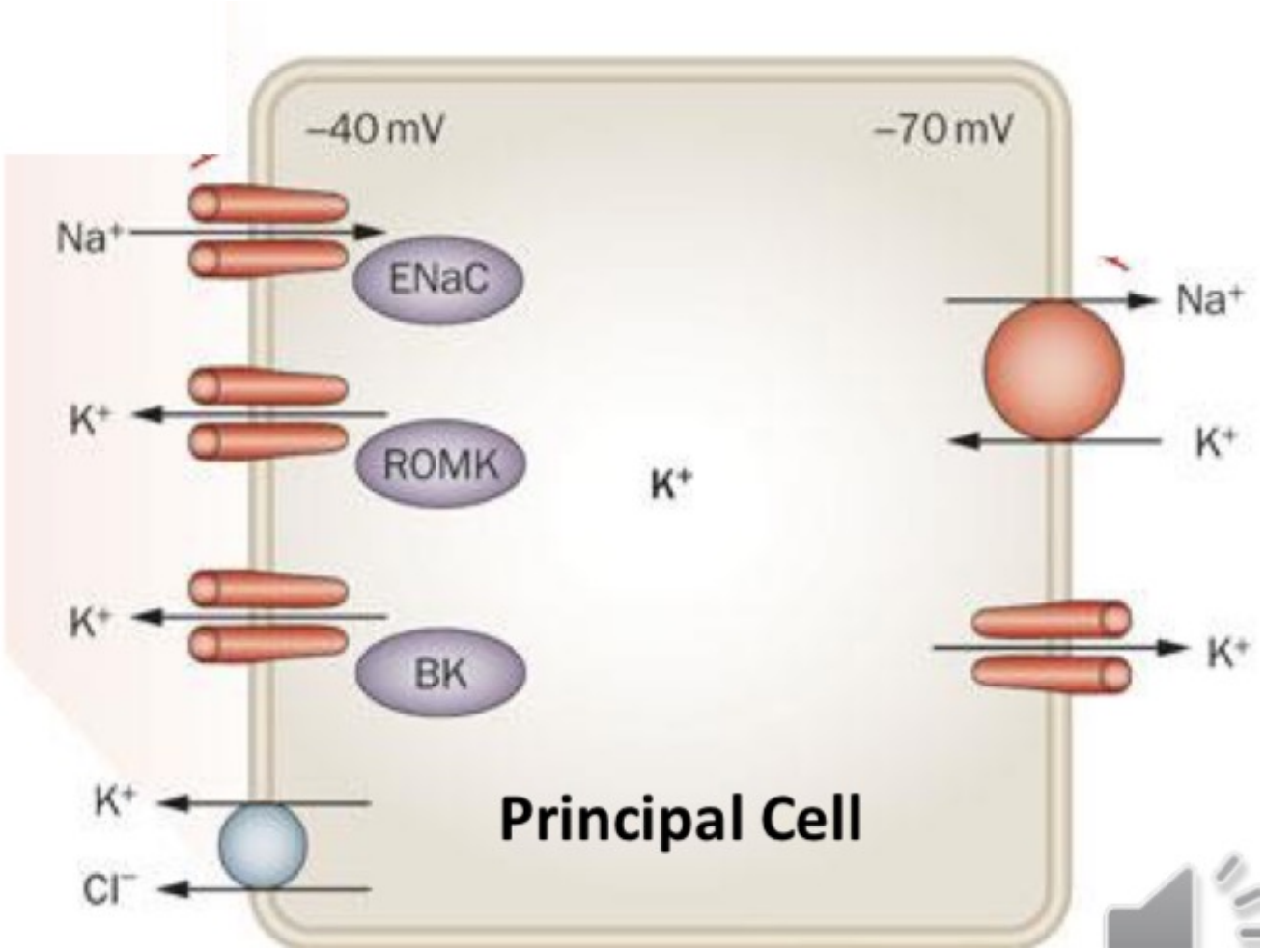
- K+ secretion by principal cells

1) K+ channels

- Renal outer medullary K+ channel; ROMK

- Ca2+ activated big-conductance K+ channel; BK

2) K+:Cl- cotransporter



Potassium: Collecting duct cont.

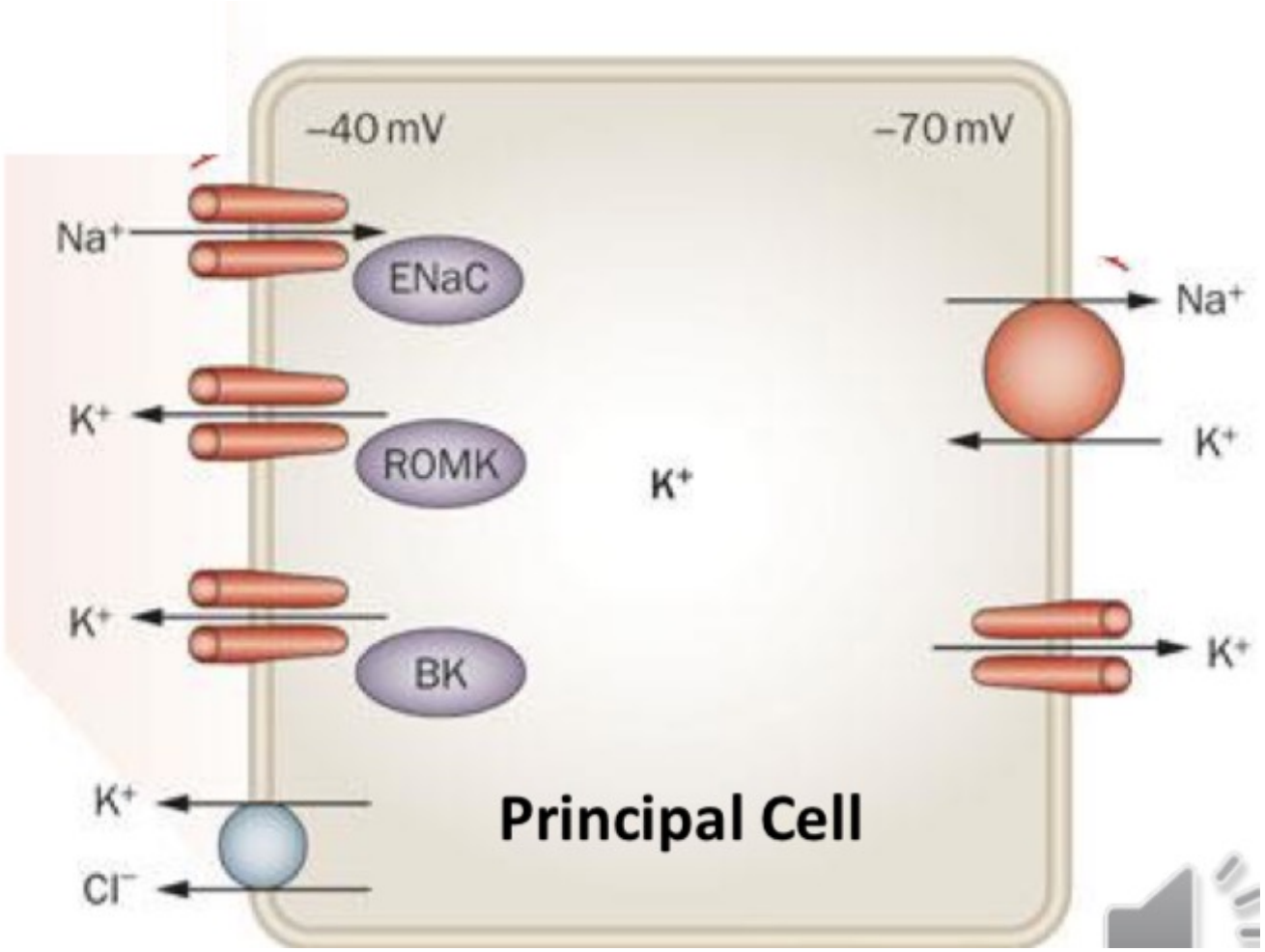
Factors affecting K+ secretion by principal cells (collecting duct)

1. Factors affecting Na+ entry through epithelial Na+ channels (ENaC).

2. Aldosterone stimulates K+ channels.

3. Tubular flow rate. High flow rates favor secretion.

4. Acid-base balance. Acidosis inhibits it and alkalosis enhances it.



Hypokalemia

Caused by:
a) Increased external losses of potassium.
- kidney e.g., diuretics, osmotic diuresis, transporter mutations (e.g., ENaC), hyperaldosteronism, alkalosis
- GI tract e.g., vomiting, diarrhoea
- skin e.g., burns, intense sweating
b) Redistribution of potassium into cells.
- metabolic alkalosis
- insulin excess
c) Inadequate potassium intake
- starvation and prolonged fasting

Organ System	Hypokalemia
Cardiac	• Dysrhythmias • Conduction defects • Increased likelihood of dysrhythmias due to digitalis
Skeletal muscle	• Weakness • Paralysis • Fasciculations and tetany
Gastrointestinal	• Ileus • Nausea • Vomiting • Abdominal distention
Renal	• Polyuria

Hyperkalemia

Caused by:
A) **Decreased external losses**
– Renal failure
– Hypoaldosteronism – Action of drugs

B) **Redistribution out of cells**
Tissue destruction/cell lysis e.g. rhabdomyolysis
Acidosis (exacerbated by lack of insulin in diabetic ketoacidosis)

Organ System	Hyperkalemia
Cardiac	• Dysrhythmias • Conduction disturbances
Skeletal muscle	• Weakness • Paresthesias • Paralysis • Hyperreflexia • Cramping
Gastrointestinal	• Nausea • Vomiting • Diarrhea

MCQ

- Which of the following defines Drug Clearance (Cl)?
  a) Amount of drug that is absorbed from the gut per unit time.
  b) Rate at which the drug is excreted from the body.
  c) Sum of all the enzymatic processes in the liver.
  d) Time taken for the plasma concentration to fall by half.
  e) Volume of plasma cleared of drug per unit time.

Pt 4: Objectives

Understand the importance of tightly regulating plasma pH.

- **Describe the generation of acid.**
- **Describe H + buffering in different compartments of the body.**
- **Describe the role of the lungs and kidneys in H + excretion.**
- **Describe the mechanisms of renal H + excretion, its relationship to bicarbonate reabsorption and ammonia excretion, and the regulation of these processes.**
- **Give some simple examples of acid-base disturbances and their correction.**

How do the kidneys alter blood pH?

Sources of H^+ gain:

1. Generation of H^+ from CO_2 ($CO_2 + H_2O = H_2CO_3 = HCO_3^- + H^+$)

- This doesn't significantly contribute to net gain of H+ ions, as it's a reversible reaction
- Hypoventilation = ↑ CO_2

2. Production of non-volatile acids from protein/organic molecule metabolism

- Acids (e.g. H_3PO_4 & H_2SO_4) are generated by breakdown of proteins, lactic acid, etc.
- **High protein** is largely responsible for generation of non-volatile acids
- Average net production of **40 - 80 mmol** / day of H^+
- H^+ from non-volatile acids are renally excreted – **not via the lungs**

3. Gain of H+ due to loss of bicarbonate via diarrhoea or other non-gastric GI fluids

How do the kidneys alter blood pH?

Sources of H^+ loss:

1. Hyperventilation

2. Use of H^+ in metabolising organic anions

- e.g. Organic anions & hydrogen ions → bicarbonate

3. Loss of H^+ via vomit

- (Vomit contains high [H^+], so results in a **net loss**

4. Loss of H+ in urine

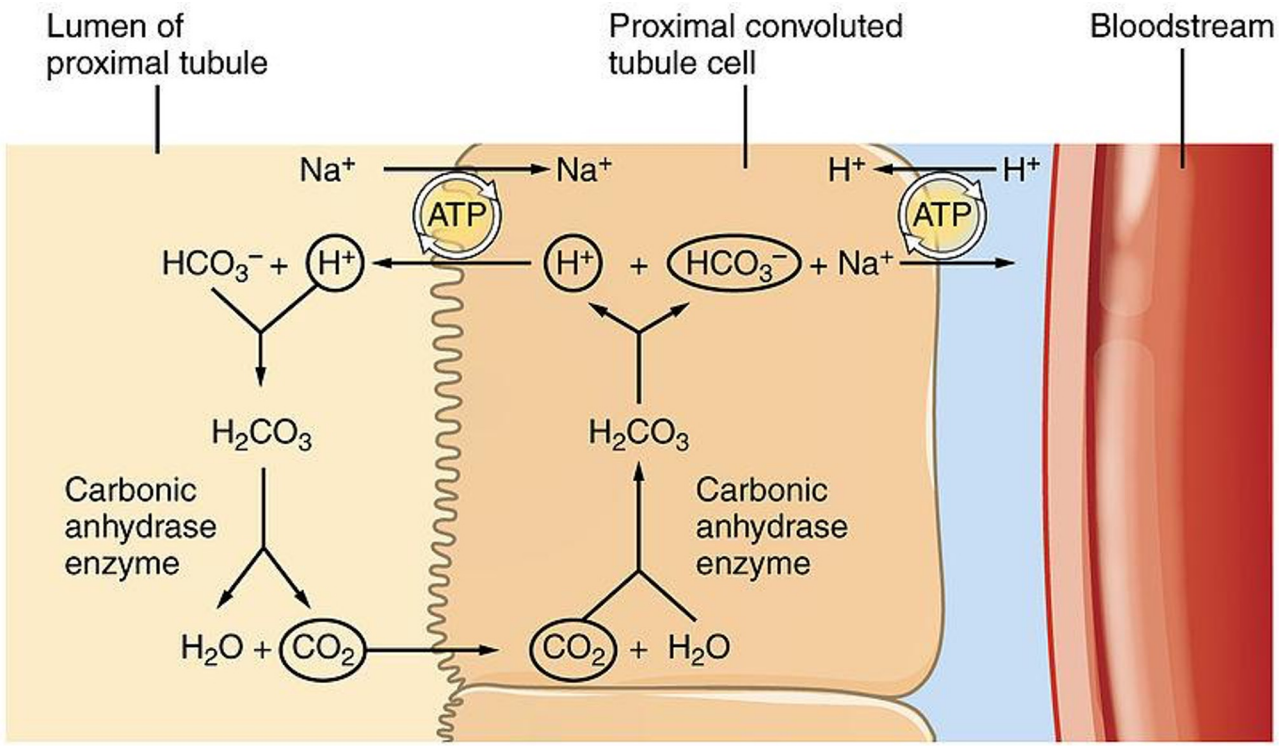
Bicarbonate Reabsorption

- Proximal tubule
- Ascending loop of Henle
- Cortical collecting ducts (specifically in α-intercalated cells)

Bicarbonate Reabsorption

1. H_2CO_3 dissociates → HCO_3^- + H^+ (in the tubular epithelial cells)
2. HCO_3^- leaves the cell → enters the peritubular capillary
   - H+ secreted into the filtrate

- Transport proteins involved:
  - H^+ / Na^+ ATPase pumps
  - H^+ / K^+ ATPase pumps
  - H^+ ATPase pumps



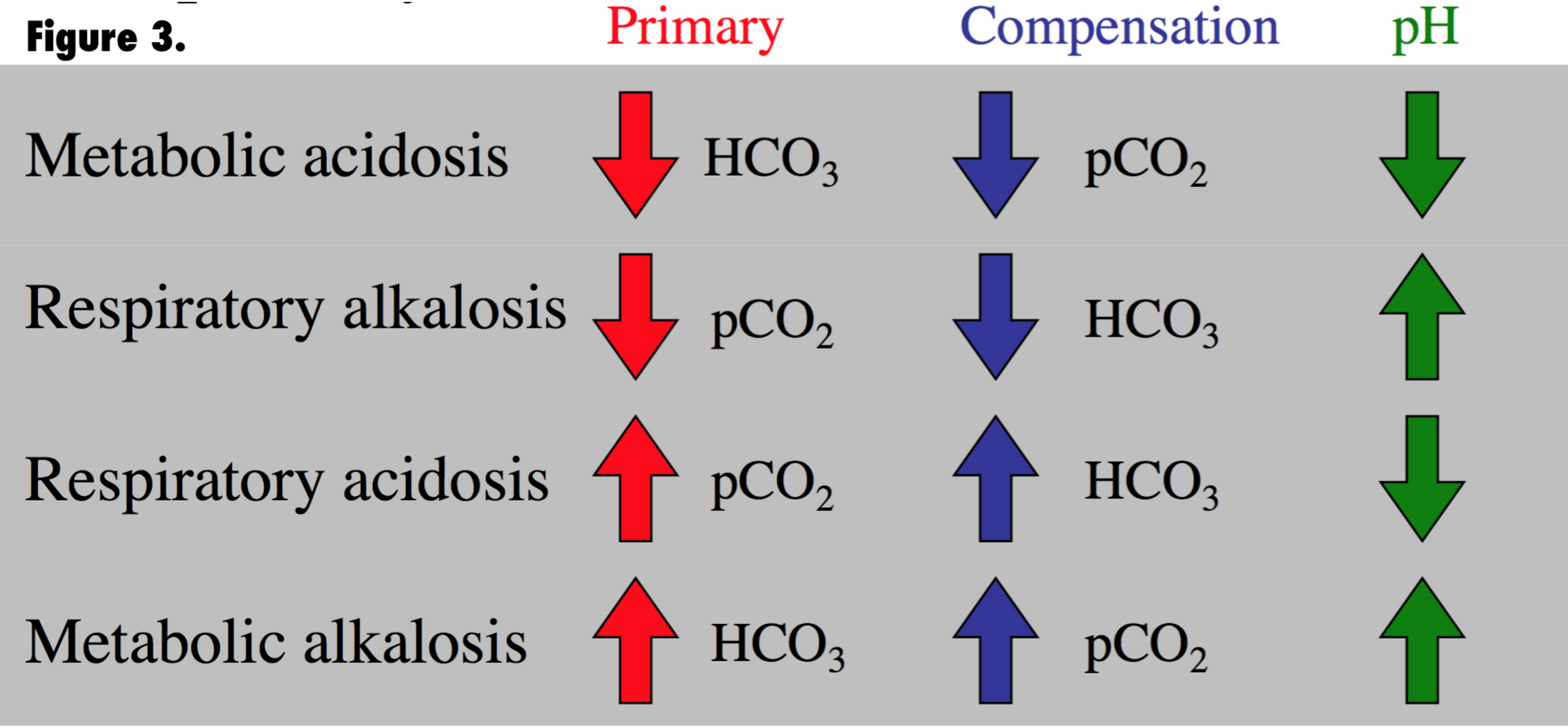
Acidosis & Alkalosis

1. Blood [HCO3-] is controlled by kidneys → …so is affected by metabolic disorders

2. Blood PCO2 is controlled by the lungs → …so is affected by respiratory disorders

[in general]

Figure 3.


Primary
Compensation
pH
Metabolic acidosis
HCO_3
pCO_2
Respiratory alkalosis
pCO_2
HCO_3
Respiratory acidosis
pCO_2
HCO_3
Metabolic alkalosis
HCO_3
pCO_2

MCQ

- Which characteristics are associated with metabolic alkalosis?
  a) pH <7.35 with high plasma HCO3
  b) pH >7.45 with high plasma HCO3
  c) pH > 7.45 with low plasma HCO3
  d) pH > 7.8 with low plasma HCO3
  e) pH <7.35 with low plasma Na

Thank you!

Feedback Form