

# 1-Introduction

26 October 2021 10:04

- Physiology: Study of how life forms function
- Different ways to achieve homeostasis: regulators (eg: mammals), avoiders (eg: monarch butterfly), conformer (snail)
- Feedback loops: stimulus -> receptor -> control centre -> effector -> homeostasis
- Hypothalamus set point: A temperature set point
- Negative feedback loops: thermoregulation, regulation of blood glucose levels, osmoregulation
- Positive feedback loops: Oxytocin-induced uterine contractions, lactation (suckling stimulates milk production, which causes more feeding), ovulation (follicle-> estrogen -> FSH+LH-> follicle development))
- Gain of function experiments: Increasing expression of genes to search for amplified phenotypic response relevant to experiment
- Loss of function experiments: Silencing or KO genes to search for gene causing a phenotype

# 2-Cell membranes and tight junctions

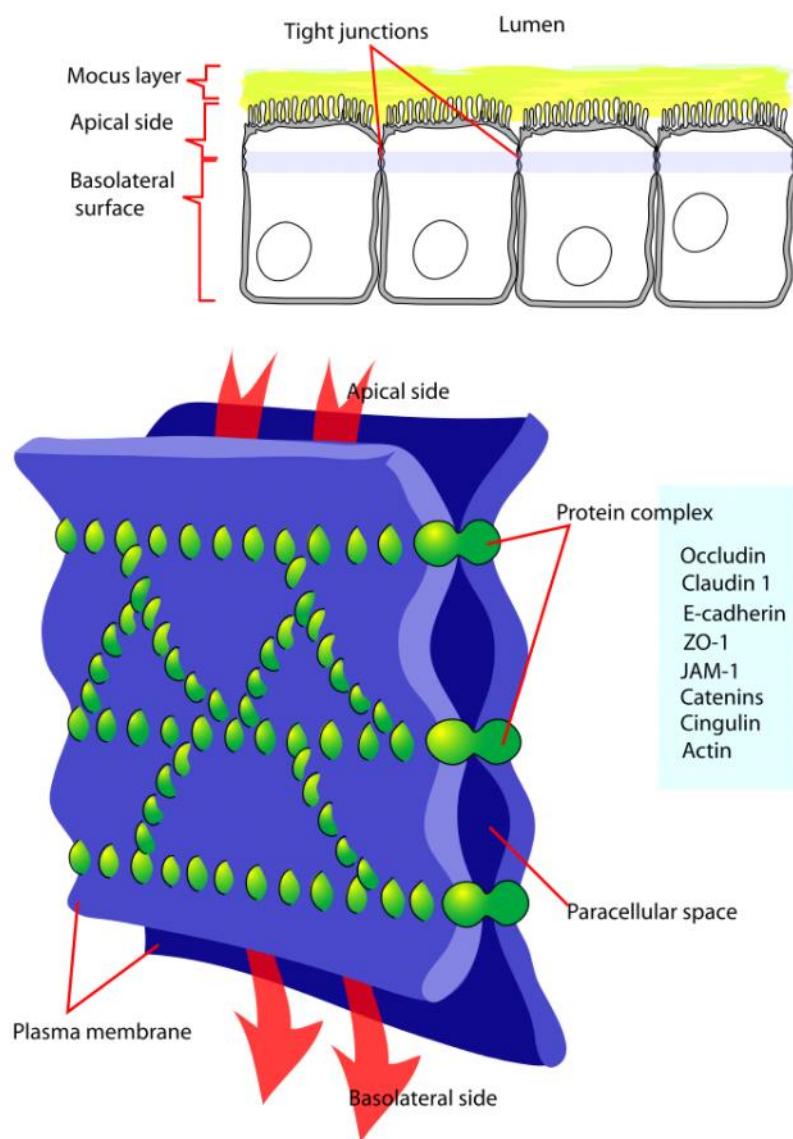
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mRNA splicing allows for the production of different isoforms

## Epithelial Cells

- Top surface is the apical surface, basal surface is the serosal surface. Cells sit on a basement membrane.
- **Brush-border cells** are found in intestinal epithelium and endocrine glands. (microvilli)
- **The functional asymmetry** of epithelial cell surface: apical surface distinct from baso-lateral surface

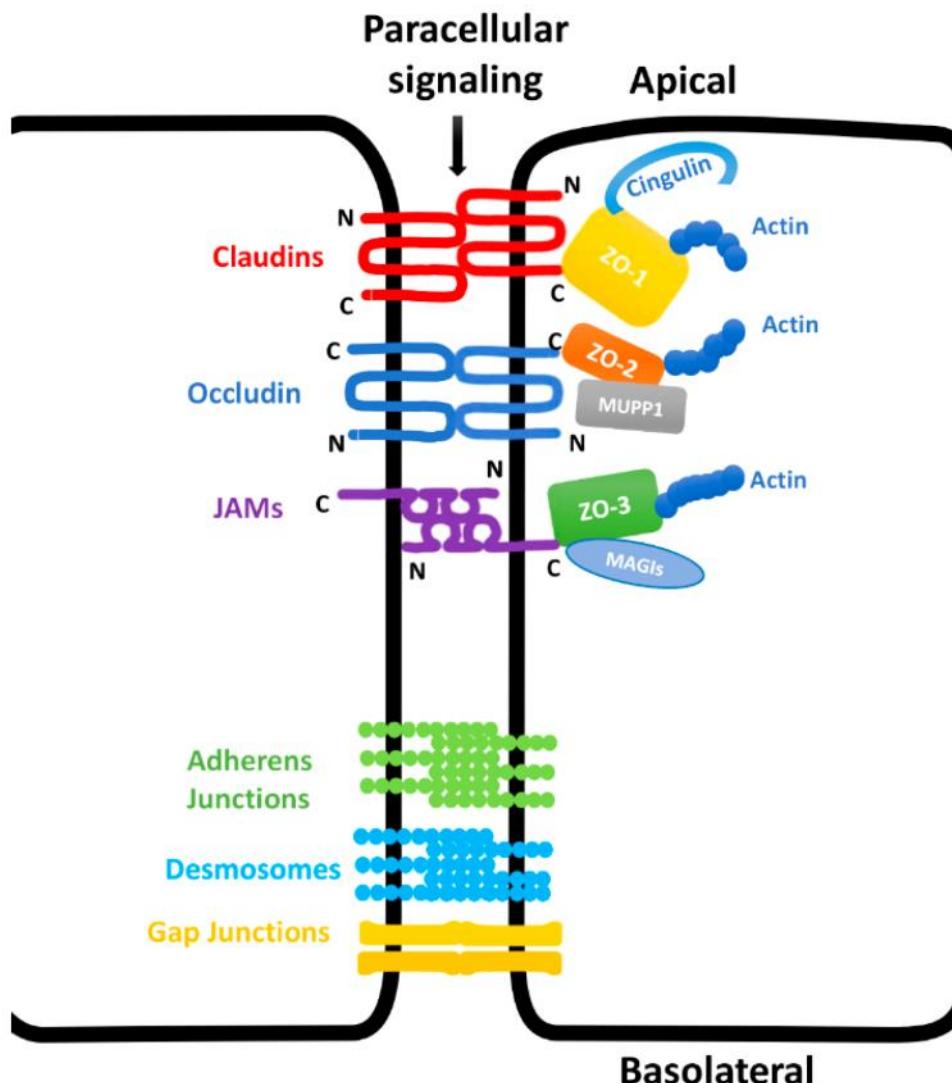
## Tight Junction (occluding junctions)



- Multiprotein junctional complexes whose function is to **prevent leakage** of solutes/water and provide **mechanical stability**

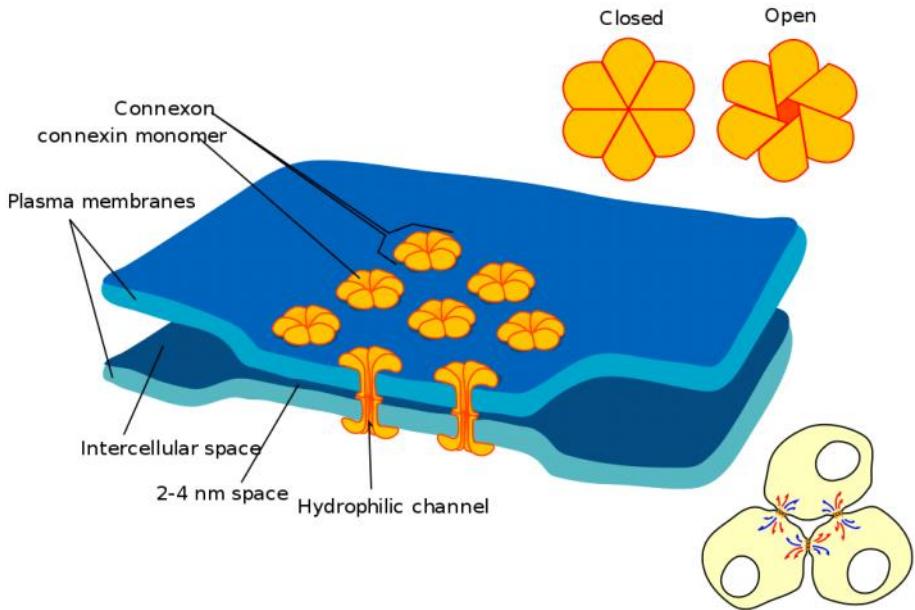
to tissues

- Found in vertebrates, and corresponding structure in invertebrates is separate junctions
- Proteins involved: **Ocludin**, **Claudin**, junctional adhesion molecules (**JAM**), **E-cadherin**. These are transmembrane proteins that seal the junctions.



- **ZO-1 (zona occludens 1)** is an adaptor protein that links the claudins and occludins to the **cytoskeletal components**. Acts as a marker for a tight junction.
- **Paracellular transport:** transfer of substances across an epithelial layer by passing it through the intercellular space. Tight junctions seal the paracellular pathway. Paracellular pathway important where transmembrane transport is insufficient (eg: avian intestine)

### Gap Junctions



- Type of **intercellular connection** that connects **cytoplasm** of two adjacent cells
- Made of **homo hexamer of connexin** proteins.
- Functions: electrical, chemical communication, transmembrane transport of molecules < 400 Da

### Desmosomes

- **Adhesive protein complexes** that bind two cells are localised to intercellular junctions. **Strong complex**, found in tissue that undergo **mechanical stress** (cardiac tissue)
- Cell membranes are 6-10nm thick, two molecules thick, and are electrically polarised. The double bond in of the tails causes a bend which reduces compactness of packing of phospholipids in the membrane and contributes to the fluidity.
- Transport of water

Water can diffuse through cell membrane but **solubility of water in membrane is low** so this accounts for very small percentage of transport. Most transport occurs through **aquaporins**.

- Gases permeable  
Small uncharged polar molecules (water, urea): slightly permeable  
Large uncharged polar molecules (glucose); impermeable  
Ions: impermeable  
Charged polar molecules (amino acids, nucleic acids): impermeable
- Categories of membrane proteins: channels (permits simple diffusions), transporter (binds non covalently and reversibly to transport molecules), enzymes, receptors, structural proteins

# 3- Channel Transporters

02 November 2021 15:08

- Difference of channels vs transporters: Channels are membrane-spanning water-filled pores through which substrates passively diffuse down their electrochemical gradients whenever the regulatory gate is open. Transporters undergo a cycle of conformational changes linked to substrate binding and dissociation on opposite sides of the membrane

## Simple Diffusion

- Important for small gases
- Charged molecules diffuse as per not only chemical but also electrical gradient. Sometimes the electrical gradient opposes the chemical gradient.

## Channels

- Some are leaky and are always open (resting channels). Ion channels allow for movement as per the concentration gradient. They are highly selective but do not actually bind to the ions

## Gated-ion channels

Open under certain circumstances but content diffuses as per gradient. Types:

- Voltage gated channels: open when membrane potential changes
- Phosphorylation gated channel: kinase adds phosphate to the channel to trigger opening
- Stretch gated (tension gated) channels: opened by cytoskeletal elements
- Ligand gated channel: opened by binding of ligand, and can act as receptors

Facilitated diffusion: Occurs in direction of chemical gradient, and the solute binds reversibly to a transporter. Eg: movement of glucose from plasma into cells.

## Pumps (active transport mechanisms)

- Eg: in action potentials, the Na-K pumps keep the concentration gradient set up, in fish the pumps maintain high conc of ions in blood vs the freshwater, and pumps transport sugar + amino acid from gut into blood.

## Transporters

Electroneutral symport: symports where the electrochemical gradient across the membrane is preserved (eg:  $\text{Na}^+$  and  $\text{Cl}^-$  entering together)

Electrogenic symport: symport that is not electrically balanced (eg: bringing amino acid with  $\text{Na}^+$ )

Primary active transport: draws energy immediately from ATP hydrolysis. Mostly transmembrane ATPases.

Secondary active transport: energy from electrochemical gradient set up by ATP.  $\text{Na}^+$  is the common co-transporter

Symporter: SGLT: co-transports glucose and  $\text{Na}^+$

Antiporter: Na-Ca exchanger: rapid recovery after  $\text{Ca}^+$  spike

# 5-Oxygen

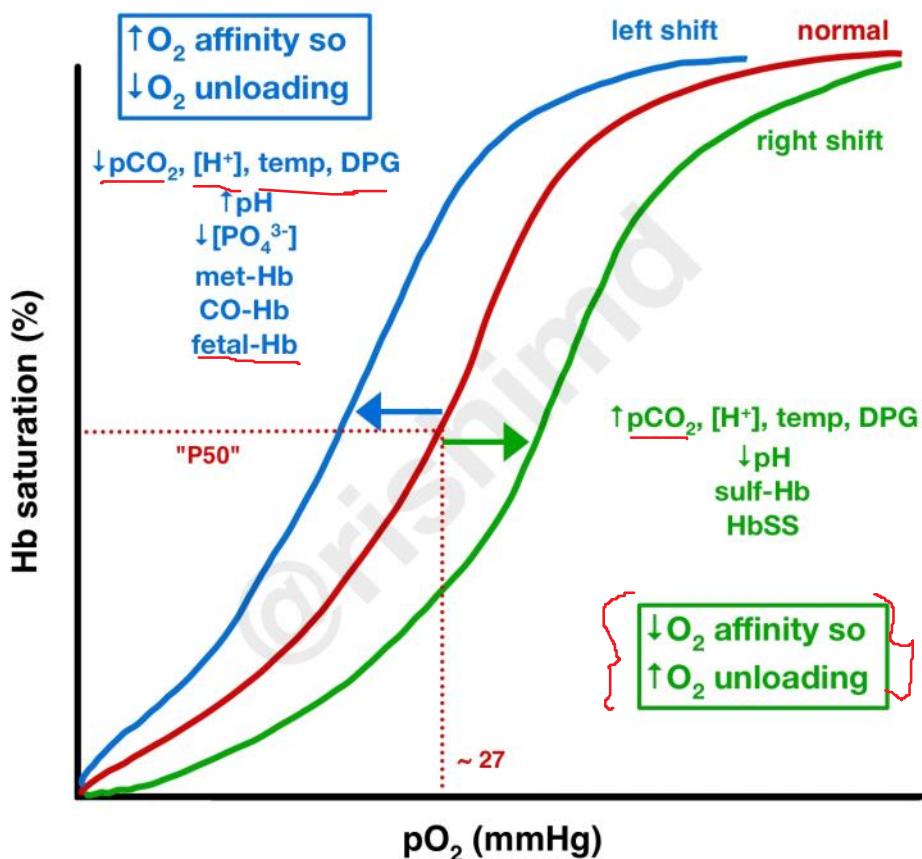
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- ATP cannot be transported through body and is not stored to a great extent
- There are possibly better sources of energy but ATP is the dominant energy currency

Factors affecting level of oxygen in a cell

- Distance from vasculature
- Environmental conditions

- Level of oxygen determines whether pyruvate enters the TCA cycle or the fermentation pathway
- Each turn of Kreb's cycle generates 3 NADH, 1 GTP, 1 FADH<sub>2</sub> (which are electron donors). The proton gradient is set up and ATP synthase generates ATP. Fatty acids and amino acids can also enter the aerobic respiration pathway
- Haemoglobin stores oxygen in erythrocytes and myoglobin stores in muscle cells and cardiac tissue
- Oxygen dissociation curve



CO<sub>2</sub> binds reversibly with haemoglobin to produce carbaminohaemoglobin

Difference in pO<sub>2</sub> between extracellular fluid and cells drives oxygen diffusion

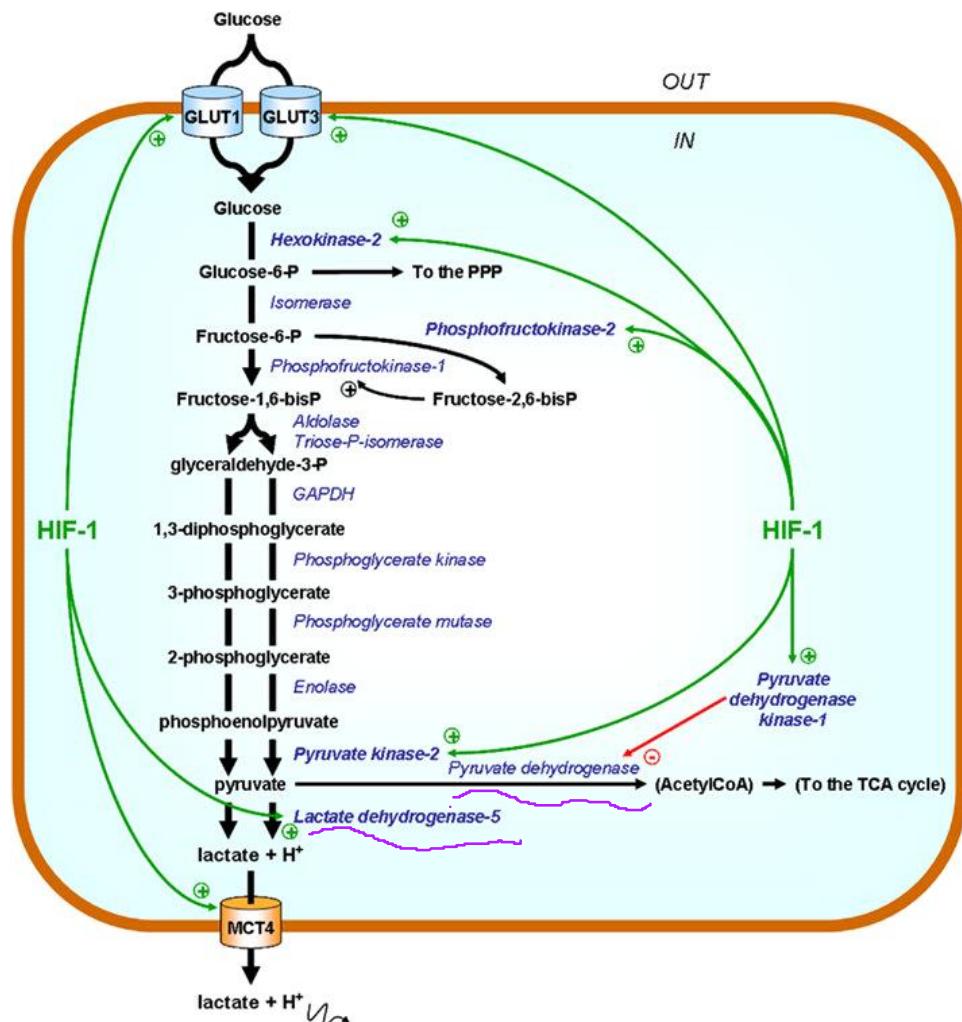
## Erythropoiesis

Erythropoietin is expressed in the kidney which stimulates hematopoietic stem cells to produce RBCs (kidney failure causes anaemia)

## Hypoxia

Erythropoietin is a hypoxia inducible gene whose expression is regulated by hypoxia response elements (HRE). Hypoxia inducible factor (HIF) is a TF whose stabilization is hypoxia inducible. HIF binds to HRE to trigger expression of EPO and other genes.

Many genes of the respiration pathway are under HREs.



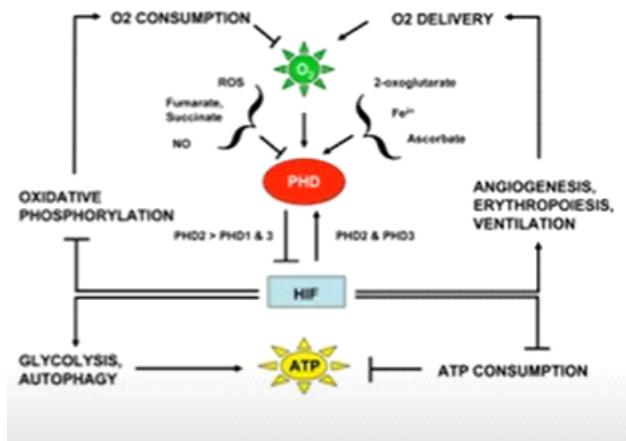
HIFs prevent entry of pyruvate into the TCA cycle while stimulating glycolysis.

Eg: HIF-1 $\alpha$  stimulates VEGF, GLUT1  
HIF - 2 $\alpha$ : TGF-alpha, cyclin D

## Oxygen sensing mechanism

HIF- prolyl hydroxylase containing domain also called prolyl hydroxylase domain (PHD) proteins are a class of proteins (PHD1, PHD2, PHD3). Cause hydroxylation of HIF-1  $\alpha$ . The Von Hippel-Lindau tumour suppressor (VHL) protein possess ubiquitin ligase activity and marks hydroxylated HIFs for degradation.

PHDs depend on oxygen concentration. More O<sub>2</sub>, more PHDs.



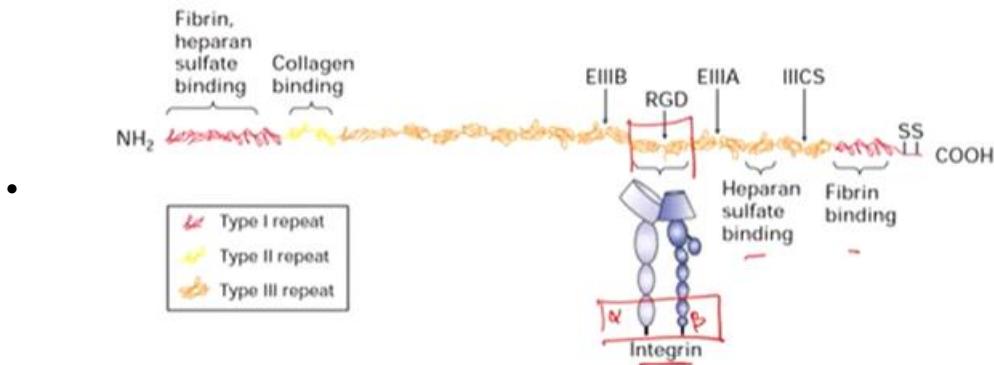
### Hypoxia in cancer

Hypoxia in tumours stimulates angiogenesis. VEGF is also regulated by HIFs. HIF-2alpha promotes hypoxic cell proliferation

# 6-cell cell comm

24 November 2021 09:26

- Autocrine/paracrine/endocrine mechanisms of cell-cell communication
- Need for cellular communication: cell development, tissue homeostasis, immune interactions
- How to study these interactions ( <https://www.nature.com/articles/s41576-020-00292-x>)
- Cell communication also plays role in tissue integrity
- Cell physiology can change due to changes in extra cellular membrane
- **Integrins:** heterodimer transmembrane proteins that facilitate cell-cell or cell-ECM adhesion. Ligands for integrin: **collagen, laminin, fibronectin** (proteins of ECM). Activation of integrins leads to lead to cytoskeletal changes or other changes.
- ECM: consists of interstitial matrix and basement membrane



- Cell migration: caused by dynamics between cell and the ECM.
- Different types of cell movement: amoeboidal, mesenchymal, lobopodial
- Eg: fibroblasts migrate as mesenchymal form
- **Extravasation:** movement of cells from vasculature to tissues. Leucocytes communicate with endothelial cells via selectin and integrin signalling which allows for extravasation.

# 7-action potential

24 November 2021 15:35

## 1. Resting membrane potential

- The number of channels of an ion dictates its permeability across a membrane

Inside	Outside
-More K	-More Na and Cl
-Negative	-Positive

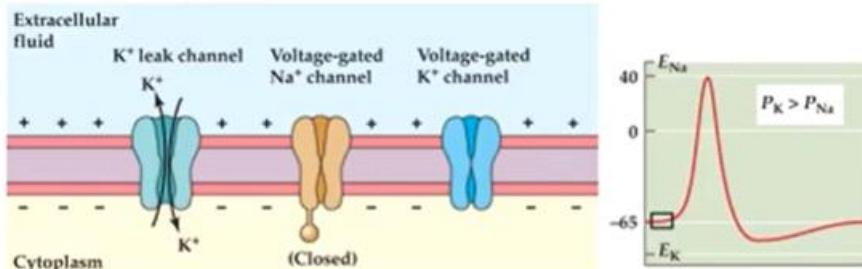
- Na-K ATPase pump maintains this concentration gradient by pumping 2 K inside and 3 Na out, but K ions also diffuse as per the conc gradient via open channels

- Resting membrane potential is negative inside the cell and the value differs for different cells ~70mV. The resting potential sets up the needed gradient for depolarization

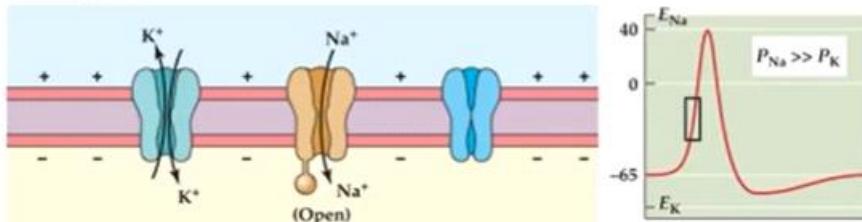
- [https://en.wikipedia.org/wiki/Resting\\_potential](https://en.wikipedia.org/wiki/Resting_potential)

- When the membrane starts depolarizing, the Na voltage gated ion channels open after a voltage threshold and Na<sup>+</sup> ions enter and this increases the potential to positive. Then a refractory period begins and the Na channels close. Then K ions leave the cell as per the gradient through voltage gated channels and the potential starts to drop and transiently the membrane is hyperpolarised before returning to rest.

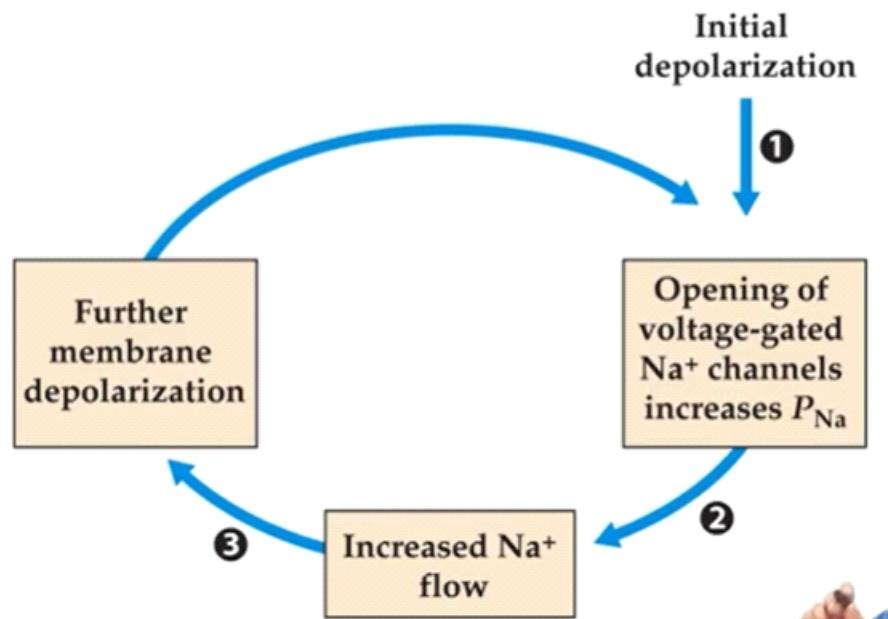
(a) Resting membrane potential



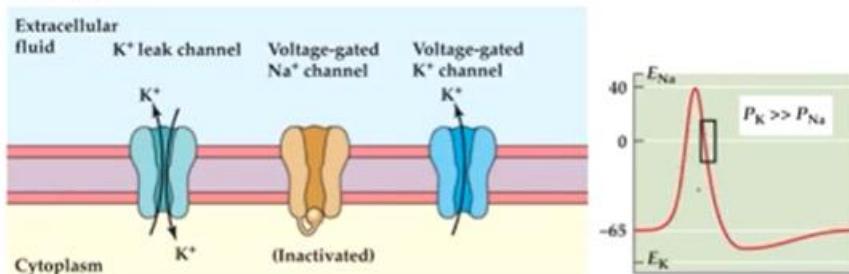
(b) Rising phase



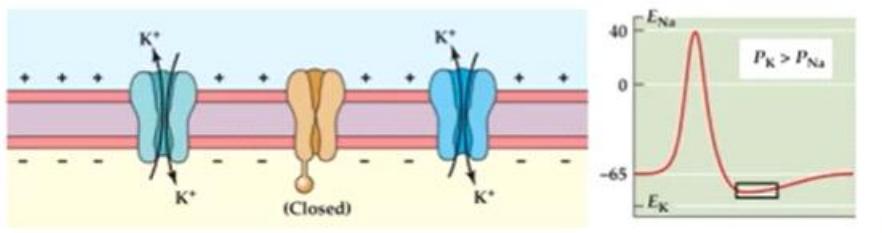
- K<sup>+</sup> leak channel allows the K<sup>+</sup> to move freely as per their conc gradient
- Hodgkin cycle: positive feedback loop during depolarization



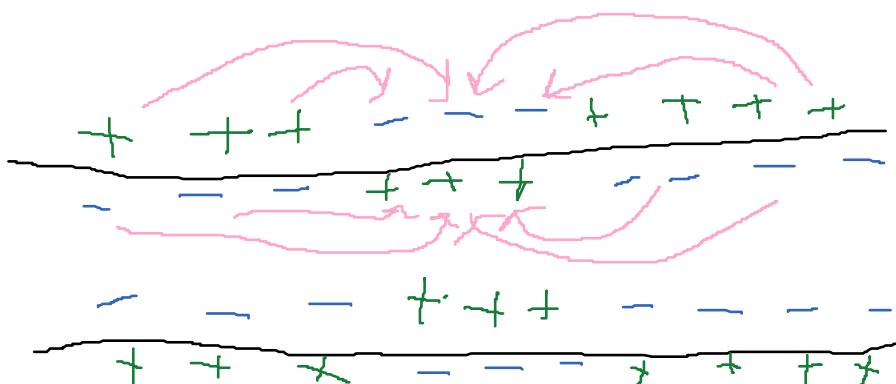
(c) Falling phase



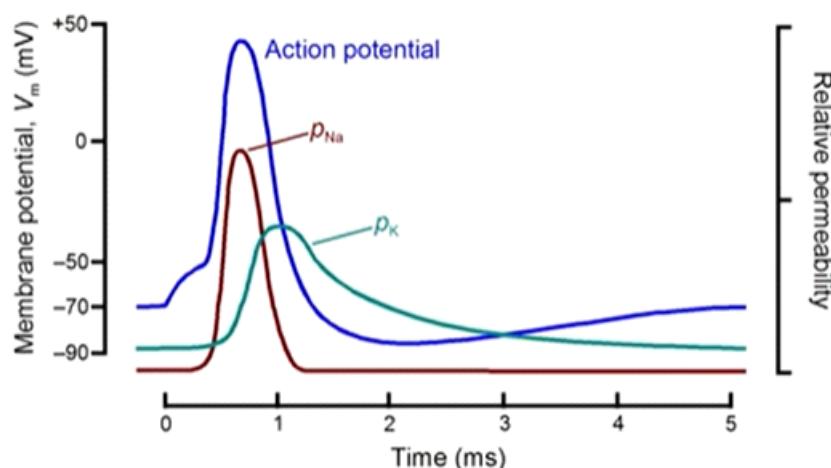
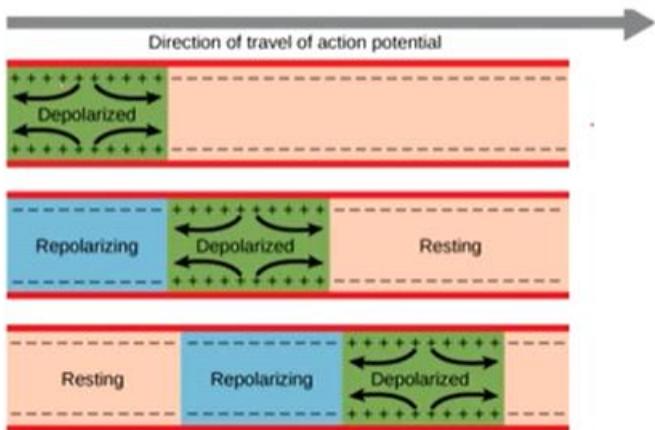
(d) Recovery



- Patch clamp assay is used to make study the movement of ions through a channel
- Propagation of action potential:



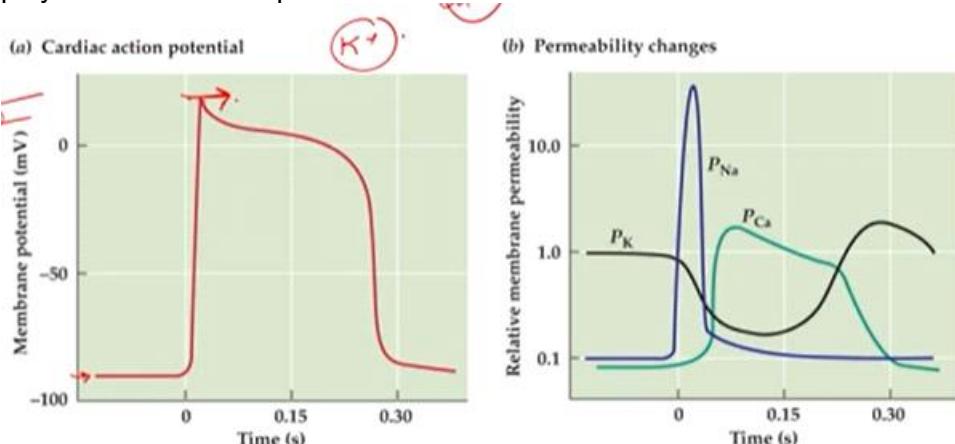
- There are local capacitive current circuits set up at the region of depolarization. These currents can stimulate the opening of  $\text{Na}^+$  gated channels but since the place where the action potential came is in the refractory period, the transmission of potential is unidirectional.
- Interneuron connect sensory and motor neurons



- Saltatory conduction: conduction in myelinated nerves. Ion exchange only happens at the nodes. Conduction is faster.

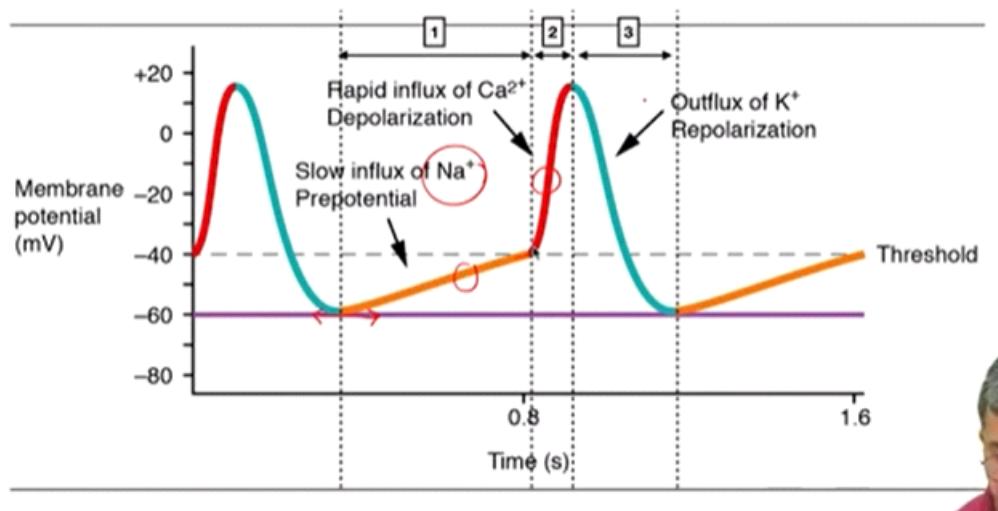
### Cardiac muscle fibre action potential

- Calcium conc in the cytoplasm is kept low by pumping out or into ER.  $\text{Ca}^{2+}$  plays a role in action potential conduction in heart muscle



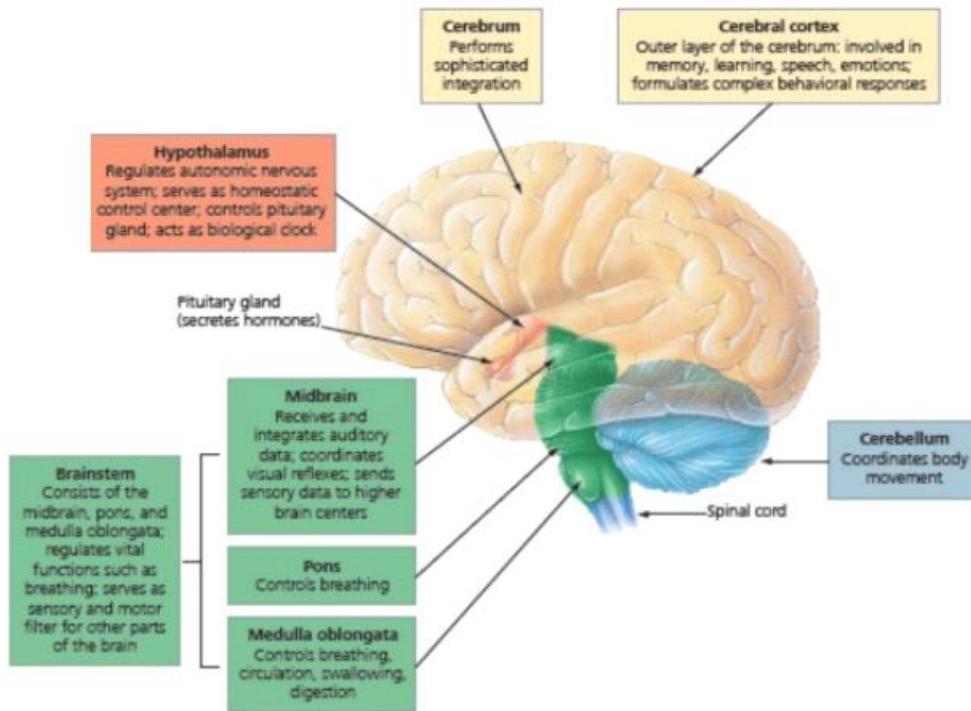
- Action potential starts with  $\text{Na}^{+}$  voltage gated ion channels that increase potential and it then falls off. Then calcium enters the cytoplasm along the concentration gradient and then  $\text{Ca}^{2+}$  is pumped back out

### Action potential generation in the SA node

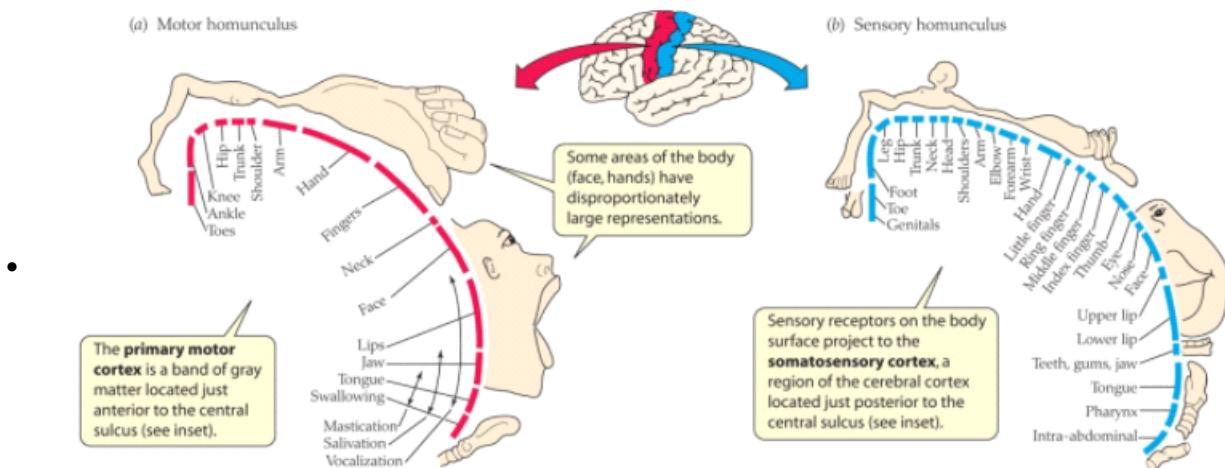


# 8-brain

24 November 2021 16:11



- Four lobes of cerebrum- **frontal, Parietal, temporal, occipital**
- **Central gyrus** separates the parietal and frontal lobes.
- **Broca's area** - for vocalization
- **Wernicke's area** - for language processing



- CSF is secreted by ependymal cells in the ventricles
- **Blood-brain barrier**  
The endothelial cells are different here and the paracellular route is limited  
**Astrocytes and pericytes** sit on the basal lamina and act as an extra layer
- Glial cells of the CNS - **ependymal cells** (on spinal cord lumen and secrete CSF), **oligodendrocytes** (hold neurons in place and ensheathe them), **astrocytes** (bind to axons and intermediates between capillaries and neurons), **microglia** (immune cells and clean up)
- Glial cells in the PNS- **Schwann cells** (secrete myelin sheath), **satellite cells** (present

around cell body of neurons)

□ □ *Kliemann D et. al Cell Report 2019*

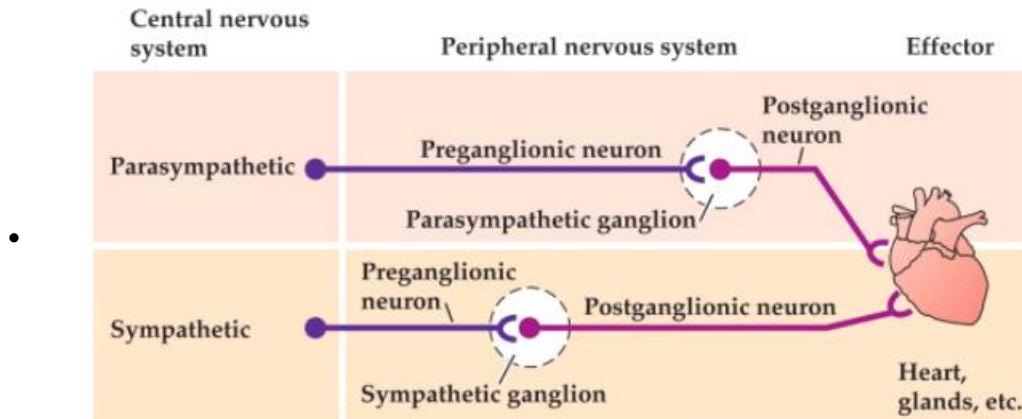
# 9-PNS

24 November 2021 16:50

## Autonomic Nervous System

- Sympathetic- fight/flight, parasympathetic- rest/digest

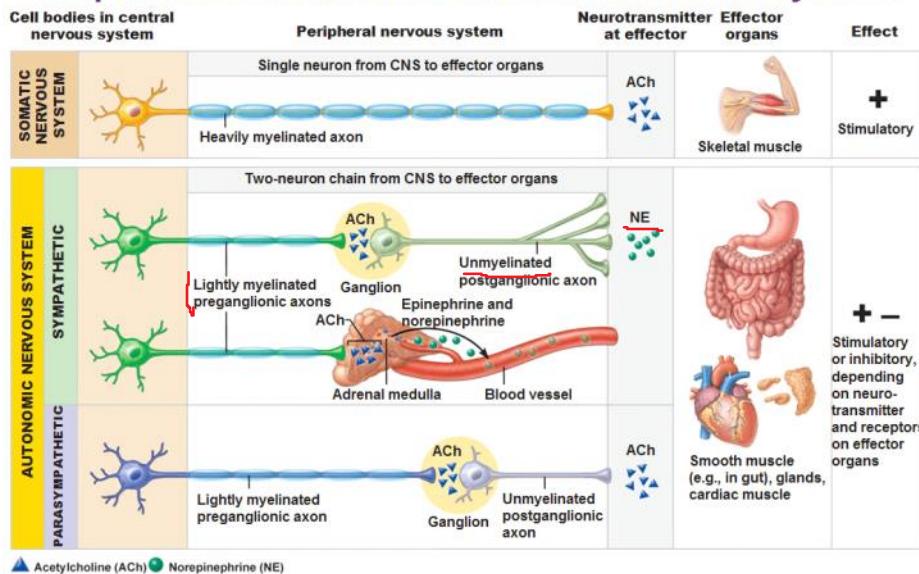
### (b) Autonomic nervous system



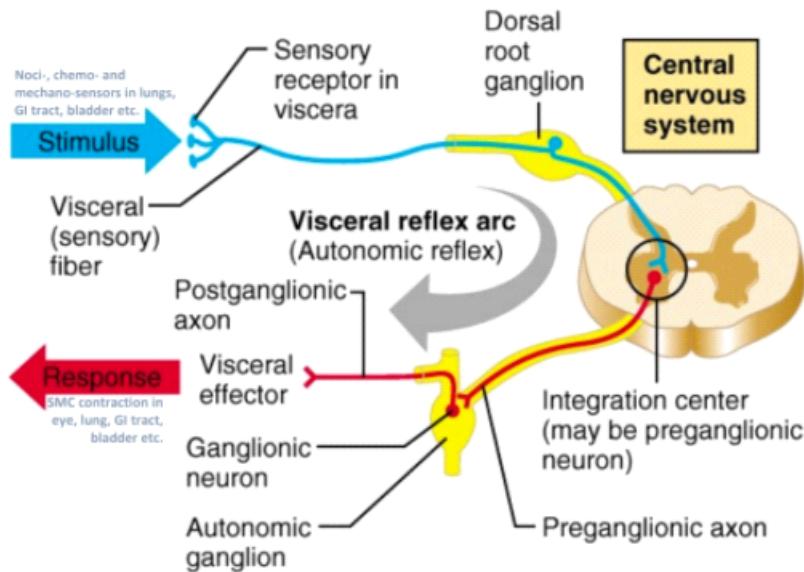
Preganglionic neuron is lightly myelinated while post-ganglionic neuron is unmyelinated

- The lengths of pre and post ganglionic neuron are different in sym and para

## Comparison of Autonomic and Somatic Motor Systems



- Visceral reflex arc in the ANS



- Dorsal root ganglion is a cluster of cell bodies responsible for transmission of sensory information to the CNS (pseudo unipolar neurons)

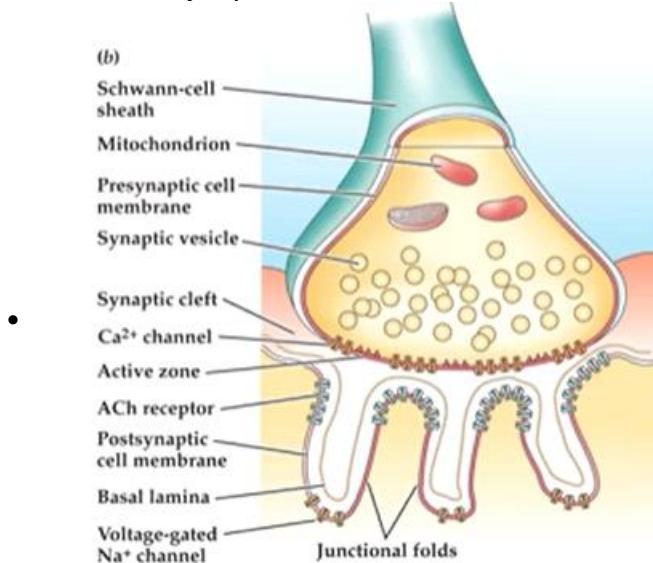
Sympathetic	Parasympathetic
-Spinal origin	-Cranial and spinal in origin
-Preganglionic neurons are cholinergic, post are noradrenergic that activates adrenergic receptors on target	-Both neurons are cholinergic

- Somatic motor pathway- cholinergic neurons
- Adrenergic receptors - alpha 1, alpha 2, beta 1, beta 2 adrenergic receptors.
- Nicotinic (ionotropic) and muscarinic (metabotropic) are cholinergic receptors
- Ach can trigger opening of  $\text{Na}^+$  ion channels to depolarize the target membrane
- Ionotropic receptors: respond by opening ligand gated ion channels, cause fast EPSP or IPSP. Eg: nicotinic Ach receptors
- Metabotropic receptors: respond with modulating metabolism and signalling (eg; GPCRs)

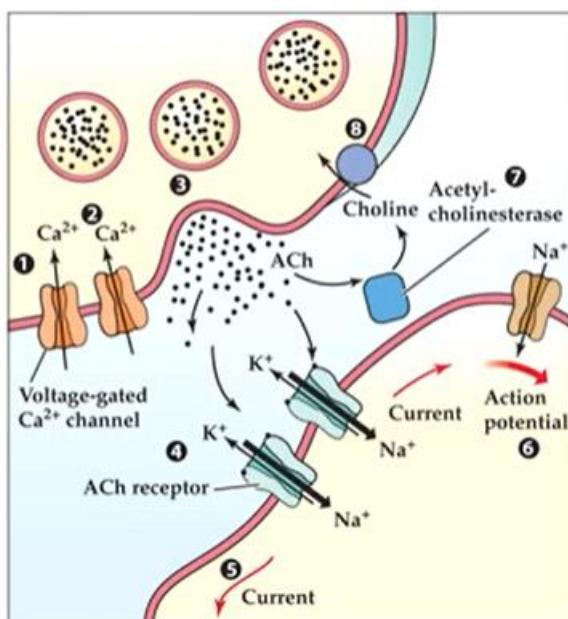
# 10-Synapse

24 November 2021 19:08

- **Electrical synapse:** action potential is transmitted by physical contact between two cells
- **Chemical synapse:** release of chemical messengers into the synaptic cleft



- Calcium enables fusion of vesicles to the membrane. Concentration of calcium is kept low by Ca ATPase pumps and Na-Ca antiporters
- Action potential -- inflow of Ca by gated ions -- release of Ach -- reaches Ach receptor (ionotropic) -- influx of Na
- Ach ---> acetate + choline (via acetylcholine esterase)  
choline + acetyl CoA --> Ach + CoA (via choline acetyl transferase)
- Excitatory postsynaptic potentials (EPSPs): Increase of positive potential. If the potential crosses a threshold, Na<sup>+</sup> gated channels open and the action potential is set up
- Inhibitory postsynaptic potentials (IPSPs): Decrease the membrane potential
- **Excitatory potential causing:** Ach, Glu
- **Inhibitory:** GABA, Gly (cause entry of Cl<sup>-</sup> ions)



- Termination of transmission:

- reuptake of neurotransmitters
- inhibition of exocytosis
- diffusion out of the cleft
- inactivation of cation channels on post synaptic membrane
- internalization of receptors

# 11-Hypothalamus and pituitary

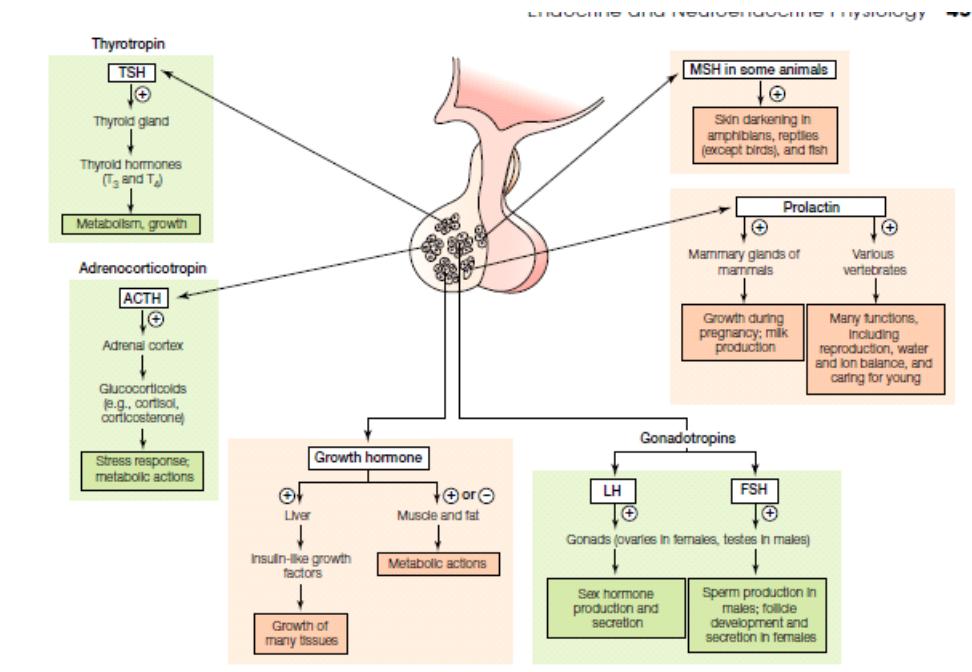
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- Anterior pituitary (adenohypophysis) : glandotropic hormones (affect endocrine organs)
- Posterior pituitary (neurohypophysis) : aglandotropic hormones (affect non-endocrine organs). Not a true endocrine gland, it secretes hormones produced by the hypothalamus. Production of ADH and oxytocin.
- Limbic system: emotions, long term memory. Hypothalamus part of limbic system.
- Functions of hypothalamus: conversion of hormonal signals into neuronal signals, conversion of neuronal signals into humoural.

Hormones of hypothalamus (which act on anterior)	Releasing hormones	Release-inhibiting hormones
	Corticotropin RH, gonadotropic RH, Somatotropin RH, thyrotropin RH	Somatostatin, prolactostatin

- Hormones independent of hypothalamus-pituitary system: pancreatic, PTH, calcitonin, calcitriol, angiotensin, aldosterone, GI hormones
- Hypothalamus -> RH or IH -> anterior lobe -> (+ or -) hormones

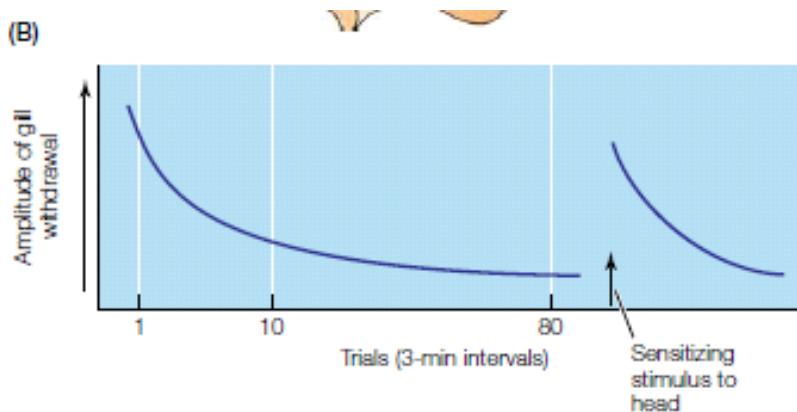
Hormones of anterior lobe	ACTH	FSH	LH	MSH	Somatotropin	TSH	Prolactin



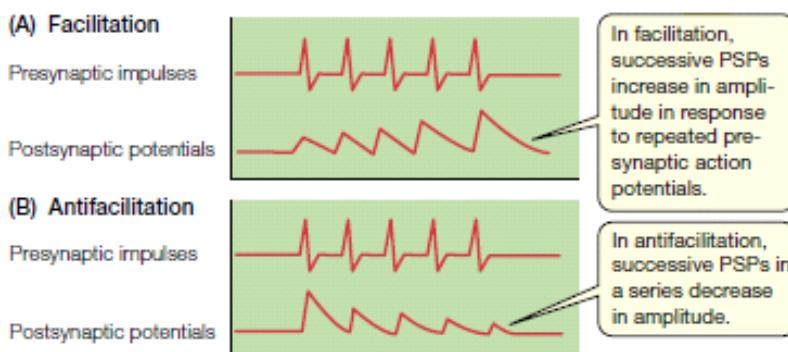
# 12-Habituation and sensitization

09 December 2021 16:32

- **Habituation:** decrease in intensity of reflex response after stimulus is presented repeatedly
- **Sensitization:** prolonged enhancement of a reflex to a stimulus which results from second stimulus that is novel or noxious.
- If the response amplitude decreases due to habituation, it can be brought back up by a sensitization stimulus.



- Model for sensitization/habituation: it follows facilitation/ anti facilitation. There is modulation of Ca<sup>2+</sup> currents in the pre-synaptic terminal to either increase/reduce neurotransmitter release
- In some facilitating interneurons are serotonergic neurons. The neurons from the sensitive part feed into the pre-synaptic sensory neurons (which originally have blocked neurotransmitter release due to habituation). Serotonin from sensitive -> GPCR -> cAMP -> Open of Ca<sup>2+</sup> -> release of neurotransmitter
- Sensitization leads to long term potentiation
- Long term potentiation: strong, repeated stimulus leading to long lasting increase in ESPS amplitude. It affects the gene expression levels in post-synaptic cell
- Tetanic stimulus: High frequency stimulation



**FIGURE 13.22** Synaptic facilitation and antifacilitation

# 13-Weight and thermal regulation

09 December 2021 16:49

- Feeding behavior depends on nutritional status/ energy metabolism
- Major control of fat deposition by ANS – catabolic actions of sympathetic nervous system (beta adrenergic receptor controlled lipase activity) and anabolic actions by parasympathetic arm (uptake of glucose and fatty acids by insulin action)
- Feeding induced parasympathetic response stimulates insulin and vice versa for sympathetic.
- Hypothalamus (arcuate nucleus) and brain stem (messages from afferent arm of vagus nerve) play roles in regulation of body weight.
- Afferent regulators of nutritional status:
  - Leptin (secreted by white adipose tissue, anorexigenic)
  - ghrelin (produced in stomach, orexigenic ),
  - GLP-1 (small intestine, anorexigenic),
  - insulin (pancreas, stimulated by high glucose level in blood)
  - Anorexigenic: hunger suppressing- CCK, insulin, serotonin, norepinephrine
  - Orexigenic: hunger stimulation- ghrelin, NPY, AgRP
- Satiety (similar to orexigenic): peptide YY, CCK, glucagon, somatostatin
- Processing in the CNS in response to afferent regulators and general signals of nutrition

Chemical	Production site	Stimulated by	Inhibited by	Action	Effect on hunger
Neuropeptide Y	Arcuate nucleus	Fasting, ghrelin	Leptin, glucose	Increase food intake, lipogenesis	orexigenic
AgRP (agouti related proteins)	Arcuate nucleus	Fasting, ghrelin	leptin		orexigenic
MCH (melanin concentrating hormone)		Flavour of food	MSH producing neurons		orexigenic
Alpha-MSH		Leptin	AgRP		anorexigenic

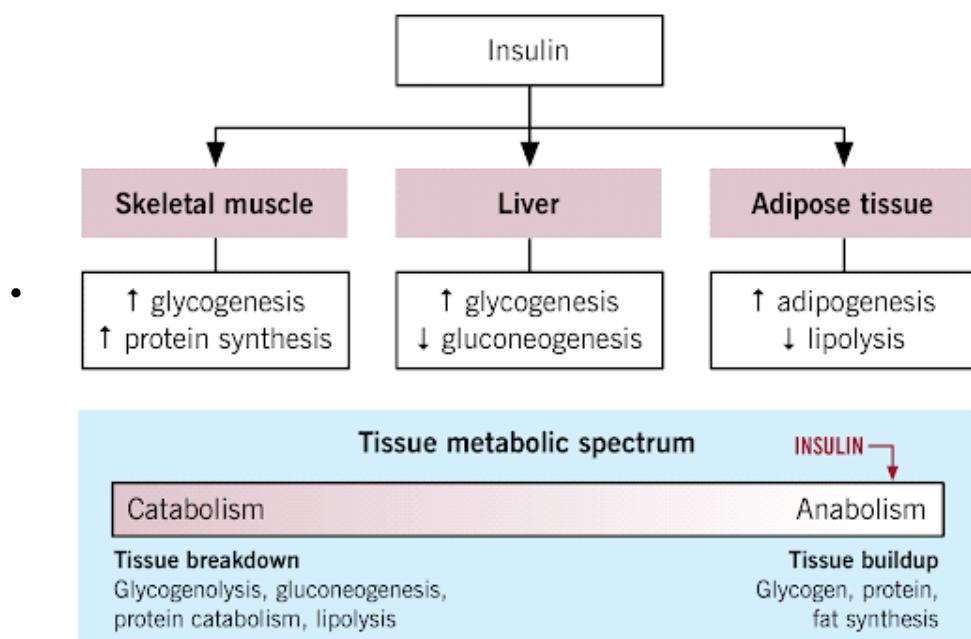
Irisin	Myocytes	Exercise	-
Serotonin/norepinephrine (anorexigenic)	ANS	Environment, low temp	Weight loss
Thyroid hormones	thyroid	Cold, fever	Illness, caloric restriction

These are efferent regulators, some with direct or indirect affects on hunger

- "browning of fats" - conversion of white adipocytes to have hybrid characteristics of white and brown adipocytes
- Weight gain -> adipose tissue -> (+) leptin/insulin -> (+) MSH (-) NPY, AgRP-> (+) energy consumption/ sympathetic stimulation (-) food uptake
- Weight loss -> (-) adipose tissue -> (-) leptin (+) ghrelin-> (+) NPY, AgRP -> (+) food uptake (-) energy consumption (+) parasympathetic activity
- UCP-1 (uncoupling protein 1): used to generate non-shivering heat. It decreases proton gradient by increasing inner membrane mitochondria permeability. There is breakdown of glucose without production of ATP.
- Proton movement is uncoupled from ATP synthase leads to wastage of energy as heat energy.

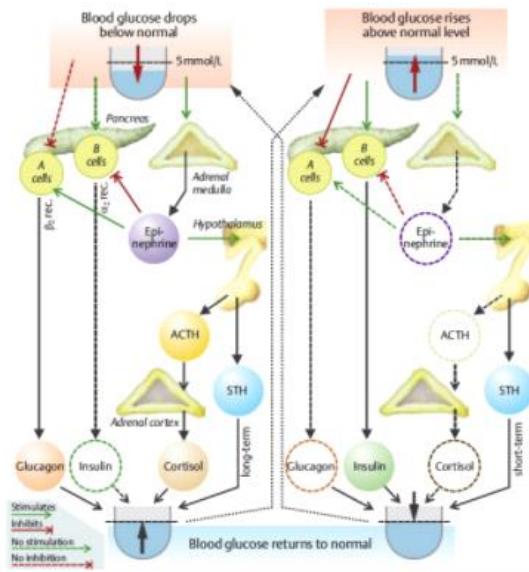
## Anabolic effects of insulin

Sultan Chaudhry



# 14-Hormonal control of glucose metabolism

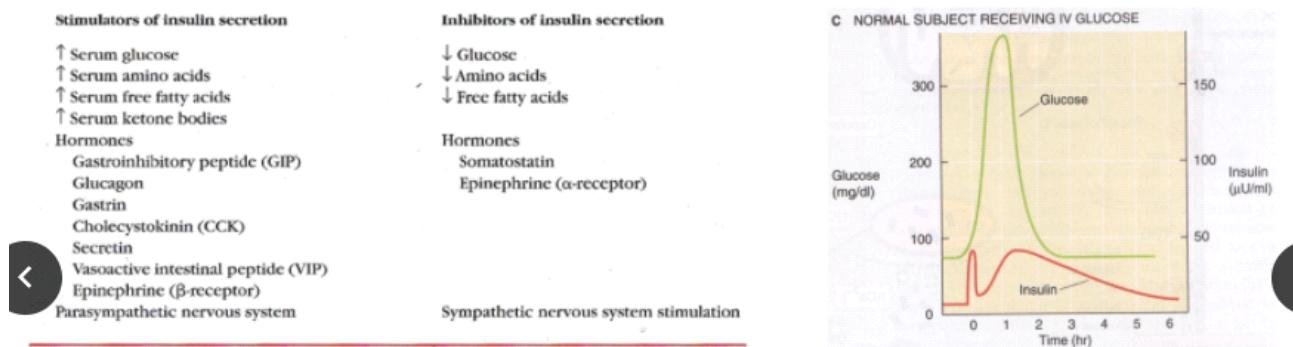
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Hormone Function	Insulin Satiated	Glucagon Buffer	Epinephrine Stress, exercise	Cortisol Supply
Glucose Uptake by cell	Muscle, fat +		Muscle +	Muscle, fat -
Glycolysis	+		+	-
Gluconeogenesis (liver)	-	+	+	+
Glycogen Synthesis $\xrightarrow{\text{red}}$ lysis	Liver, muscle $\xleftarrow{\text{blue}}$	Liver $\xrightarrow{\text{red}}$	Liver, muscle $\xrightarrow{\text{red}}$	Liver $\xleftarrow{\text{blue}}$
Fat Synthesis $\xrightarrow{\text{red}}$ lysis	Liver, fat $\xleftarrow{\text{blue}}$	Fat $\xrightarrow{\text{red}}$	Fat $\xrightarrow{\text{red}}$	Fat $\xrightarrow{\text{red}}$

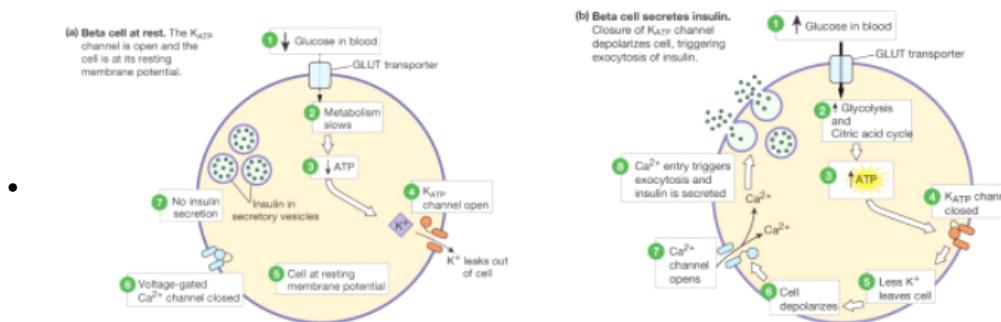
- Metabolic syndrome: insulin resistance, overweight, hypertension, abnormal cholesterol levels
- Endocrine cells in pancreas: islets of Langerhans (beta cells - insulin, alpha cells - glucagon, delta cells - somatostatin, F cells - pancreatic peptide)
- Exocrine cells: acinar cells
- Proinsulin contains the signal peptide which is removed. Proinsulin is converted into insulin by loss of c peptide (connecting peptide). C peptide levels are a way to detect how much insulin is being produced naturally in the body and is a measure of endogenous insulin production

## Regulators of insulin secretion



- No insulin is produced when plasma glucose below 50 mg/dl
- Half-maximal insulin response occurs at 150 mg/dl
- A maximum insulin response occurs at 300 mg/dl
- Insulin secretion is biphasic:
  - Upon glucose stimulation- an initial burst of secretion (5-15 min.)
  - Then a second phase of gradual increment that lasts as long as blood glucose is high

• Why is insulin secretion biphasic? Upon stimulation by an abrupt and sustained increase in the ambient glucose concentration, insulin secretion occurs following a biphasic time course. The secretion rate initially accelerates markedly before slowing down (first phase), and eventually increases again at a slower rate or stabilizes depending on the preparation and the species (second phase). One accepts that the two phases of insulin secretion are not the expression of intra-islet  $\beta$ -cell heterogeneity, two major mechanisms can be envisaged: they are known as the “storage-limited model” and the “signal-limited model” According to the “storage-limited model,” each phase of secretion corresponds to the release, by a constant signal, of a distinct pool of insulin granules, the notion of “pool” corresponding to geographically or functionally distinct granules. According to the “signal-limited model,” the biphasic response could be the result of a single biphasic stimulatory signal or of the sum of signals with different dynamics. These two models are not mutually exclusive and could coexist.

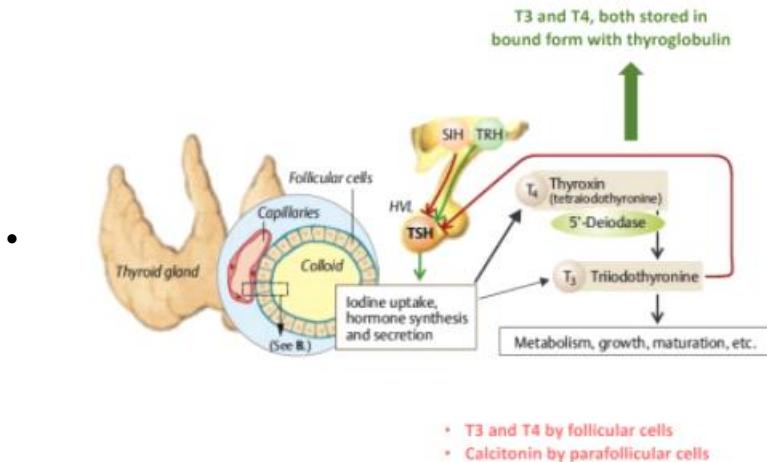


- ATP/ADP ratio determines release of insulin in the storage vesicles of beta cells
- Glucagon receptor is a GPCR
- Insulin receptor is a TRK

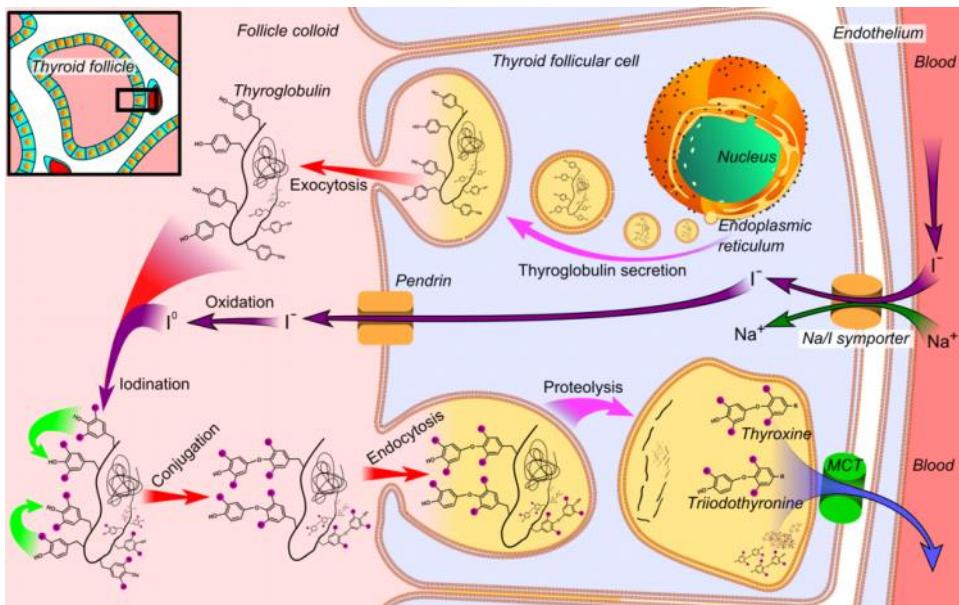
# 15-Thyroid and parathyroid

10 December 2021 23:35

- T4 (thyroxine) is the precursor of T3 (triiodothyronine). T4 is less active than T3 but they have generally the same activity.

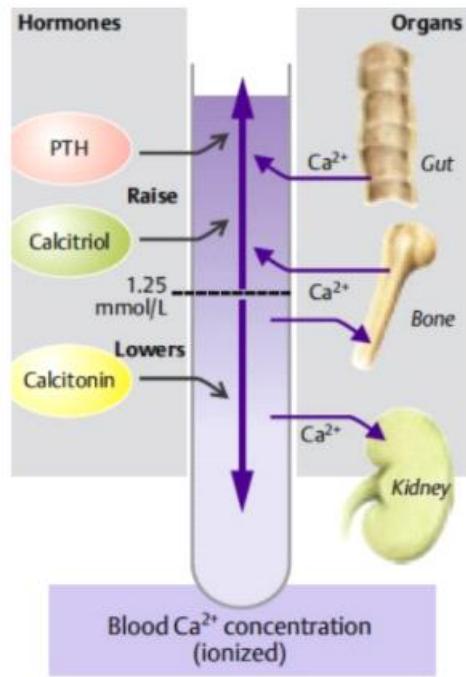


- T3 inhibits the production of TSH.
- The iodine is delivered into the follicular via the capillary
- Pendrin: anion exchanger chloride-iodide
- Thyroglobulin: large protein in the colloid and is precursor to thyroid hormones by iodination of the tyrosine residues which are then cleaved off.



- Mode of action: T4 is converted to T3 by deiodinase. T3 enters the nucleus and binds to its T3 receptors, which in turn release a corepressor and bind co-activator to initiate transcription in response tissues such as pituitary, liver, kidney, heart, skeletal muscle, lung etc.
- There is increase in metabolic rate

Calcium regulation



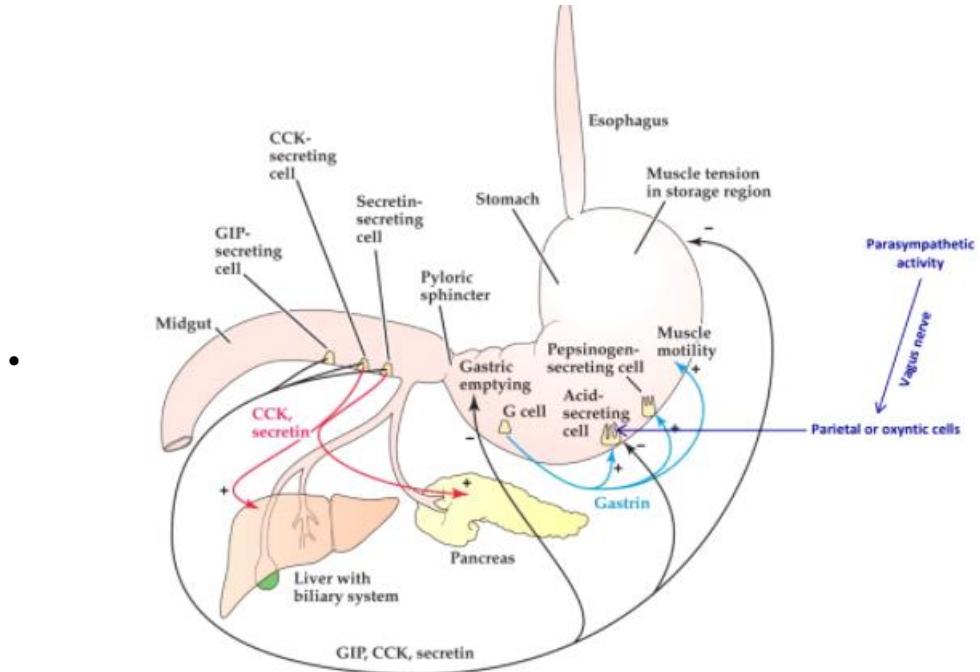
**Vitamin D - calcitriol** (active form of vitamin D)

- Most of the calcium reservoirs are in the bones
- **PTH** raises blood calcium levels by increasing absorption from intestine, release from bones, reabsorption from kidneys and conversion of vitamin D to its active form calcitriol
- Calcitonin does the opposite
- **Calcitriol activates absorption of Ca by the gut and release from bones**
- Osteoblast: secretion of mineral deposits
- Osteoclasts: release of calcium from bones

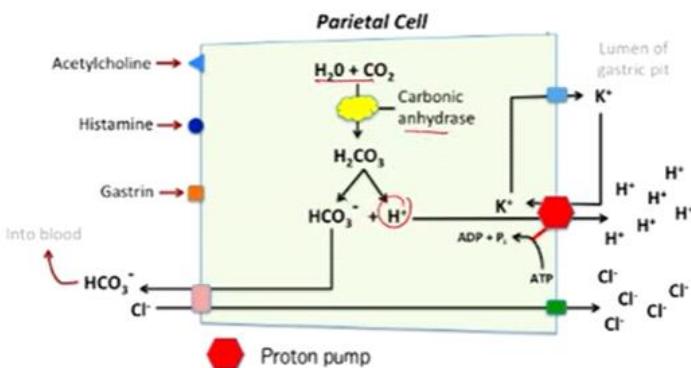
# 16-Nutrition

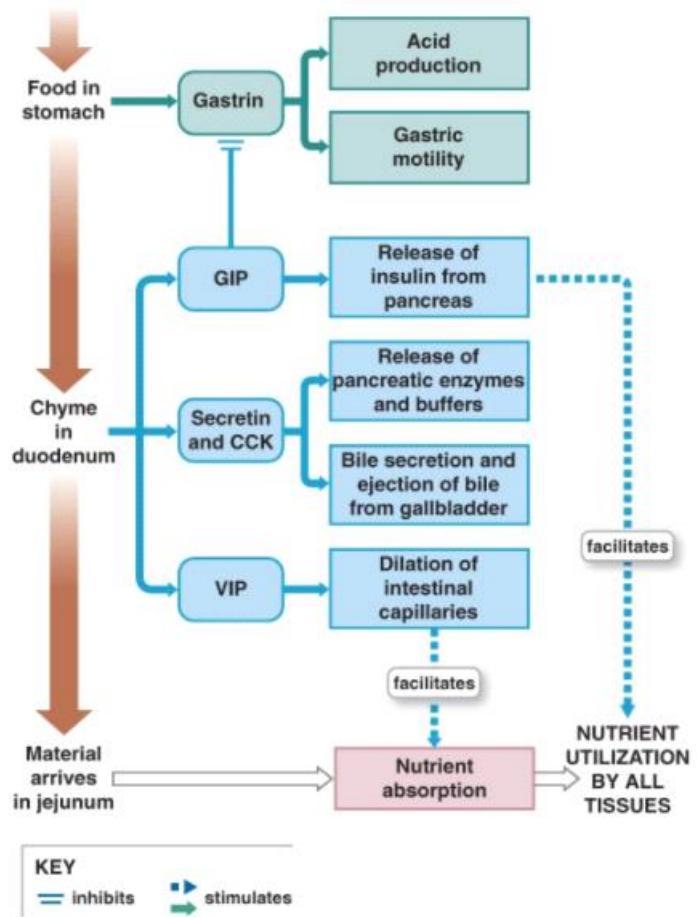
12 December 2021 00:12

- Peristalsis: the circular muscles contract behind the bolus and the longitudinal muscles contract in front of the bolus. There is prevention of reverse movement
- Saliva: dissolves food for tasting, hypotonic for rinsing taste receptors, contains alpha amylase, IgG and lysozymes and bicarbonate



- G cells → gastrin → parietal cells to secrete acid, pepsinogen secreting cells to secrete pepsin, increase in muscle motility
- When food reaches duodenum, CCK, secretin and GIP produced → stimulation of pancreas and liver and inhibition of acid secretion by parietal cells
- Secretin improves production of bile salts, bicarbonate
- CCK stimulates smooth muscles of gall bladder to release bile
- Acidification of stomach needed for pepsin production from pepsinogen
- GIP: gastrin inhibitory peptide
- VIP: vasoactive intestinal peptide

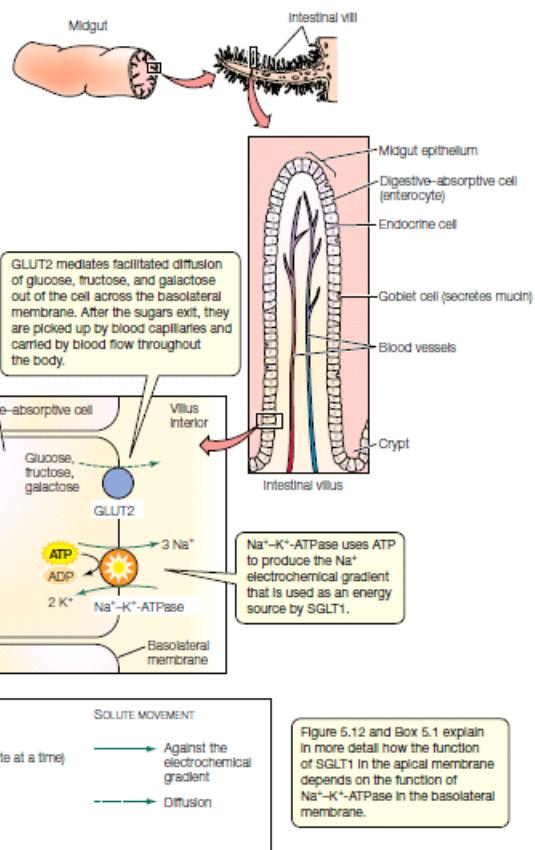




### Carbohydrate digestion

- Pancreatic and salivary amylase are isoenzymes (different genes) to form maltose (mostly)
- sucrase, lactase, maltase are embedded in the apical membrane of mucosal cells (in mammals)
- SGLT - Na-glucose symport (secondary transport) across the apical membrane
- GLUT5 (apical membrane): Facilitated diffusion fructose into epithelial cell
- GLUT2 (basal membrane) - Facilitated diffusion of all monosaccharides

**FIGURE 6.20** The structure of the vertebrate midgut and the mechanism of absorption of monosaccharides (glucose, fructose, and galactose). The insets show how the surface area of the midgut epithelium—composed principally of digestive-absorptive epithelial cells—is enlarged by the presence of folds and projections. The drawings are of the human midgut. There are huge numbers of minute fingerlike structures (each less than 1 mm long), called intestinal villi (singular villus). Collectively they greatly increase the total surface area of the epithelium and thus the numbers of digestive-absorptive epithelial cells. Four membrane transporter proteins of those cells—SGLT1, Na<sup>+</sup>-K<sup>+</sup>-ATPase, GLUT2, and GLUT5—play key roles in the absorption of monosaccharides, as shown. GLUT2, shown here only in the basolateral membrane, sometimes also is present in the apical membrane. Cells turn over rapidly in the midgut epithelium; for example, the average life span of an epithelial cell in humans is about 3–4 days. This rate of cell turnover means equally rapid turnover of the transporter proteins involved in absorption. See Figure 2.5 for more cytological detail.



## Protein digestion

- Exopeptidases: carboxypeptidase
- Endopeptidases: trypsin, chymotrypsin, elastase, collagenase
- Trypsin: Arg-Leu
- Chymotrypsin: C terminal of aromatic acids - Phe, Tyr, Trp
- Carboxypeptidase B: C terminal ends of basic amino acids
- Carboxypeptidase A: C terminus of aromatic or branched side chains
- Transportation generally occurs via secondary Na<sup>+</sup> mediated active transportation

## Hormones and factors in digestions

Name	Source	Target	Effect
Gastrin	G cells (stimulation by presence of food in stomach)	<ul style="list-style-type: none"> <li>Parietal cells to secrete acid</li> <li>Pepsinogen secreting cells</li> <li>Smooth muscles of stomach</li> </ul>	<ul style="list-style-type: none"> <li>Acid production, pepsinogen secretion, stomach peristalsis</li> </ul>
CCK	Duodenum	<ul style="list-style-type: none"> <li>Pancreas</li> <li>Gall bladder</li> <li>Stomach</li> </ul>	<ul style="list-style-type: none"> <li>Release of bile from gall bladder</li> <li>Release of enzymes from pancreas</li> <li>Prevent gastric emptying</li> <li>Inhibition of acid production</li> </ul>
GIP	Duodenum	<ul style="list-style-type: none"> <li>Stomach muscles</li> <li>Parietal cells</li> </ul>	<ul style="list-style-type: none"> <li>Prevent gastric emptying</li> <li>Inhibition of acid production</li> </ul>
Secretin	Duodenum	<ul style="list-style-type: none"> <li>Pancreas</li> <li>gallbladder</li> </ul>	<ul style="list-style-type: none"> <li>Production of HCO<sub>3</sub><sup>-</sup>, bile salts</li> <li>Release of enzymes from</li> </ul>

pancreas

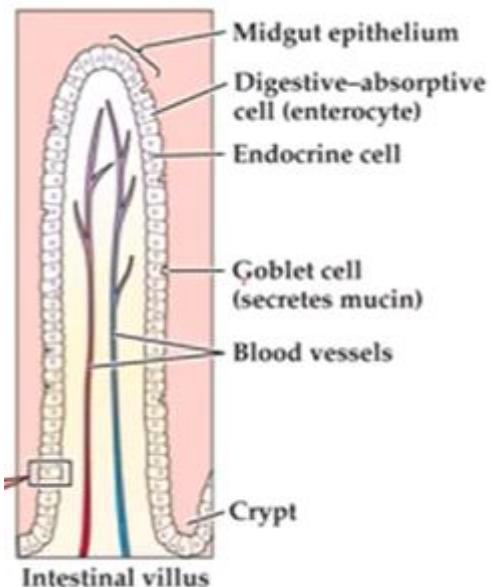
- Prevent gastric emptying
- Inhibition of acid production

# 17-Regulation of digestion

12 December 2021 18:40

Local reflexes	Stretch sensors (oesophagus, stomach) and chemosensor (mucosal epithelium)
External innervation	Para/Sympathetic system, visceral afferent fibres
Neurotransmitters	Relaxation by norepinephrine, acetylcholine, VIP Gastrin releasing peptide (GRP) -> gastrin
Hormones	Gastrin, CCK, Secretin, GIP, Glucagon. VIP

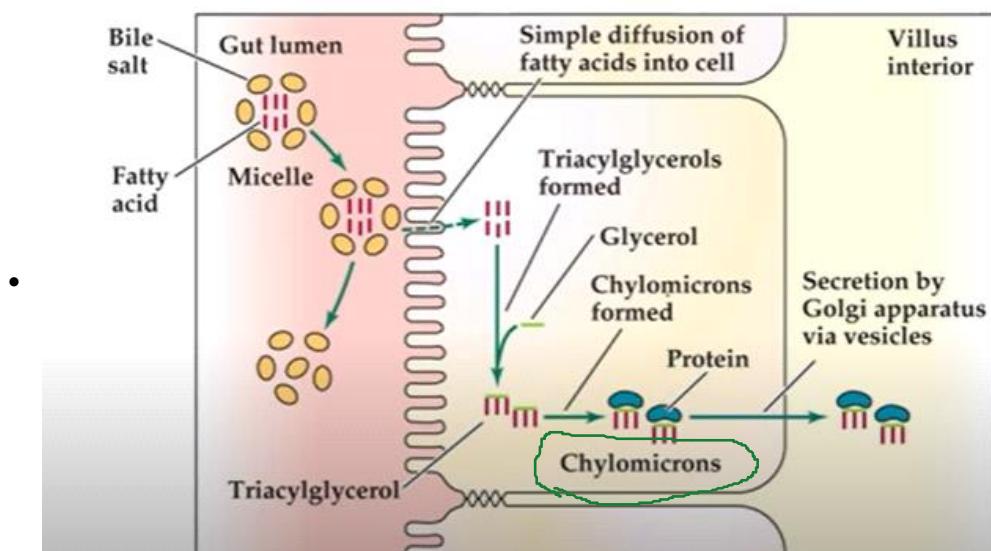
- Jejunum epithelial surface is folded to form plicae, and each plicae has many villi.



- Goblet cells: secret mucin
- The epithelium dies off often and are shed. New cells are formed in the crypt and are pushed up the villus.

## Lipid Digestion

- Bile salts are amphipathic and act to emulsify fats. Salts are recycled.
- General lipases, phospholipases, esterases
- Micelles of fatty acids and glycerol are taken up

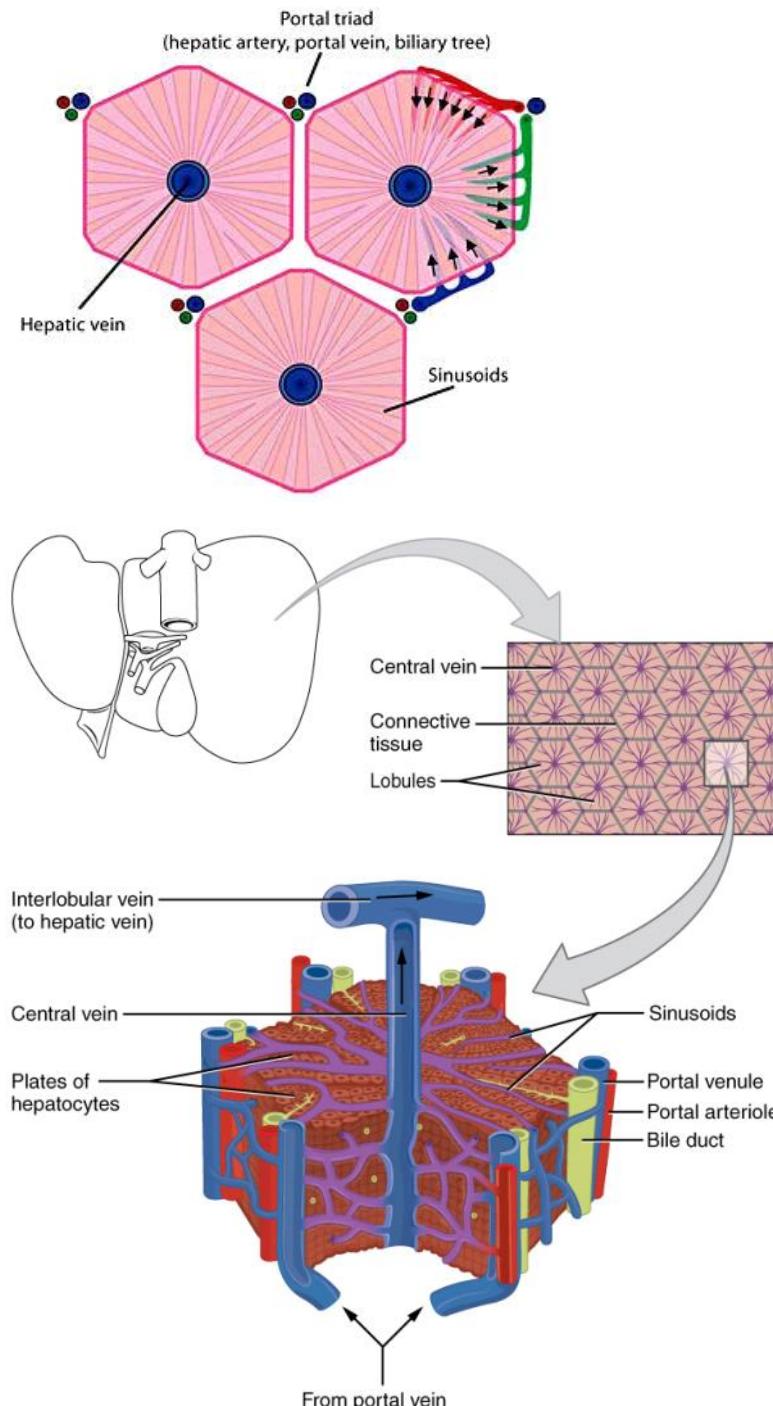


- Chylomicron enters the blood
- Apolipoproteins: activate lipases, mediates delivery of triglycerides, cholesterol from chylomicron by ligand receptors
- Control of bile secretion: secretin + CCK
- Water, Na is absorbed mostly in jejunum
- Aldosterone acts on colon to affect Na absorption
- Na is pumped inside the cell and the water follows via osmosis

# 18-Liver

14 December 2021 14:15

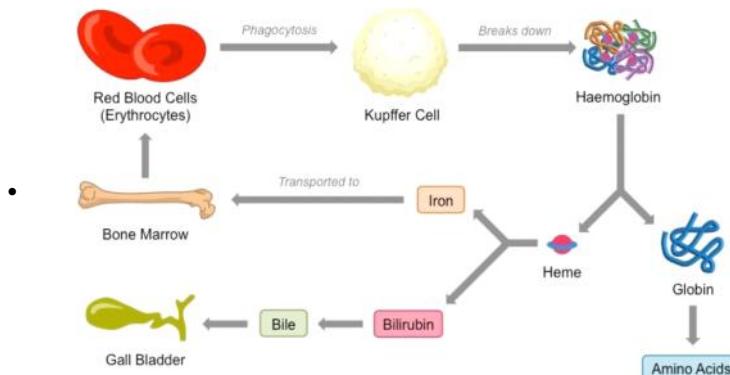
- Left and right lobe are very similar
- Blood enters via hepatic artery and portal system
- Blood leaves by hepatic vein
- Liver has ability for self regeneration
- Hepatocyte: functional unit of liver
- Nutrient storage, bile production, detoxification, plasma production (albumin)
- Cytochrome P450 is over expressed in liver cells and is a marker for toxicity
- Diagram: Functional unit is lobule



- Blood flows in direction opposite to bile
- Kupffer cells: macrophages in the liver that lie in the sinusoidal space
- Blood flows from hepatic artery and portal vein into the sinusoids towards hepatic vein
- Bile flows from hepatocytes in the bile canaliculi to the bile duct

- Erythrocyte recycling: Spleen is the major graveyard of RBCs. Kupffer cells phagocytose RBCs, and split haemoglobin into haeme (iron is removed from this to release bilirubin, and iron goes to bone marrow cells) + globins (split into amino acids and returned to blood)
- Heme-> biliverdin->bilirubin
- Ferritin stores iron in the liver, transferin transfers Fe in the plasma to bone marrow

Process of Erythrocyte and Haemoglobin Recycling

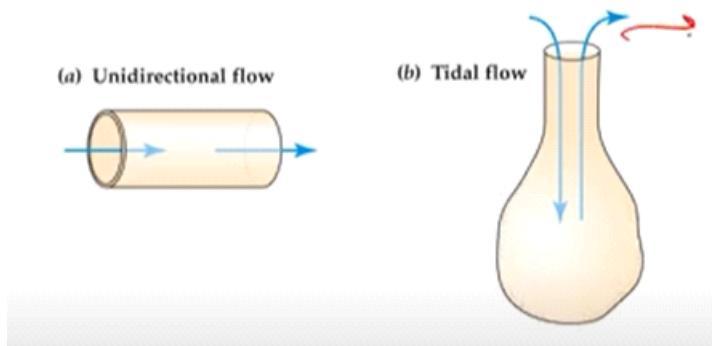


- Liver performs: glycogenesis, glycogenolysis, gluconeogenesis
- Production of plasma proteins, clotting factors.

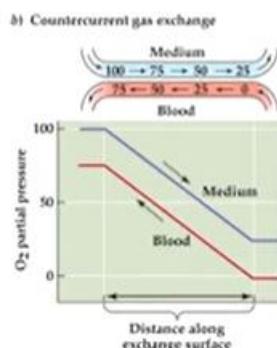
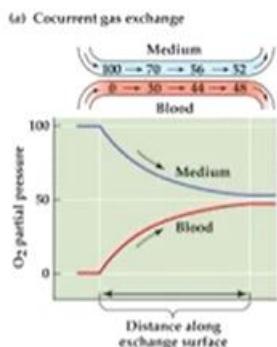
# 19-Principles of gaseous exchange/

14 December 2021 14:39

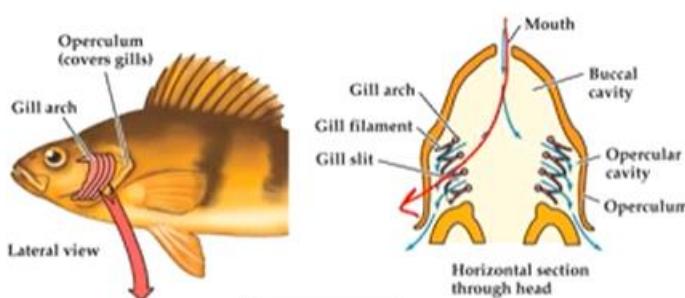
- Diffusion follows Fick's law
- Concentration and partial pressures are different
- Different breathing structures: internal lungs, external gills, internal gills
- The further you go from the air interface,  $pO_2$  drops



Tidal is less efficient

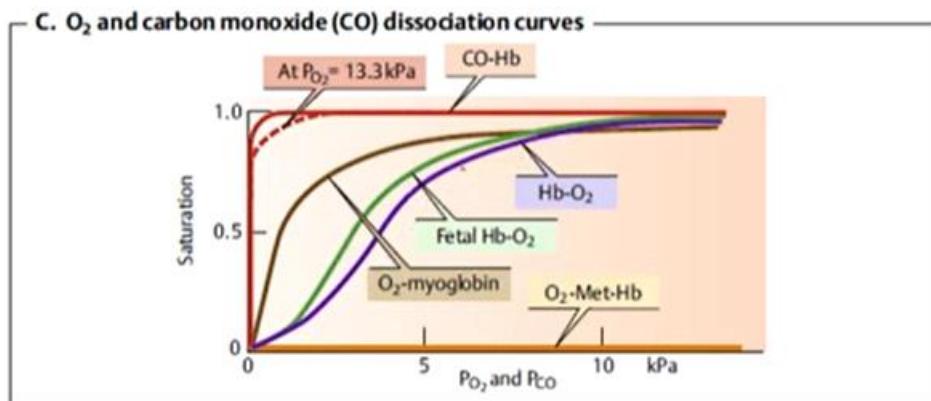
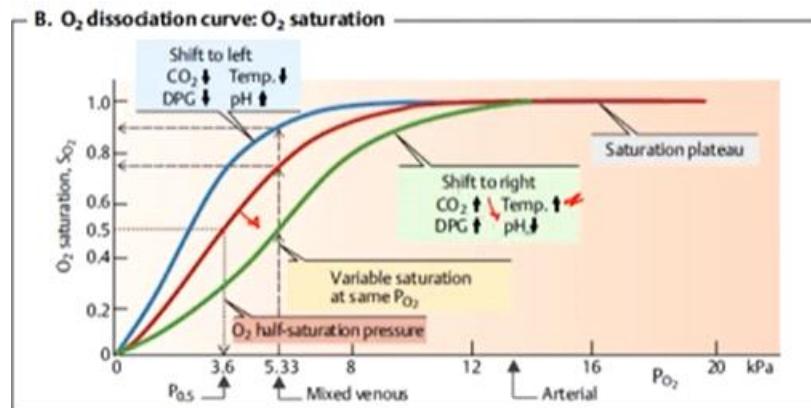


- Countercurrent keep a constant pp difference
- Birds have cross-current system (do not know which is more efficient)
- Breathing in fish:



- Haemoglobin - increases oxygen carrying capacity of cells, transfers  $CO_2$  and  $O_2$  and acts as a buffer

- Antarctic fish do not have respiratory pigment - body is cool enough for high level of saturation
- 2 alpha + 2 beta chains in globin in adult
- Myoglobin - in muscle cells
- 1 Hb - 4 molecules of O<sub>2</sub>
- Tight form of haemoglobin - less binding capacity (few O<sub>2</sub> attached)
- Relaxed form of haemoglobin - more binding affinity (more O<sub>2</sub> attached)
- Example of positive co-operation between proteins
- Fetal haemoglobin: 2 alpha + 2 gamma chains in globin (which has higher affinity)
- More Hb shifts oxygen dissociation curve left
- Low pO<sub>2</sub> → dissociation of O<sub>2</sub> from Hb and vice versa

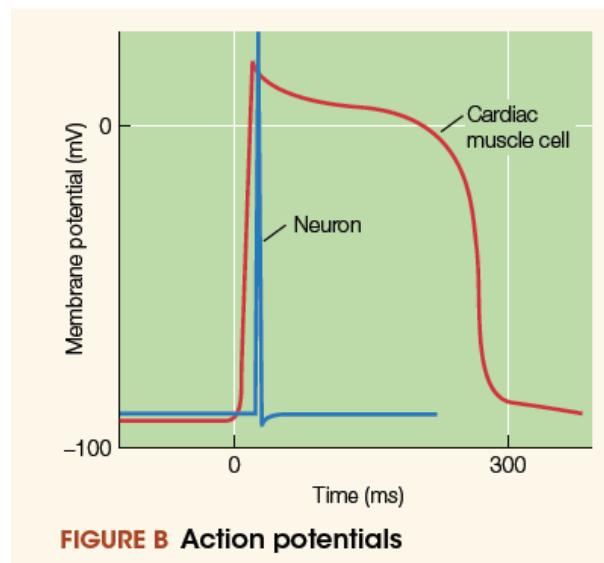


- HCO<sub>3</sub><sup>-</sup> is the main way to transport CO<sub>2</sub>

# 20-Cardiovascular System

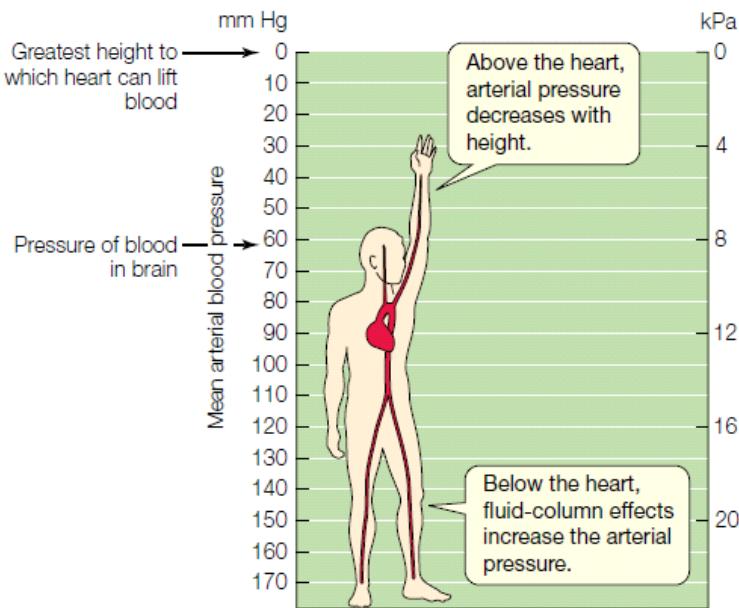
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1. Circulation: pressure driven bulk flow of a body fluid
  - Provides a source of hydraulic pressure for organ function
  - Blood pressure is a stimulus for angiogenesis
2. Cardiac cells are separated by intercalated discs. Strong mechanical adhesion to allow transmission of mechanical force and continuous cytoplasm for electrical conduction across gap junctions
3. The different heart valves open/shut by pressures in the chambers
  - Myocardium is supplied by blood via coronary arteries. In other animals, spongy myocardium allows diffusion of blood from chamber lumen to inside the myocardium.



4. There is a requirement for a long action potential for a sustained contraction of heart muscles
5. Principles of fluid flow in vascular systems
  - In arteries blood pressure rises and falls over the heart cycle
  - Blood pressure: amount by which the pressure of the blood exceed ambient pressure
  - Blood pressure is algebraic sum of pressure by heart + fluid column pressure. To measure just pressure produced by heart, it should be measured in the same horizontal plane as the heart.

(B) Mean blood pressure in major arteries of a quietly standing person



- The blood pressure is higher in the legs than the aorta but blood still flows from aorta to the legs. Blood flows from where its total fluid energy is higher to where total fluid energy is lower.
- For a person lying flat, we can assume that the pressure due to fluid column is same everywhere
- The rate of flow in blood vessel can be determined by Poiseuille's equation. Rate of flow is directly proportional to fourth power of radius
- Blood passing through a vessel experiences a drop in pressure due to loss of energy due to viscosity

#### 7. Arteries

- Highly elastic to stretch to receive blood of varying pressures and maintain a mostly steady pressure. (pressure damping effect and pressure reservoir effect)
- Blood pressure does not drop substantially as blood flows through arteries, but the walls get thinner and the capillaries get smaller. However the thin walls are still able to withstand high blood pressure (which is almost same as main arteries) explained by Laplace Law (circumferential tension = radius \* ΔP)
- Arterioles have thick muscular walls required for vasoconstrictor control of blood flow by changing the radius.

#### 8. Capillaries

- Only single layer of vascular endothelium
- Contain small gaps between cells
- Very dense in skeletal muscles, myocardium and brain

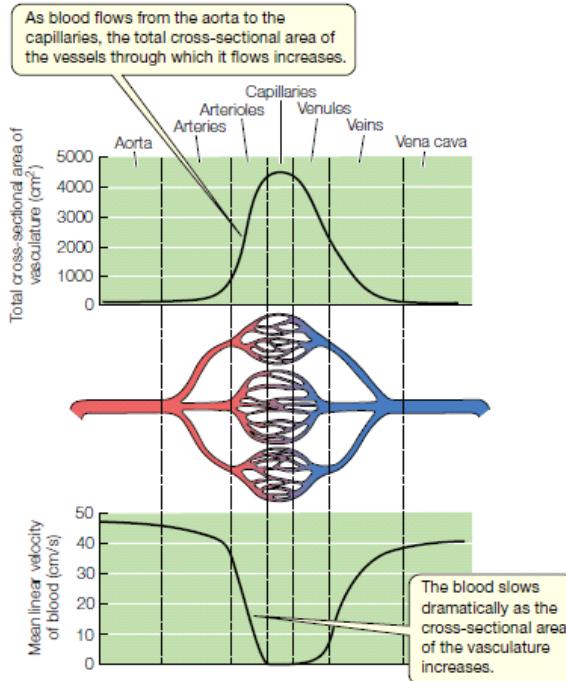
#### 9. Veins

- Blood pressure declines after leaving capillaries, so veins do not require elastic walls to withstand pressure
- They contain valves ensure consistent flow towards heart

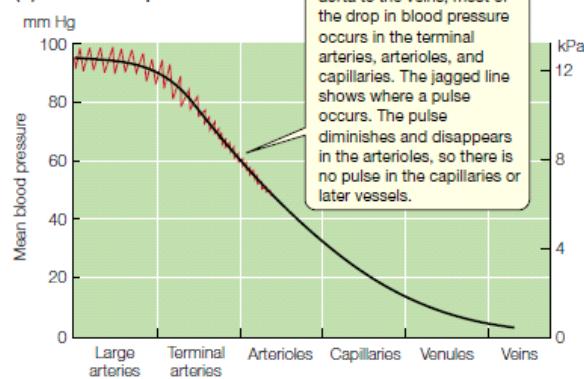
#### 10. Dynamics of blood flow

- Blood pressures are highest among birds and mammals
- As blood enters microcirculatory beds, linear velocity drops as total cross sectional area increases. Slow flow allows the blood to remain long enough for exchange with tissues
- Blood pressure drops dramatically as it passes through the capillaries due to increased resistance

(A) Vascular cross-sectional area and blood linear velocity



(B) Mean blood pressure



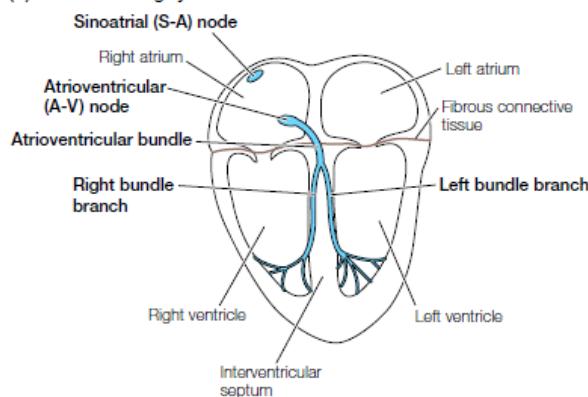
11. Fluid exchanges

- Difference in hydrostatic pressure between blood plasma and the ECF favours movement of water into the tissue while osmotic pressure is higher in the blood and favours movement of water from ECF to the plasma
- Volume of blood passing per unit time is same in pulmonary and systemic circulations because they are connected in series. The pulmonary pathway is low resistance and hence low arterial pressure is needed to drive fluid. Hence plasma does not move too much into the alveoli

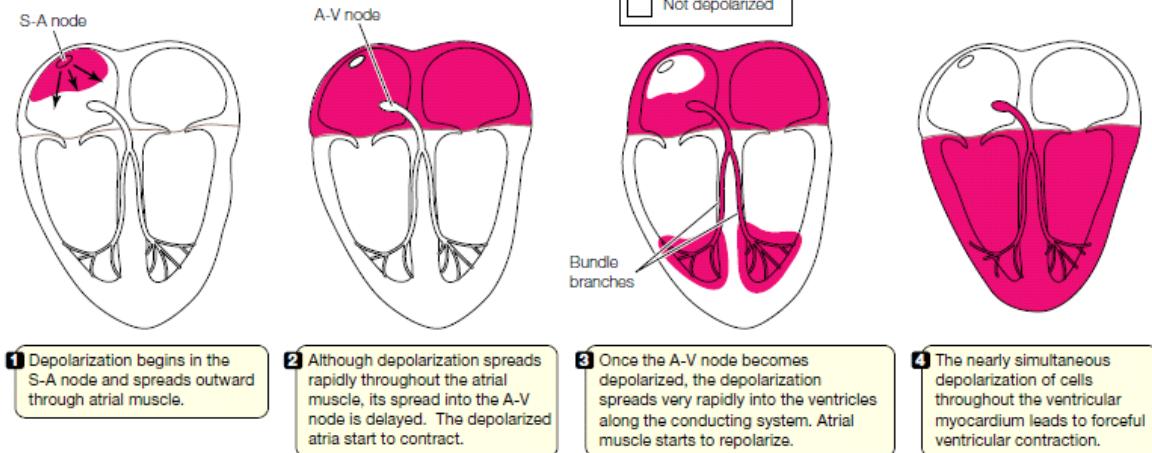
12. Electrical impulse conduction in the heart

- Most vertebrate hearts and myogenic.
- Impulse from one part can be rapidly conducted to all parts of the heart
- SA node: modified muscle cells with poor contractility with ability for spontaneous depolarization
- The atrial and ventricular myocardium is separated by connective tissue impermeable to electrical conduction. There is an additional conductive system (AV node, Bundle of His, Purkinje fibres) that play a role in the sequential contraction of the chambers.

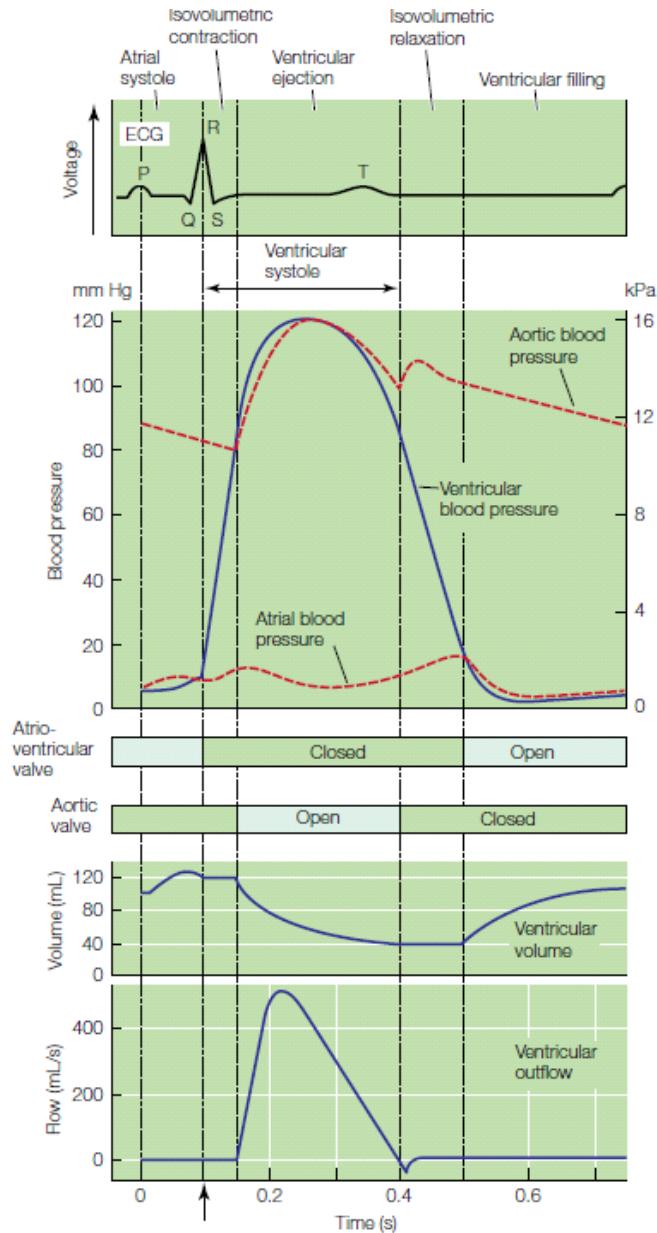
## (A) The conducting system and sinoatrial node



## (B) The initiation and spread of depolarization during a heartbeat



**FIGURE 25.4 The conducting system and the process of conduction in the mammalian heart** (A) The morphological arrangement of the conducting system and the position of the sino-atrial node. The branches of the right and left bundle branches are in fact more elaborate than shown; traveling along the inner surfaces of the ventricles and across the ventricular cavities, they run to much of the inner wall of each ventricle. (B) The initiation and conduction of depolarization during a heartbeat. Box 7.5 shows actual images of the spread of depolarization in the surface layers of the ventricles. (A after Scher and Spach 1979; B after Rushmer 1976.)



**FIGURE 25.2 The heart as a pump: The dynamics of the left side of the human heart** The heart cycle is divided into five phases, labeled at the top and demarcated by the vertical lines that run through the diagram. The diagram shows the synchronous changes that occur in left ventricular blood pressure, systemic aortic blood pressure, left atrial blood pressure, ventricular volume, the rate of blood flow out of the ventricle, and the closing and opening of the atrioventricular and aortic valves in humans at rest. The arrow at the bottom marks the start of ventricular systole. The ECG (see top panel) is the electrocardiogram discussed later in this chapter.

At the time marked by the arrow at the bottom of Figure 25.2, ventricular systole begins. Whereas the pressure inside the ventricle was lower than that inside the atrium during the time just before the arrow, as soon as the ventricle starts to contract (marked by the arrow), the ventricular pressure rises abruptly to exceed the atrial pressure, causing the atrioventricular valve between the chambers to flip shut. For a brief interval of time (about 0.05 s), however, the ventricular pressure remains below the pressure in the systemic aorta, meaning that the aortic valve is not forced open. During this interval, therefore, both the inflow and outflow valves of the ventricle are shut. The volume of blood in the ventricle during this time is thus constant, and the interval is called the phase of **isovolumetric contraction** ("contraction with unchanging volume") or **isometric**

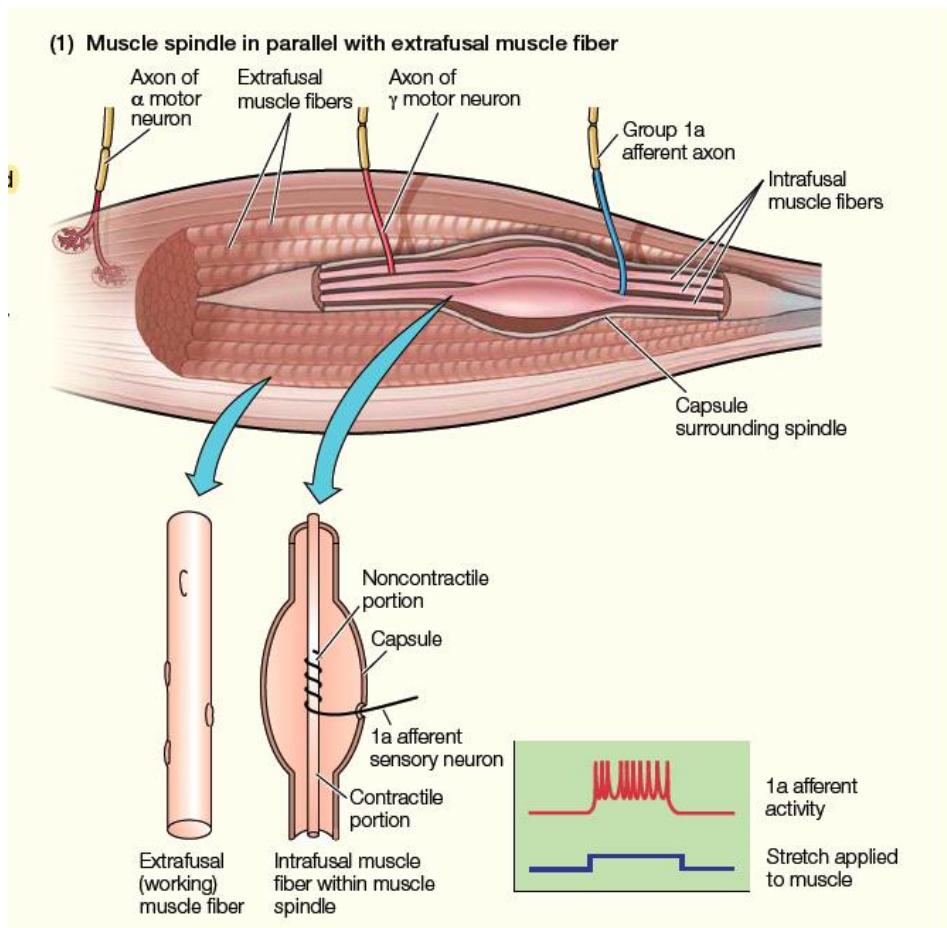
**contraction.** The contraction of the ventricle on the fixed volume of blood within causes the blood pressure inside the ventricle to rise rapidly. As soon as the ventricular pressure rises high enough to exceed the aortic pressure, the aortic valve flips open, and the blood in the ventricle accelerates extremely rapidly, gushing out into the aorta (thus increasing aortic pressure). The opening of the aortic valve marks the start of the phase of **ventricular ejection**. Toward the end of this phase, the aortic pressure comes to exceed the ventricular pressure slightly, but ejection of blood into the aorta continues for a while—at a rapidly falling rate—because of blood momentum. Ultimately, the ventricle starts to relax. The ventricular pressure then falls rapidly away from the aortic pressure, and the aortic valve shuts. A period of **isovolumetric relaxation** follows, as ventricular pressure falls with both the inflow and outflow valves shut. When the ventricular pressure drops below the atrial pressure, the atrioventricular valve opens inward to the ventricle, and **ventricular filling** begins. Most filling of the ventricle occurs *before* atrial systole—that is, before the atrial muscle contracts; the motive force for this filling is the pressure built up by *accumulation* of pulmonary venous blood in the atrium. When atrial systole occurs, it forces some additional blood into the ventricle just before the next ventricular systole.

# 21- Muscles

12 February 2022 10:37

## 1. Muscle spindles

- **Proprioceptor:** mechanoreceptors associated with musculoskeletal system
- Muscle spindle: monitors length of muscle, allows knowledge of where muscle
- Intrafusal fibres: associated with **group 1a afferent neurons**. When muscle is stretched, action potential is generated. Fibres do not generate much tension.
- **Gamma motor neurons:** cause small contractions in intrafusal fibres and cause stretch of intrafusal fibres, activating 1a afferent neurons (sending out 'stretched signal')
- **Alpha neurons:** to the contractile extrafusal load bearing fibres

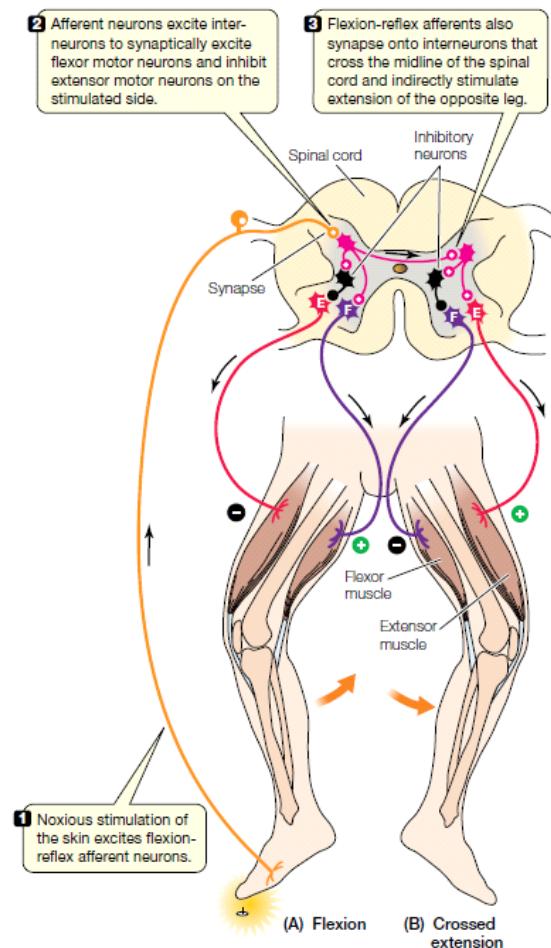


## 2. Stretch reflex

- Tends to oppose muscle stretch. If muscle is stretched, causes muscle to contract
- **1a afferent neurons** directly innervate motor neuron in the reflex arc without interneurons. Lead to EPSPs in motor neuron and contraction in muscle
- **Principle of reciprocity:** coordination of contraction of one muscle and inhibition of contraction of antagonistic muscle. Prevents counteracting muscle contractions
- Divergence: each presynaptic feeds into many post synaptic
- Convergence: many postsynaptic feed into presynaptic
- Stretch reflex maintains posture against changes

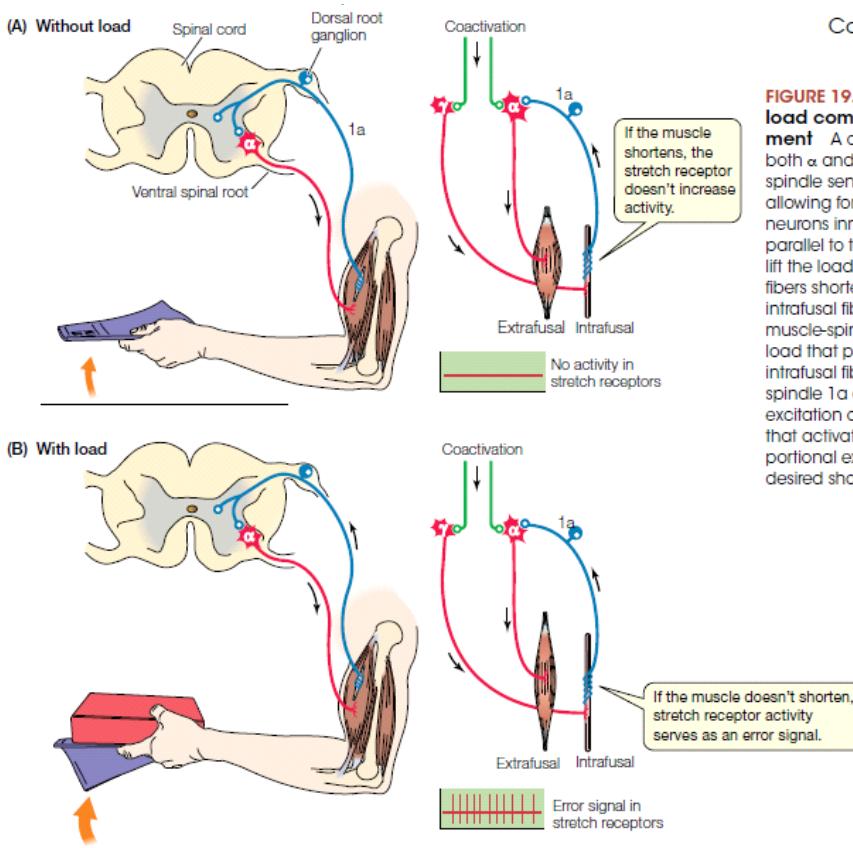
## 2. Flexion reflex

- **Stimulus causes flexion** (removal of foot after stepping on sharp object)



**FIGURE 19.2 The neural circuit of the flexion reflex and the crossed extension reflex.** The flexion reflex mediates protective withdrawal of a limb (A), whereas the crossed extension reflex extends the opposite limb for compensatory support (B). Smaller arrows indicate direction of nerve impulse propagation; plus signs (+) indicate increases in activity, and minus signs (-) indicate decreases. Open circles indicate excitatory synapses; closed circles are inhibitory synapses. F, flexor motor neuron; E, extensor motor neuron.

3. CNS is primary activator of motor neurons while spinal reflex is secondary and acts to provide sensory feedback about muscle contraction status and mediate stretch compensation
4. Stretch reflex mediated load compensation



## 5. Locust flight

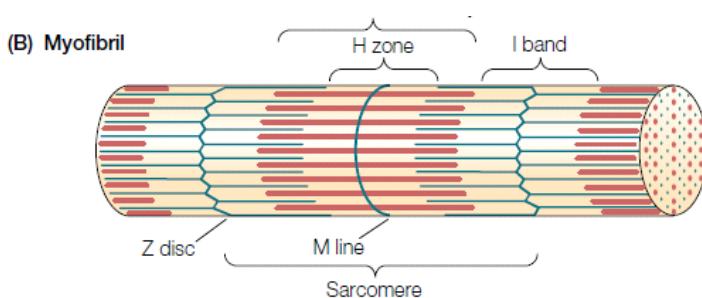
- Rhythmic behaviour: motor output is stable, repetitive, predictable and cyclic
- Alternating activation of levator muscles to bring wings up, and depressor muscles to bring wings down
- Peripheral control hypothesis: receptors which sense the location of wing (up or down) are responsible for driving cyclic behaviour (wing sensed up-activate depressor-wing sensed down-activate levator)
- Central control hypothesis: a neural circuit (control pattern generator) is responsible
- CPG is sufficient for flight but is supplemented by peripheral information

## 6. Different skeletal muscle types

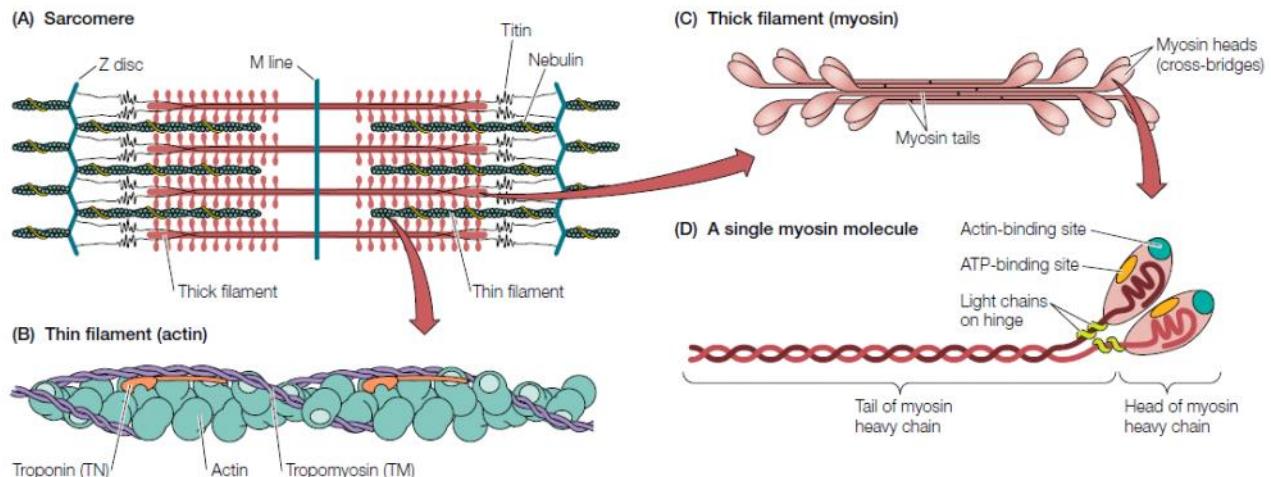
Type 1 - Slow oxidative	Type 2A - Fast oxidative glycolytic	Type 2B - Fast glycolytic
Red oxidative fibers	Oxidative glycolytic fibers	Glycolytic fibers, reliance on anaerobic
Abundant myoglobin	Abundant myoglobin	Less myoglobin
Slow	Intermediate	Fast
Slow, continued contraction: maintain posture	Rapid contractions and short bursts of activities	Small muscles to move hands and eyes
More mitochondria	Many mitochondria	Fewer mitochondria
Slow to fatigue	Slow to fatigue	Fast to fatigue

## 7. Muscle structure

- Each fascicle contains many muscle fibers, each muscle fiber has many myofibrils
- Cells are multinucleate
- Each myofibril is 1-2  $\mu\text{m}$  in diameter and is as long as the muscle fibre
- 1 sarcomere: between two adjacent Z lines



## 8. Sarcomere



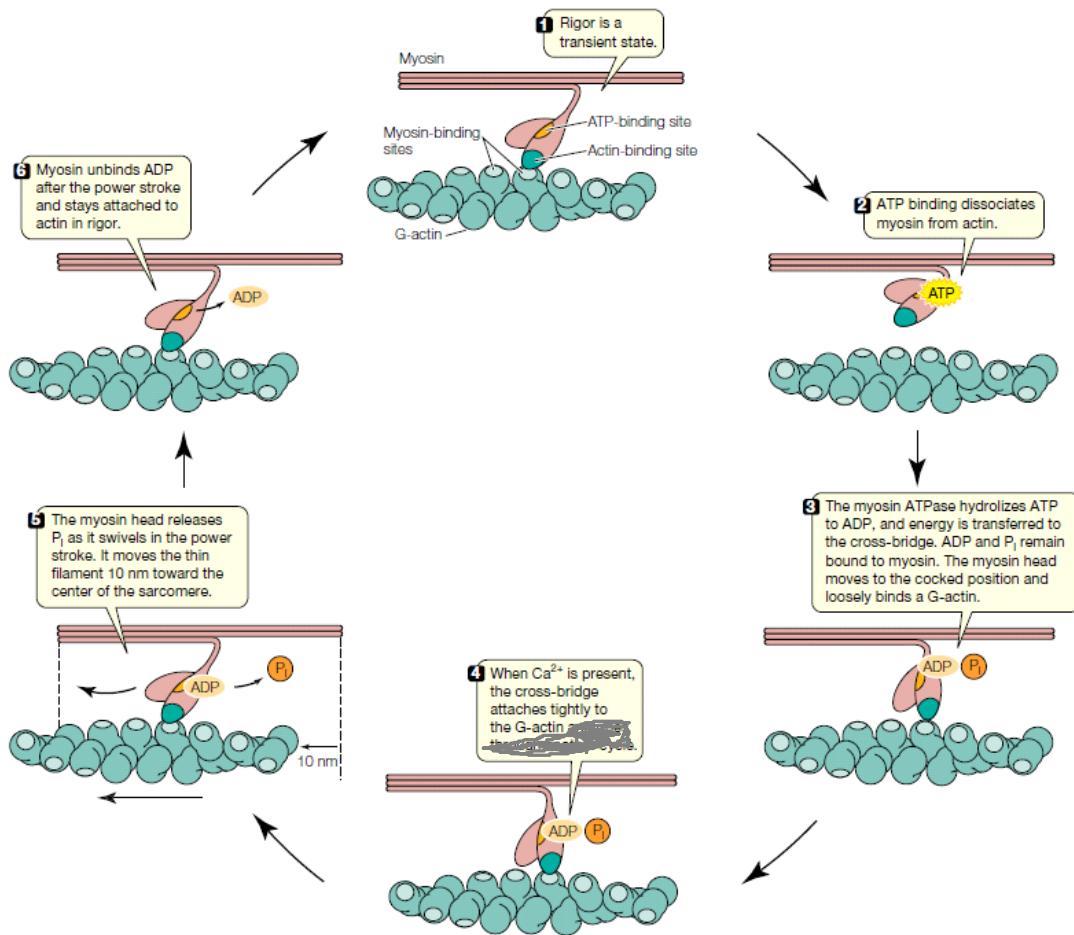
**FIGURE 20.2 The sarcomere is the functional unit of striated muscle** (A) Thick and thin myofilaments overlap and slide by each other to generate contractions. (B) Each thin filament is made of two chains of globular actin molecules arranged in a loose helix. The regulatory proteins tropomyosin (TM) and troponin (TN) are also components of the thin filament. (C) Myosin molecules form the thick filament. (D) Each myosin molecule contains two heavy chains of amino acids. The two chains coiled around each other form the tail. The amino-terminal end of each heavy chain forms one of the heads. The head

region has a site for binding actin and a different site for binding and hydrolyzing ATP. A hinge region connects the head to the tail. The myosin molecule also includes two smaller light chains associated with each head. Thus each complete myosin molecule contains six polypeptide chains: two heavy and four light. The molecular composition of the heavy and light chains varies in different types of muscles. The different myosin isoforms of heavy chains and light chains confer variations of functional properties, such as the rate at which the myosin ATPase hydrolyzes ATP.

- Actin filaments are anchored to the Z disc. Formed by a helix of F actin (which itself is composed of G actin)
- Myosin ATP binding site contains ATPase activity
- A band: Have myosin chains and actin filaments (partially)
- I band: Only actin filaments and are lighter
- H zone: only contains myosin filaments
- Titin: runs from the Z disc to the M line, confers extensibility to the fibres
- Nebulin: runs the length of the actin filament and stabilizes it
- Dystrophin: anchors the actin to the sarcolemma

## 9. Contraction of the sarcomere- Sliding filament theory

- The filaments do not shorten but rather they slide by each other and the actin is drawn towards the M zone

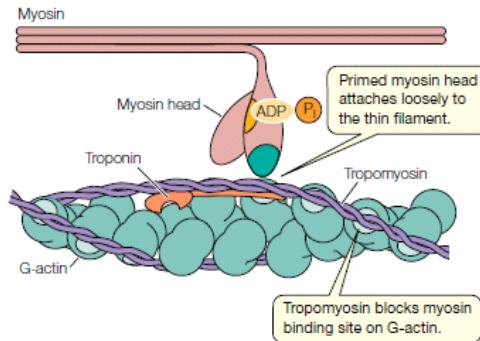


**FIGURE 20.5 A single cross-bridge cycle uses one molecule of ATP and moves the actin filament about 10 nm. Each cross-bridge goes through several cycles during a single contraction.**

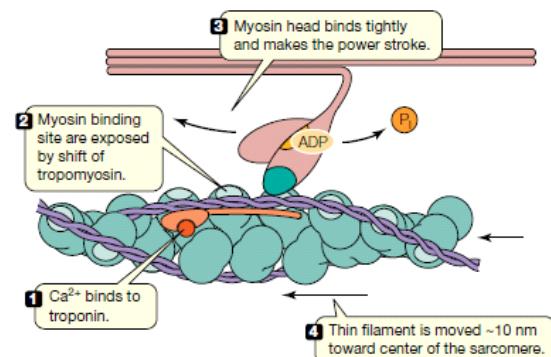
The two myosin heads function independently, and only one binds to actin at a time. Structural studies suggest that no more than four myosin heads can attach over a span of seven G-actin monomers.

- **The cross bridges operate asynchronously and independently**
- In resting state is step 3 where ADP+Pi is bound but in the absence of calcium is unable to form a strong crosslink
- **Intracellular concentrations of  $Ca^{2+}$  are kept below  $10^{-7} M$  and  $Ca^{2+}$  is the main modulator of muscle activity**
  - ◊ During contraction the H band and the I band shorten. A band is the same size

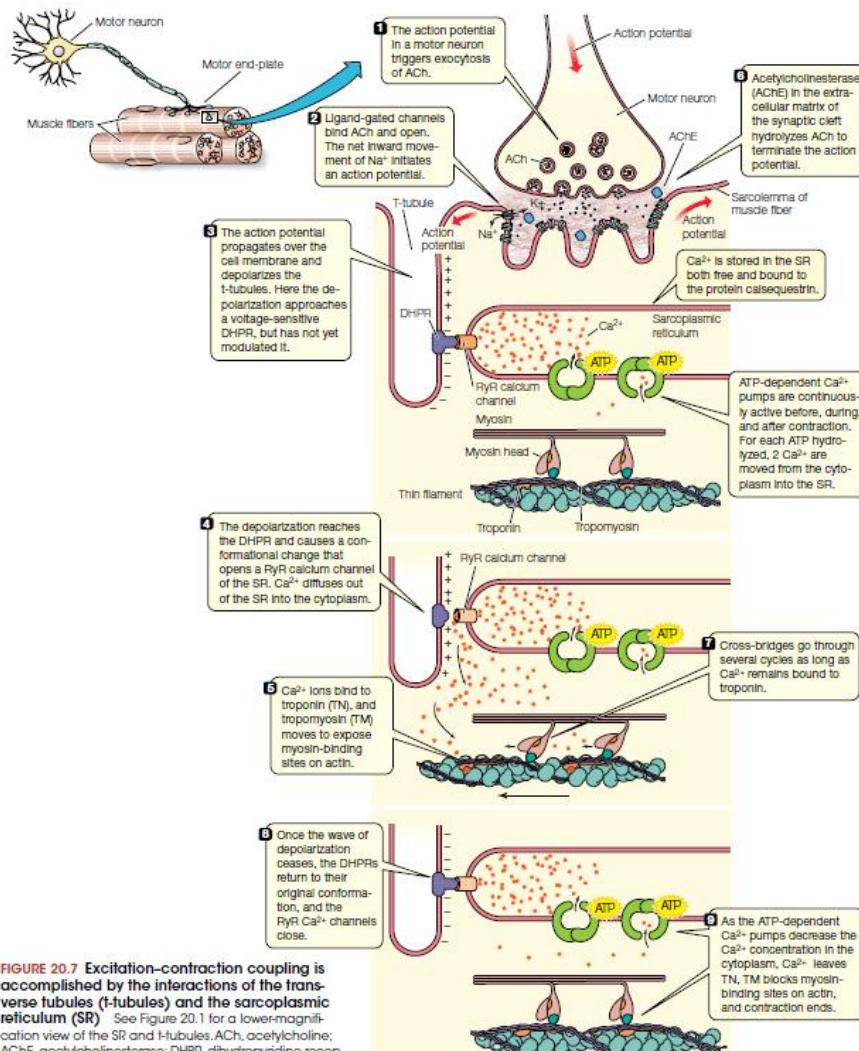
(A) A muscle cell is relaxed when no  $\text{Ca}^{2+}$  ions are present in the cytoplasm



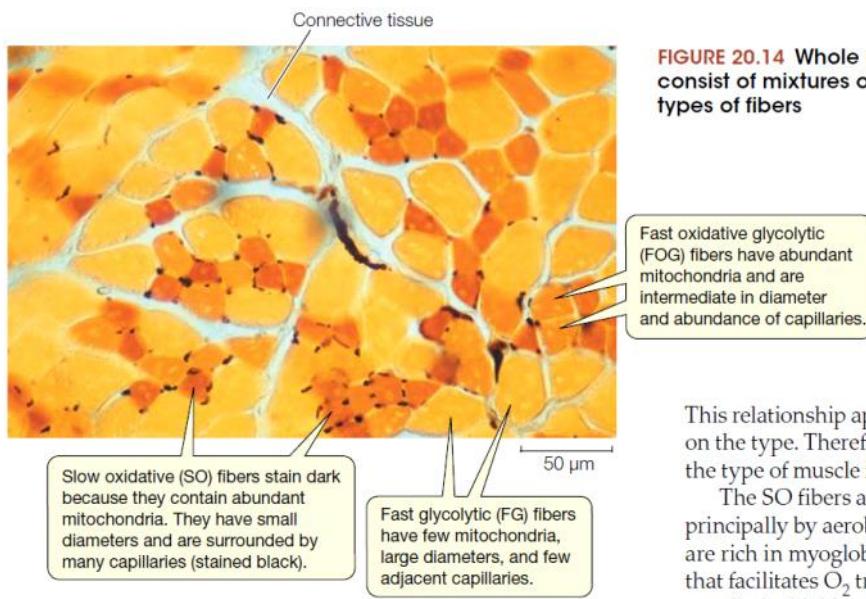
(B)  $\text{Ca}^{2+}$  ions released from the SR permit cross-bridge action



**FIGURE 20.6**  $\text{Ca}^{2+}$  ions, troponin (TN), and tropomyosin (TM) regulate contraction (A) When  $\text{Ca}^{2+}$  ions are scarce in the cytoplasm, the TN-I subunit binds to two adjacent actin monomers, and the TN-T subunit binds to the tropomyosin molecule. These connections hold TM in a position that covers the myosin-binding sites on actin and inhibits cross-bridge action. (B) The TN-C subunit binds to  $\text{Ca}^{2+}$  ions when they are released from the sarcoplasmic reticulum. This binding causes conformational changes that detach TN-I from actin and allow TM to roll over the actin surface. The changed position of TM, as well as allosteric changes, permits cross-bridge action.



**FIGURE 20.7** Excitation-contraction coupling is accomplished by the interactions of the transverse tubules (T-tubules) and the sarcoplasmic reticulum (SR). See Figure 20.1 for a lower-magnification view of the SR and T-tubules. ACh, acetylcholine; AChE, acetylcholinesterase; DHPR, dihydropyridine receptor; RyR, ryanodine receptor.



**FIGURE 20.14** Whole muscles consist of mixtures of different types of fibers

This relationship applies on the type. Therefore the type of muscle fiber

The SO fibers are mainly supplied by aerobic capillaries. They are rich in myoglobin (a protein that facilitates  $\text{O}_2$  transport) and are supplied with blood capillaries.

## 10. Smooth muscles

- Actin and myosin is not organized into sarcomeres hence the unstriated appearance
- Do not have T tubules, nebulin. They are uninucleate and are spindle shaped

Single unit smooth muscles	Multiunit smooth muscles
Most cells are electrically coupled via gap junctions	Cells not coupled as much, individual cells are under direct neuronal control
Function and contract as one unit	Contract as multifunctional unit

GI tract, vasoconstrictors

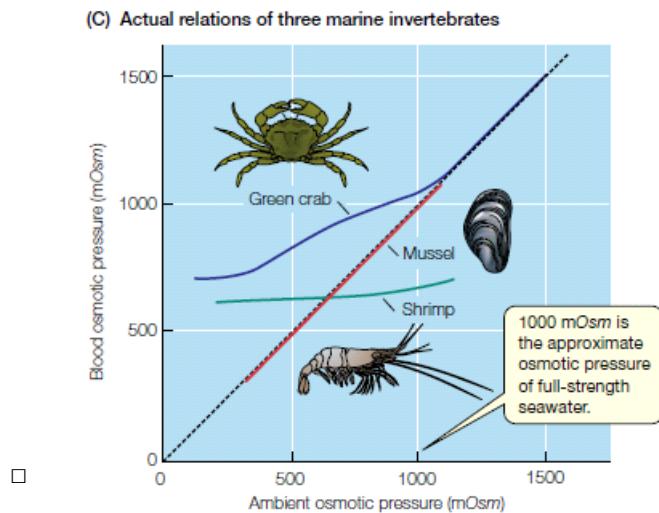
Hair erectors, large arteries

- Smooth muscles do not use troponin or tropomyosin to regulate contraction. It is activated by myosin light chain kinase (MLCK) which itself is activated by calmodulin-Ca<sup>2+</sup> activity

# 22- Osmoregulation

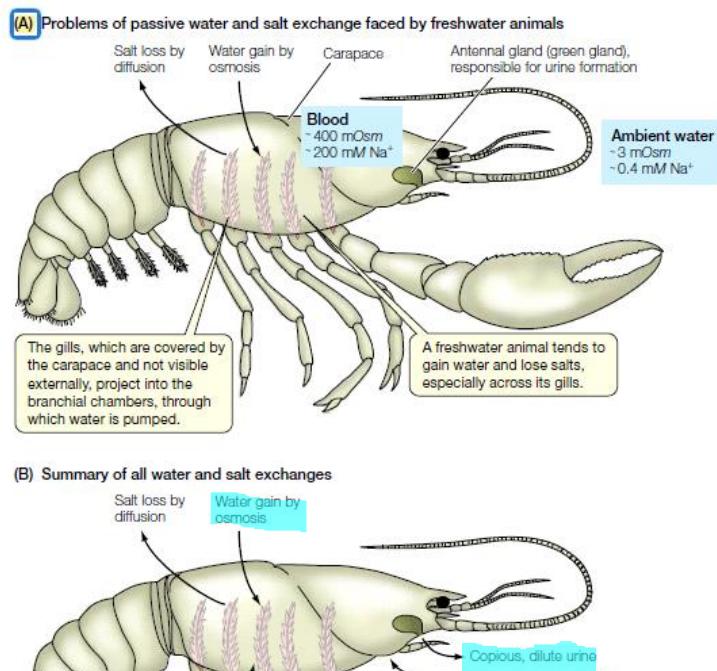
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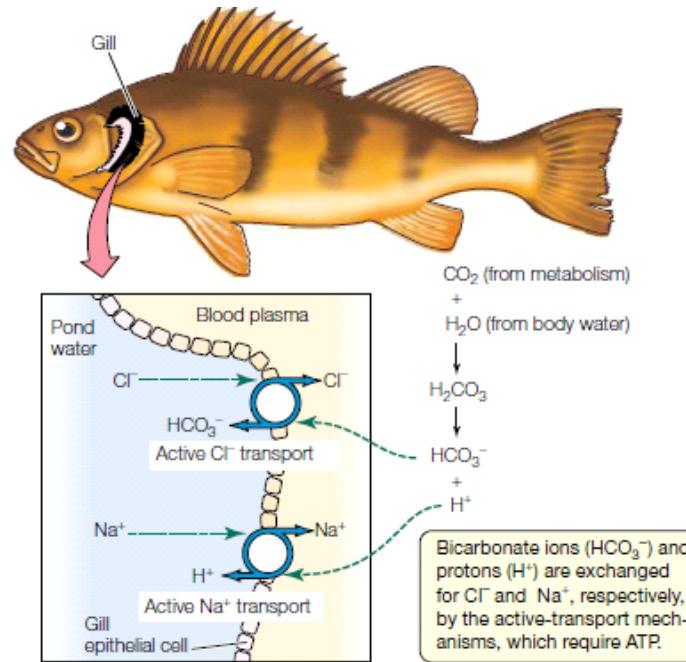
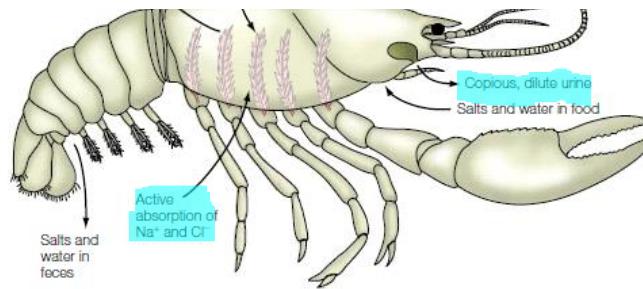
- Three types of body fluid composition maintenance are possible
  - Osmotic regulation
  - Ionic regulation
  - Volume regulation
- There three forms are distinct from each other



**FIGURE 27.3 Osmotic regulation and conformity** In each graph, each solid line shows the osmotic pressure of blood plasma as a function of the ambient (environmental) osmotic pressure; the dashed line is a line of equality between blood osmotic pressure and ambient osmotic pressure (an isosmotic line). Osmotic pressures are expressed in units of milliosmolarity (mOsm). (A, B) The osmotic pressure of the blood plasma as a function of the osmotic pressure of the ambient water in (A) a perfect osmotic regulator and (B) a perfect osmotic conformer. (C) The osmotic pressure of the blood plasma as a function of the ambient osmotic pressure is shown for three species of marine invertebrates: *Mytilus edulis*, the blue mussel; *Carcinus maenas*, the green crab; and *Palaemonetes varians*, a species of grass shrimp. The mussel is a strict osmotic conformer. The crab regulates in waters more dilute than seawater but is an osmotic conformer at higher ambient osmotic pressures. The shrimp regulates over a wide range of ambient osmotic pressures. (C after Hill and Wyse 1989.)

## 2. Osmoregulation in freshwater organisms

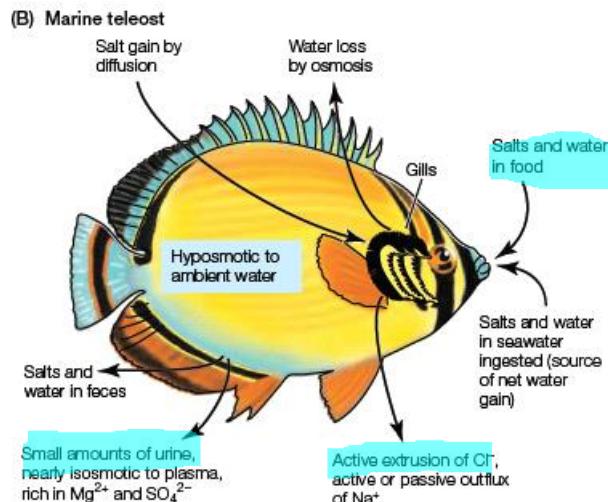




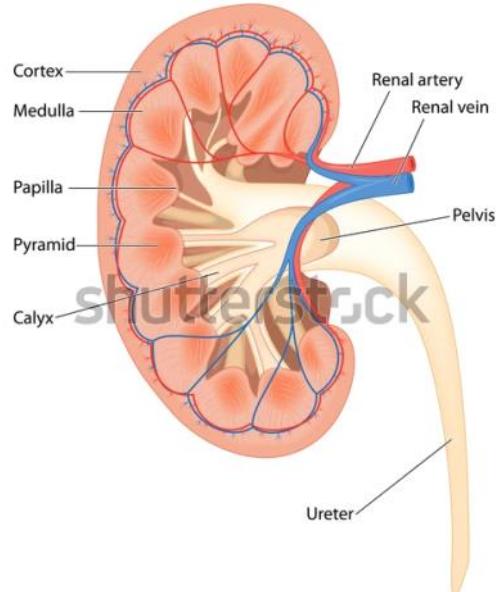
**FIGURE 28.2 Ion exchanges mediated by active  $\text{Na}^+$  and  $\text{Cl}^-$  transport in the gill epithelium of freshwater teleost fish** The mechanisms of active transport exist within single epithelial cells. The view here is a whole-epithelium view and therefore, as discussed in Chapter 5 (see Figure 5.14), does not specify the cell-membrane mechanisms involved. The cell-membrane mechanisms are discussed in Box 5.2.

- The gills cells have high mitochondrial content to increase energy production needed for active transport of ions from the ambient environment (low concentration) to body fluid (high concentration)

### 3. Osmoregulation in marine animals



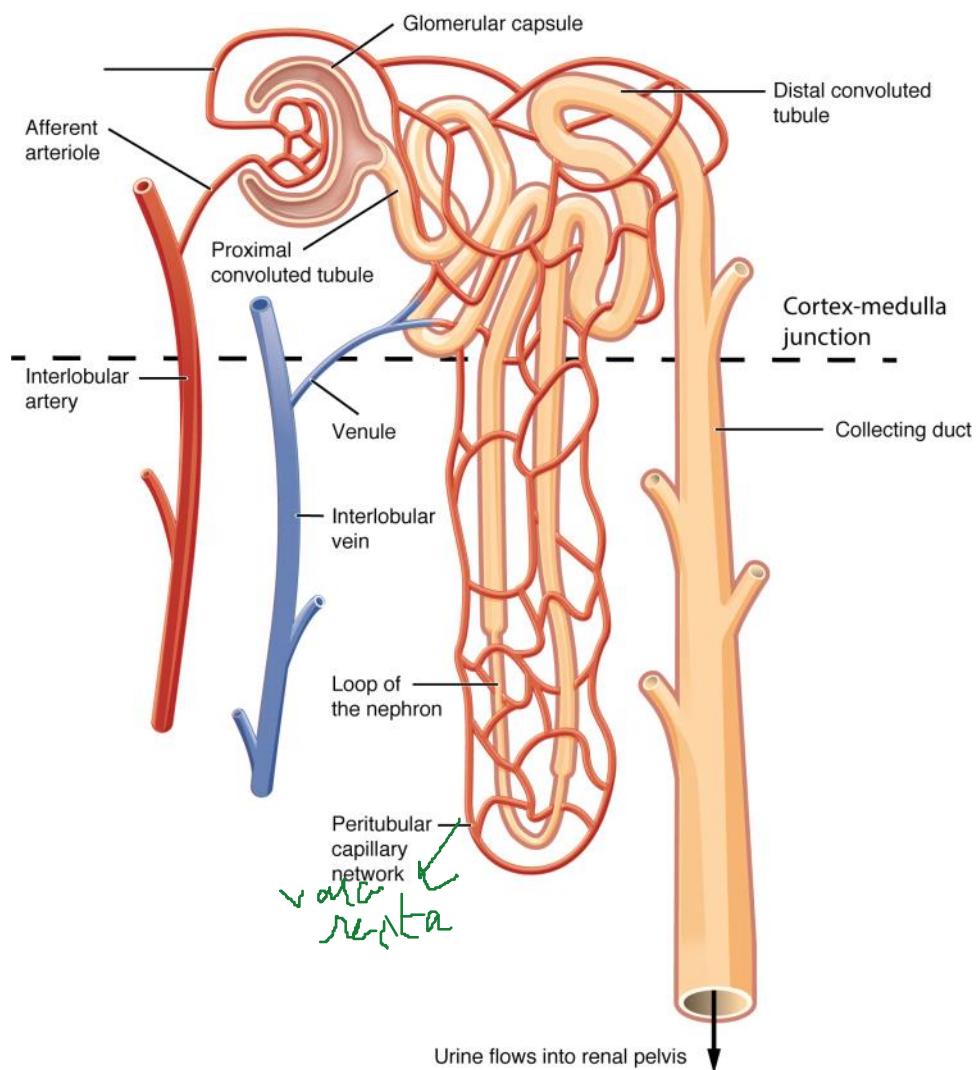
### 4. Cross section of kidney



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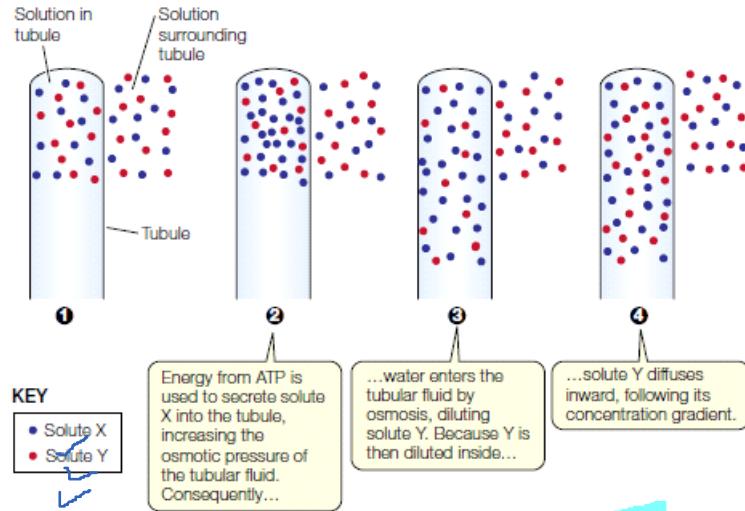
##### 5. Structure of nephron

- Some nephrons have juxtamedullary bowman's capsule and long loop of Henle that extend into the medulla



##### 6. Active solute secretion

- One of the other methods (apart from ultrafiltration) for the formation of primary urine



**FIGURE 29.2 Formation of primary urine by active solute secretion**

In this model system, there are two uncharged solutes. Although the renal tubule is completely surrounded by the outside solution, only a small sample of the outside solution is shown at the upper right of the tubule in each step. For simplicity, the outside solution is assumed to stay constant in volume and composition. Movement of water into the tubule is represented by an increase in the length of the tubule filled with solution.

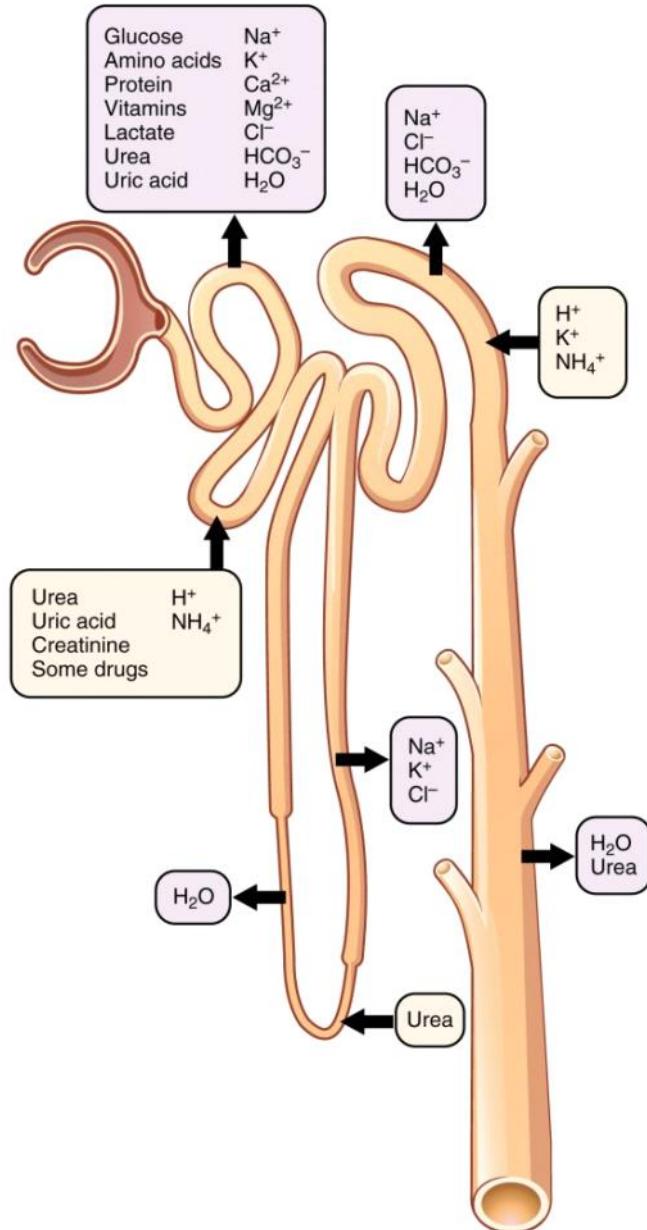
## 6. Functions of kidney

- Maintaining osmolarity
- Maintain pH
- Removing metabolic wastes
- Reabsorbing useful substances
- Endocrine organ

## 7. Ultrafiltration

- The net hydrostatic pressure inside the glomerulus drive ultrafiltration
- Primary urine is produced after ultrafiltration
- Nephrons are made of a single layer of epithelial cells
- Glomerular filtration rate: rate of primary urine formation by ultrafiltration
- GFR greatly exceeds the rate of excretion implying that most of the water of primary urine is reabsorbed
- Podocytes in the bowman's capsule form pores
- +Blood pressure inside the glomerulus  
-Colloidal osmotic pressure from inside the capsule  
-Capsule fluid hydrostatic pressure
- The afferent arterioles are responsible for determining the GFR

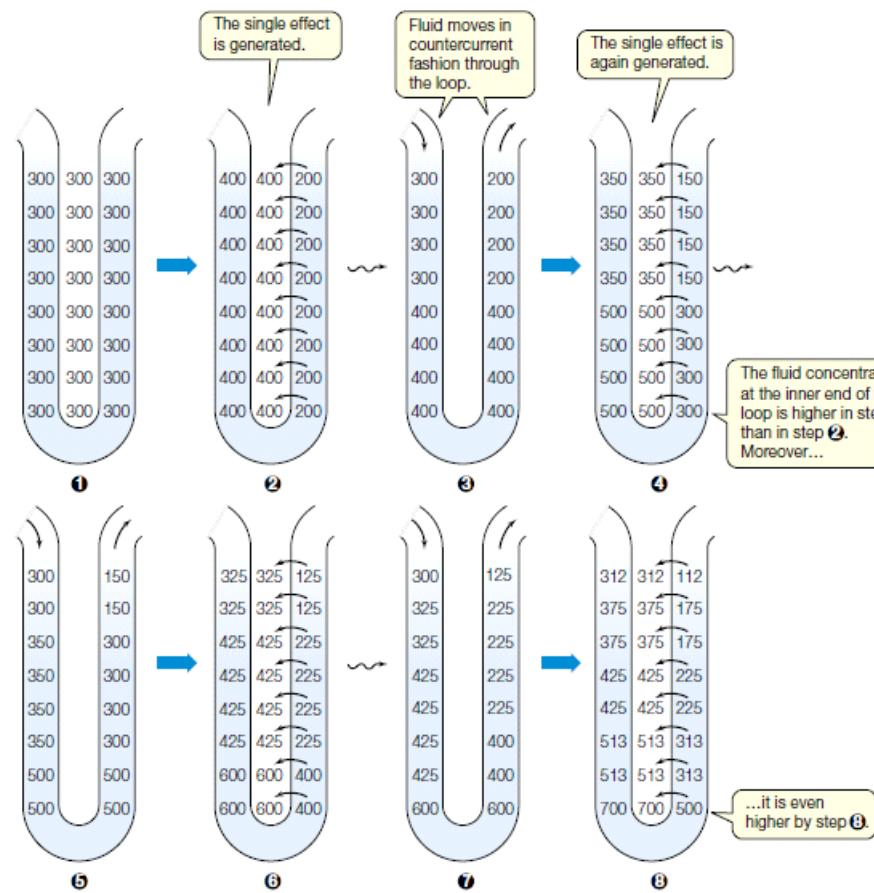
## 8. Reabsorption



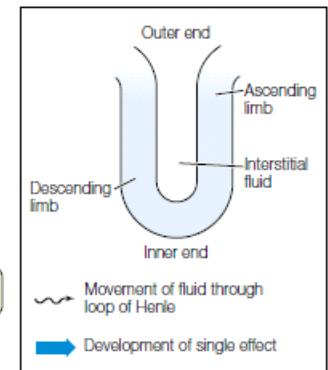
- Processes that occur after primary urine formation are the predominant regulatory processes
  - The epithelium along the length of the nephron have different transporters and membranes
  - The concentration of nonurea solutes as the urine moves through the nephron is due to the exit of water
  - Medullary interstitial fluids are high concentration and concentration increases in depth with the medulla. As urine passes through the collecting duct through the medulla, more water moves into the interstitial fluid of medulla
9. Single effect
- Ascending limb actively pumps out NaCl into the interstitial fluid, creating a osmolarity gradient. NaCl concentration and osmotic pressure drops
  - Water moves out from the descending limb and reaches equilibrium with the interstitial fluid. NaCl also enters. Pressure and concentration rises in the ascending limb to match the interstitial fluid
  - Single effect is created by ATP expenditure
  - Single effect generates a side-to-side osmolarity gradient of 200
10. Countercurrent multiplier
- Countercurrent multiplier uses the single effect to generate an end-to-end osmolarity gradient of 600
  - This end-to-end gradient is what allows urine to be concentrated as it passes deeper through the medulla via the collecting ducts
  - Single effect -> 200 difference between ascending limb and interstitial fluid -> osmolarity rises in interstitial fluid -> osmolarity rises up in descending tube to match it -> fluid moves through the loop

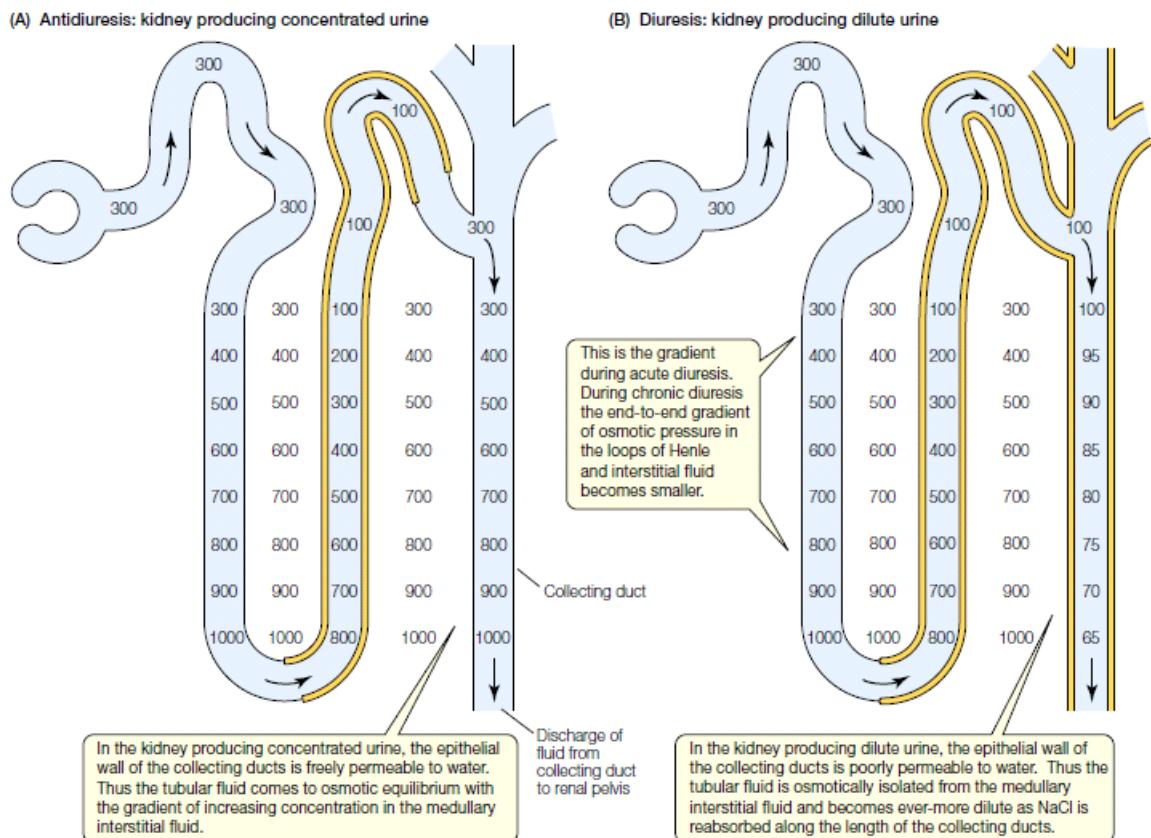
and process it repeated

(B) The process of countercurrent multiplication



KEY





**FIGURE 29.14 Osmotic pressures attributable to nonurea solutes in the nephrons and collecting ducts during antidiuresis and diuresis** Thick yellow borders symbolize tubules that are poorly permeable to water. Tubules without yellow borders are permeable to water. The change in the water permeability of the collecting ducts between antidiuresis (A) and diuresis (B) is mediated by insertion and

removal of aquaporins in apical cell membranes of the collecting-duct epithelium, as discussed later. The interstitial fluids (white areas) exhibit similar gradients of osmotic pressure throughout the medulla. The numbers, expressed in units of milliosmolarity, are approximate and intended only to illustrate general trends.

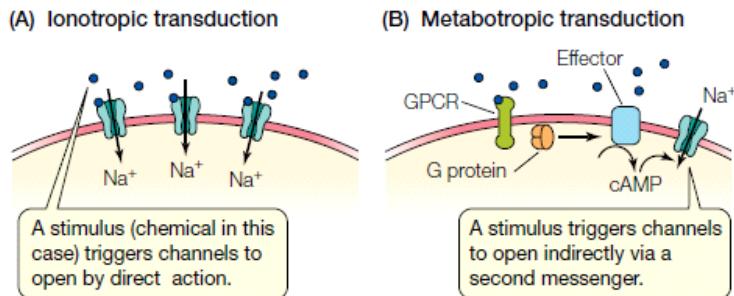
Countercurrent multiplier	Counter current exchanges
Relies on active transport to set up a gradient	No use of energy
Creation of gradient	Exacerbate existing gradient

11. Regulation
  - Aldosterone increases NaCl and water reabsorption by upregulating Na<sup>+</sup>/K<sup>+</sup> ATPase sodium channel
  - ADH increases permeability of DCT to water allowing for greater water reuptake by increasing the concentration of aquaporins. It is stimulated by increase in blood osmotic pressure and more concentrated urine is released
12. Adrenal glands
  - Androgens
  - Glucocorticoids
  - Corticosterone
  - Mineralocorticoids such as aldosterone
  - Catecholamines such as adrenaline
13. Regulation of blood volume
  - Juxtaglomerular cells (JG cells), also known as granular cells are cells in the kidney that synthesize, store, and secrete the enzyme renin. Stimulated by a drop in BP
  - Angiotensinogen --renin--> angiotensin 1 ---ACE---> angiotensin 2
  - Angiotensin 2 stimulates constriction of systemic arterioles, promotes thirst, stimulates ADH and aldosterone production. Net effect to increase mean arterial blood pressure by raising blood volume

# 23-Sensory systems

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Metabotropic receptors	Ionotropic receptors
1. Mechanoreception, thermo, electro and some forms of taste perception	Vision, vertebrate olfaction, some taste

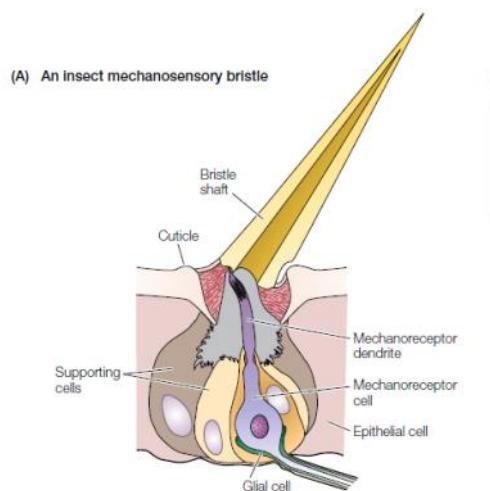


**FIGURE 14.1** Two kinds of sensory transduction mechanisms

Sensory stimuli activate sensory receptor molecules in one of two ways. (A) Stimulus-gated ion channels open directly in response to an applied stimulus, constituting an ionotropic mechanism. (B) Stimulus energy activates a metabotropic G protein-coupled receptor (GPCR), triggering a metabolic cascade (see Figure 13.6D) that results in activation of the sensory cell. The examples shown are chemoreceptor proteins, but the two types of transduction apply to all kinds of sensory receptors.

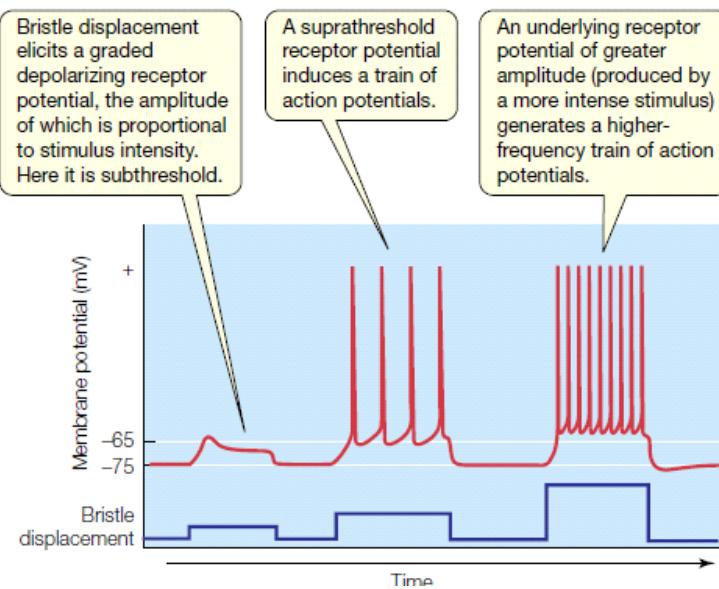
## 2. Mechanoreception and touch

- Mediate sense of touch, pressure, equilibrium, hearing and osmotic stimulation
- Sensillum: sense organ in insects. Stretch gated ion channels sense deformation of the bristle, opening non-selective cation channels and causing depolarization
- Stronger the stimulus, higher the frequency of action potentials



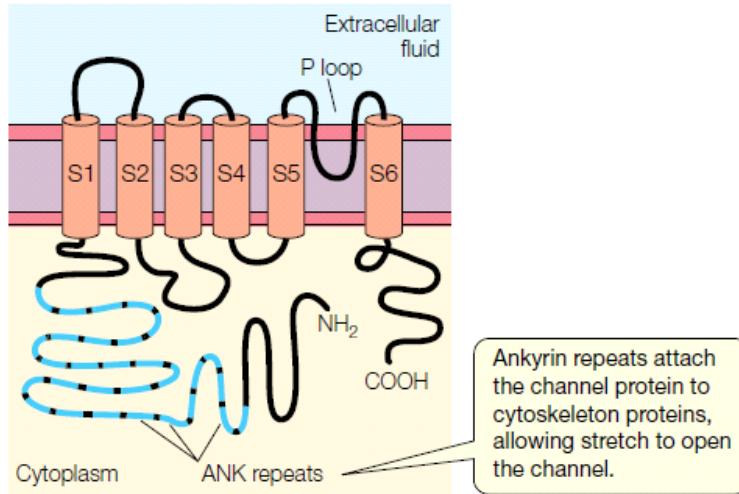
**FIGURE 14.3** Insect cuticular mechanoreception (A) An insect mechanosensory bristle (bristle sensillum) contains a bipolar sensory neuron, the dendrite of which is distorted by movement of the bristle shaft, leading to activation of the neuron. (B) The general response of a receptor cell to stimulation, illustrated here with an insect sensillum, is to produce a graded, depolarizing receptor potential, the amplitude of which is proportional to the intensity of the stimulus. The receptor potential induces a train of action potentials, the frequency of which is a code for stimulus intensity. (A after Thurm 1964, Bullock and Horridge 1965, and Keil 1997.)

(B) Mechanoreceptor responses to bristle displacement

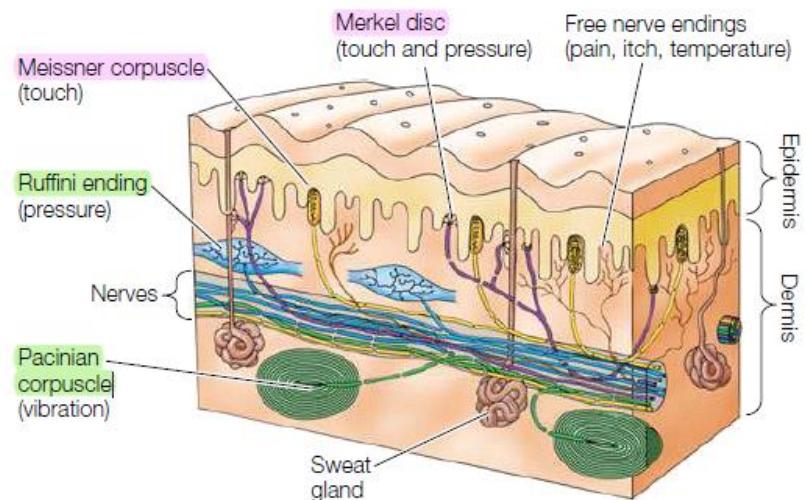


- Stretch-activated channels were discovered by patch clamp studies
3. NOMPC
- NO mechanoreceptor potential C is a transient receptor potential (TRP) channel from drosophila
  - Similar structure to voltage gated Na channels
  - Present in other sensory systems as well

(B) The structure of the NOMPC mechanosensory ion channel



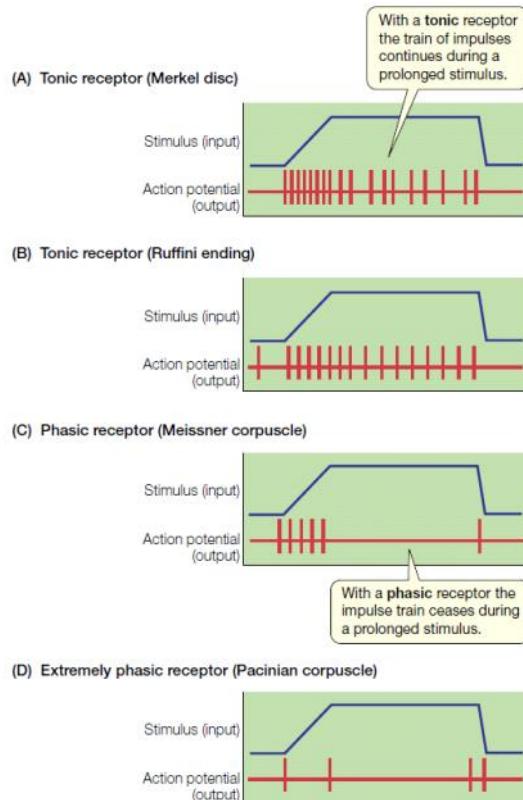
4. Mammalian touch receptors
- Association of epithelial cells and distal ends of neurons whose cell bodies reside in the dorsal root ganglion adjacent to spine
  - The distal processes of the DRG cells form 4 specialized receptors: Merkel disc, Meissner corpuscle, Ruffini ending, Pacinian corpuscle



**FIGURE 14.5 Mechanoreceptor cells in mammalian skin** A small area of skin contains many mechanosensory endings of sensory neurons, the cell bodies of which are located in dorsal root ganglia (see Figure 15.3). The sensory endings have four kinds of specialized endings with epithelial cells. Merkel discs and Meissner corpuscles are superficial, just beneath the epidermis. Pacinian corpuscles and Ruffini endings are larger and more deeply located. All respond to mechanical stimulation. Free nerve endings respond to other stimuli.

##### 5. Tonic and phasic adaptation

- Adaptation: decrease in frequency of action potentials in response to continuous stimulation
- Two kinds of adaptation: tonic (slow) and phasic (fast)
- Tonic: adapt slowly, action potential lasts as long as the stimulation. Eg: Merkel disc, Ruffini endings
- Phasic: Rapidly adapt, best for sensing changes in pressure. Eg; Meissner corpuscle
- Extremely phasic: the Pacinian corpuscle is so phasic that it only produces few action potentials (at the start and end of stimulus) and sense sudden indentation of the skin



## 6. Statocyst

- A statocyst contains grains of sand or a secretion of calcium carbonate. This relatively dense mineral material sinks within the statocyst and stimulates receptor cells beneath it by bending their cilia. In this way an uncomplicated structure can provide reliable information about orientation relative to gravity, as well

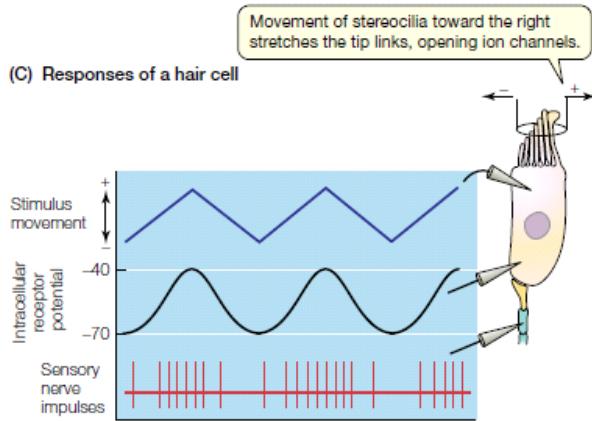
## 7. Tympanal organs

- Auditory sensation in insects with a circular tympanum
- Mechanosensory cells are attached to the eardrum and sense movement
- Moths have two tympanal organs on either side and give us spatial information about location of source of sound
- Poor at detecting frequency differences but can detect intensity differences

## 8. Vertebrate hair cells

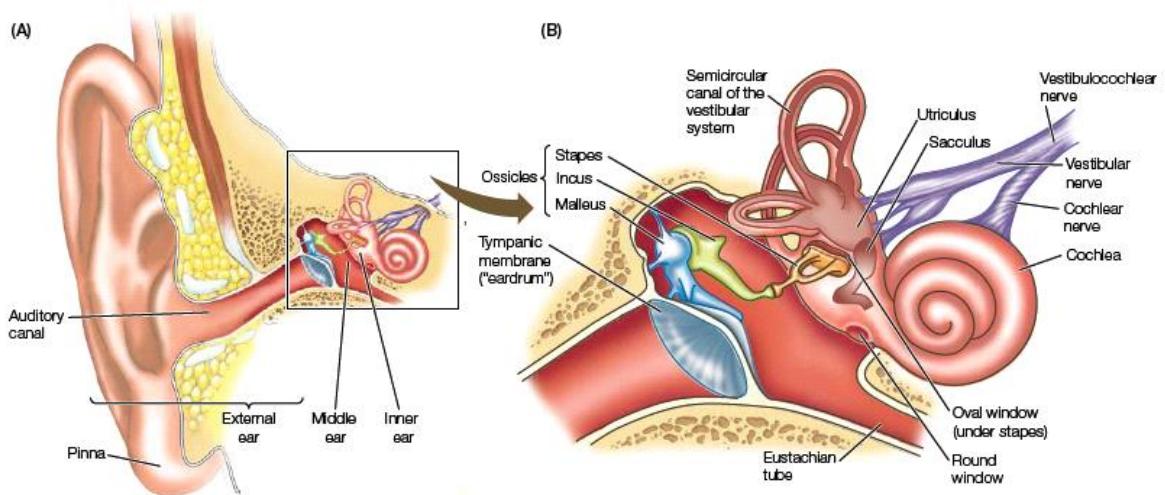
Hair cells are the sensory mechanoreceptor cells in the vertebrate acoustico-lateralis system, which includes the vestibular organs (for balance and detection of acceleration), the lateral line system of surface receptors in fish and amphibians (which detect water flow as well as other stimuli), and the mammalian cochlea, an auditory organ that we discuss shortly

- Hair cell is an epithelial cell whose apical surface has microvilli called stereocilia
- Hair cells do not have axons but they release neurotransmitters onto afferent neurons
- Displacement of cilia depolarizes the membrane which causes neurotransmitter release onto the post synaptic cranial sensory nerves



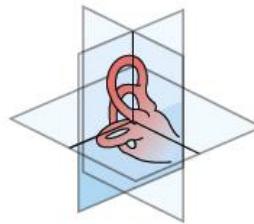
- Adjacent stereocilia are joined by 'tip links'. Movement in one direction depolarizes cells and in the other direction closes channels
- The channels open in a few microseconds, allowing the perception of sounds in the kilohertz regions

## 9. Human ear

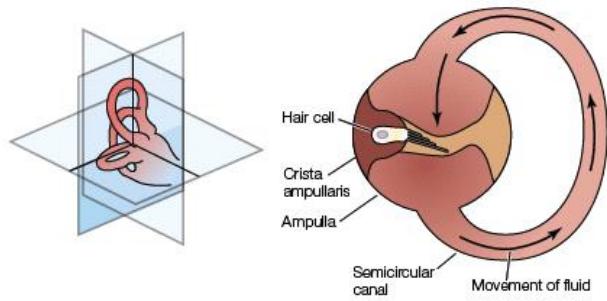


**FIGURE 14.8 Anatomy of the mammalian ear** (A) Structure of the human ear. (B) Components of the inner ear. The semicircular canal receptors are stimulated by head rotation. The utriculus and saccus contain macular hair cells that are stimulated by linear motion of the head and by gravity. The cochlea contains auditory receptors. (C) The three semicircular canals of the inner ear are at approximately right angles to each other, so that any angular movement of the head stimulates at least one of them. (D) With rotation of the head, fluid movement in the canal stimulates the hair cells.

(C) Orientation of semicircular canals



(D) Stimulation in semicircular canals



## 9. Vestibule and ampulla

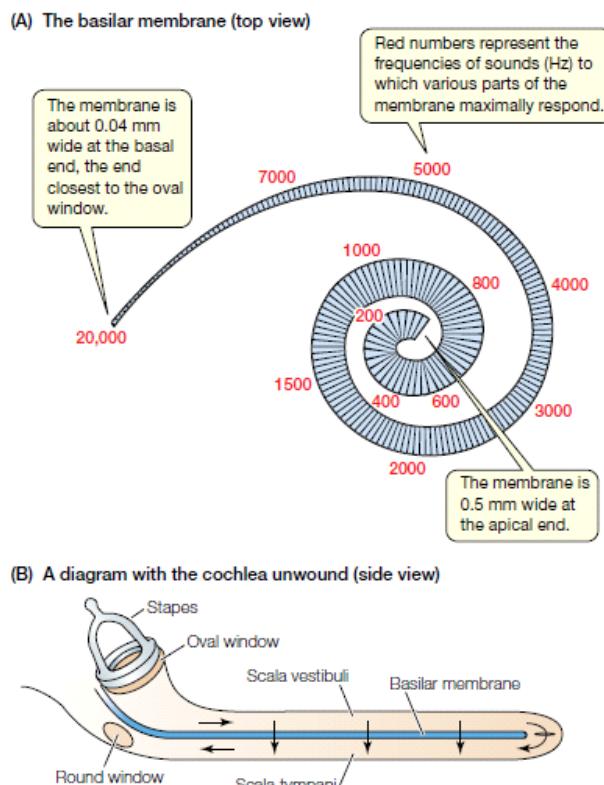
- Semi-circular canals sense angular acceleration of the head
- Utriculus (hair cells are horizontal) and saccus (hair cells vertical) sense linear velocity
- Semicircular canals are oriented in all three planes
- Labyrinth = cochlea + canals
- In the canal, a region called the ampulla contains a cluster of hair cells in a structure called the crista ampullaris
- Acceleration of the head causes fluid (endolymph) in the ampulla to slosh against the hair bundles of the hair cells
- In the utriculus and saccus: the hair cells are covered by a gelatinous mass called the otolithic membrane into which the hair bundles protrude. A dense network of crystals of calcium carbonate lies on top of the otolithic membrane (otoliths). When gravity shifts the crystals move

slowly due to their inertial mass and this is detected by the hair cells

## 9. Ossicles

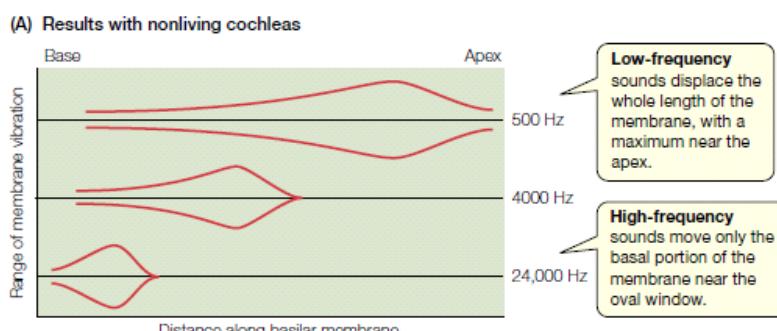
- The ossicles work to transmit sound energy from air to the liquid of inner ear.
- Only a fraction of sound energy is normally transmitted to the liquid, and the ossicles work to augment this by transmitting same force to smaller and smaller areas to the smallest area, the stapes which joins the oval window
- Liquids poorly conduct sounds because are not as compressible as air

## 10. Cochlea

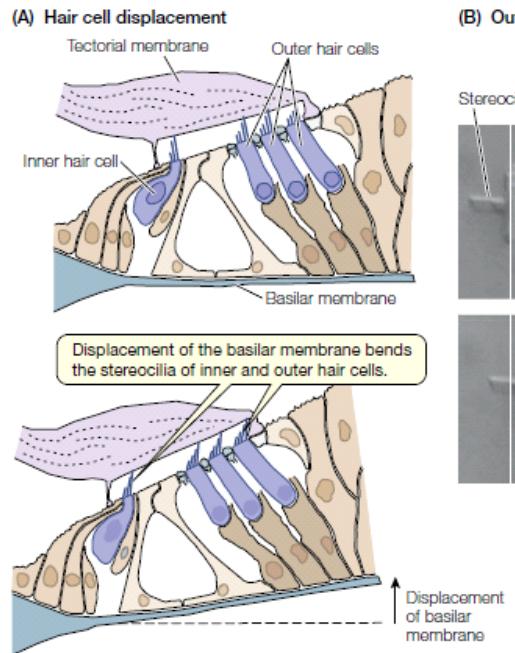


**FIGURE 14.9 Anatomy of the cochlea** (A) The surface of the basilar membrane, seen from above. The basilar membrane is narrower and stiffer at its basal end (near the oval window) than at its apical end. (B) A diagrammatic representation of how the inner ear would appear if the cochlea were unwound. The basilar membrane (seen in side view) separates the upper scala vestibuli from the lower scala tympani.

- The hair cells are contained on the basilar membrane in the organ of corti
- The differences in width and rigidity along its length give the basilar membrane a variable mechanical compliance, so that sound waves of different frequencies vibrate the basilar membrane maximally at different points along its length
- High frequency sounds- stiff part of basilar membrane- near oval window
  - Low frequency sounds - less stiff part - near apical region



- The hair cells are covered by a flap of tissue termed the tectorial membrane. The stereocilia of the hair cells are very close to or in contact with the tectorial membrane.
- As the basilar membrane moves up and down, it causes the stereocilia to push up against the tectorial membrane, so that the hair bundle is displaced.
- Displacement in one direction depolarizes the hair cell membrane potential, and displacement in the opposite direction hyperpolarizes it

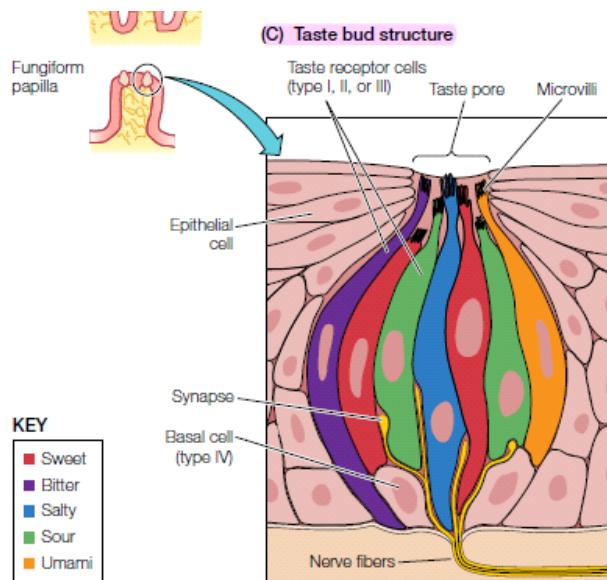


#### 11. Chemoreception

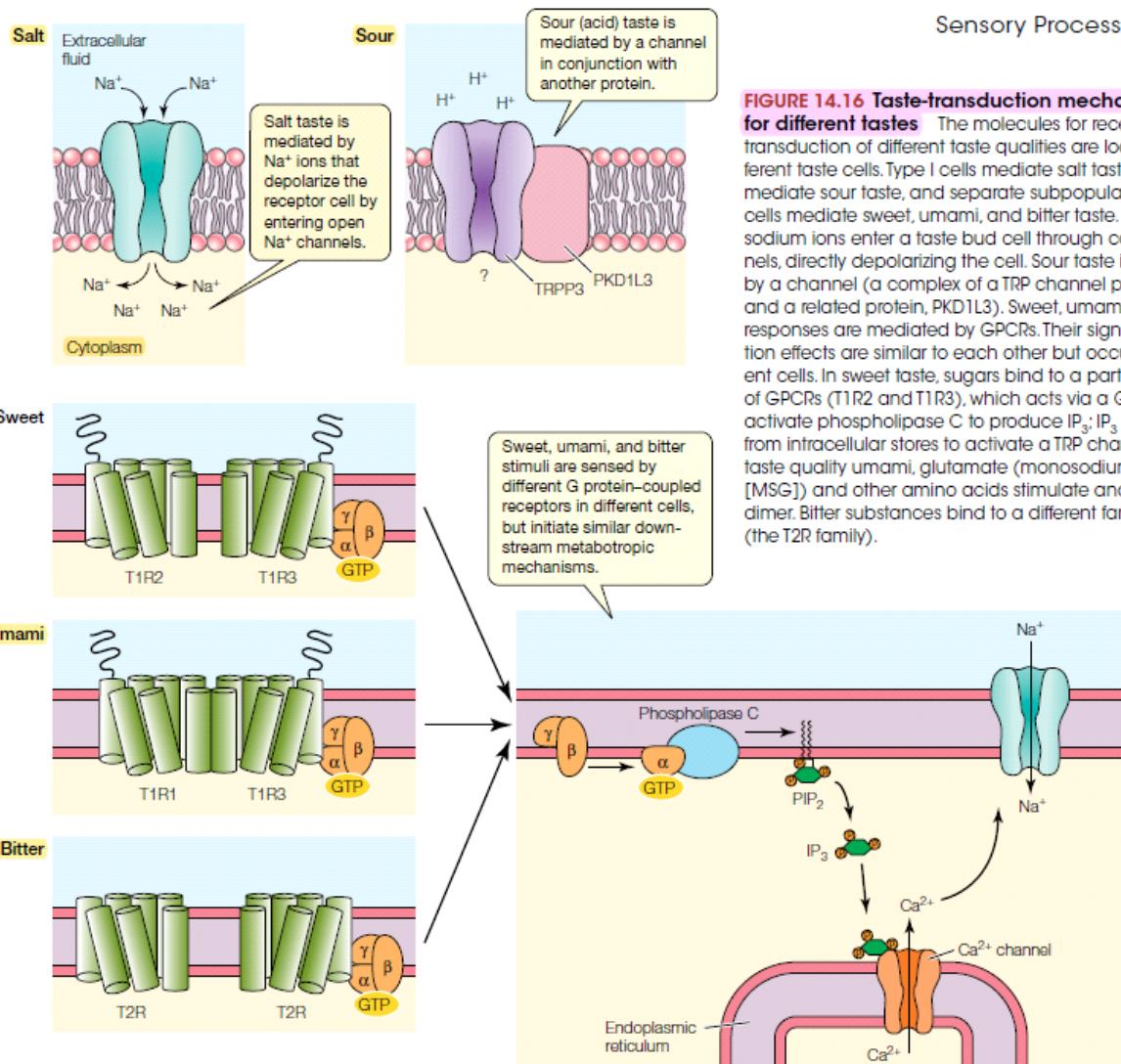
- Can be divided into olfaction and taste
- In insects, there are 2-4 different chemoreceptor neurons in a taste bristle or sensilla
- Frequency of action potentials increase with increasing concentration of the food (eg: sugar)

#### 12. Taste in mammals

- Vertebrate taste receptor cells are epithelial sensory cells that synapse onto cranial nerves
- Taste cells are confined to the taste buds, and taste buds are located on papillae

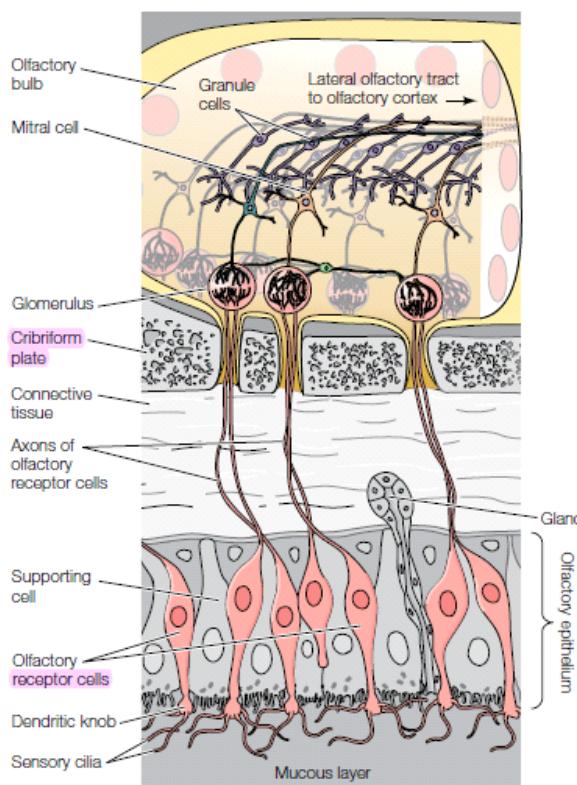


- Taste receptors have short life and are continually made by the basal cell
- Different tastes and their transduction mechanisms are on separate cells

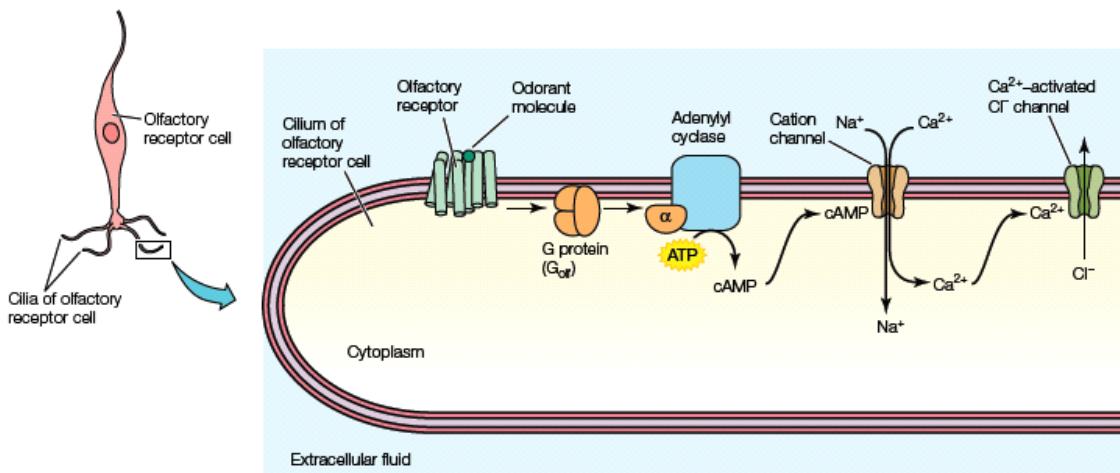


13. Olfaction in mammals
- The main system is olfactory epithelium that lines the inside of the nasal cavity
  - The olfactory receptor itself is a bipolar neuron whose dendrites have cilia that contain the receptor molecules

- Odorant must first dissolve in the mucous



**FIGURE 14.18 Vertebrate olfactory receptors** Olfactory receptor cells are small bipolar neurons, the sensory cilia of which extend into the mucous layer of the nasal cavity. Their axons perforate the bone of the cribriform plate to end in glomeruli of the olfactory bulb of the brain. Mitral cells and granule cells integrate olfactory information, and the mitral cell axons carry the information to the olfactory cortex.



**FIGURE 14.20 Olfactory transduction mechanisms in cilia membranes of olfactory receptor cells** Many odorants act to increase cAMP. The odorant binds to an odorant receptor on the ciliary membrane; the receptor activates a G protein to activate adenylyl

cyclase, producing cAMP. Cyclic AMP binds to and opens a cation channel, allowing entry of Na<sup>+</sup> and Ca<sup>2+</sup> ions and depolarizing the cell. Ca<sup>2+</sup> binds to Ca<sup>2+</sup>-activated Cl<sup>-</sup> channels, which permit Cl<sup>-</sup> efflux that augments the depolarization.

#### 14. Photoreception

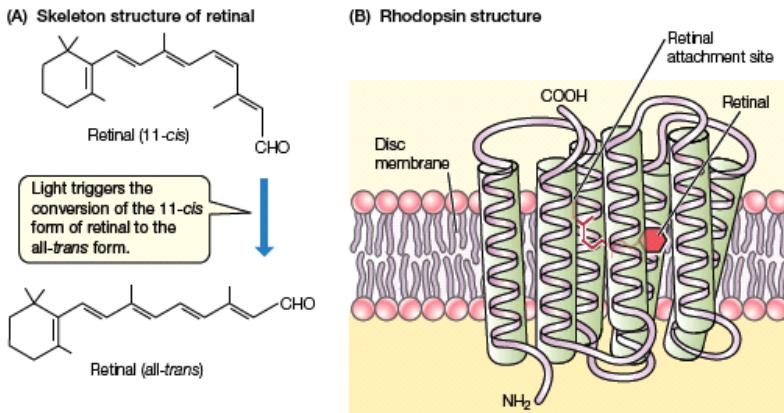
Camera eyes	Compound eye
Lens forms one image on an array of photoreceptors	Several ommatidium form their own image to produce a tile mosaic

#### 15. Rhodopsin

- Photopigment has a non-peptide chromophore that absorbs photons and then triggers a

## transduction cascade

- Retinal: chromophore that is associated with integral membrane protein- opsin



**FIGURE 14.23 Rhodopsin is a photopigment composed of two parts: retinal and opsin** (A) Skeleton chemical structure of retinal, which exists in two isomers (11-cis and all-trans). Light triggers a conformation change from 11-cis to all-trans retinal. (B) Three-dimensional structure of the protein (opsin) in vertebrate rhodopsin. Seven  $\alpha$ -helical regions of the protein span the membrane; retinal is attached to an amino acid residue in the seventh helix. (The red retinal would actually be hidden behind the nearer helices but is shown as if it were visible through them.)

- Many different rhodopsins but with different opsins but same retinal
- The conformational change from cis retinal to trans retinal causes transformation which initiates G protein downstream

## 16. Fovea

- A depression in the retina that has high acuity with highly dense cones

## 17. Blind spot

- The point in the optical disc where the axons exit as the optic nerve

## 18. Rods vs cones

	Rod Cells	Cone Cells
Location in retina	Found around periphery	Found around centre (fovea)
Optimal light conditions	Dim light ('night' vision)	Bright light ('day' vision)
Visual acuity	Low resolution (many rods : one bipolar cell)	High resolution (one cone : one bipolar cell)
Colour sensitivity	All wavelengths	Certain wavelengths (red, green, blue)
Type of vision	Achromatic (black and white)	Colour
Number of types	One (all contain rhodopsin)	Three different iodopsin pigments
Relative abundance	Many	Fewer

- Photopsins (also known as Cone opsins) are the photoreceptor proteins found in the cone cells of the retina that are the basis of color vision.
- Photopsins bind the chromophore retinal to form iodopsins. Iodopsins are used in daylight vision and are analogous to rhodopsin (visual purple) that is used in night vision.

## 20. Reversed positioning of rods and cones in the retina

(B) Retinal cells

