

Medical Physiology I

**For Pharmacy Students
(GAMBY)**

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Introduction

Objectives

At the end of this course, you will be able to:

- Define physiology
- Explain the level of organization of human body
- Comprehend the importance of maintaining homeostasis in normal range
- Identify feedback mechanisms of homeostasis

Definition & History of Physiology

- **Aristotle** (384 - 322 B.C.) was the first person to coin the term **physiology**
- According to Aristotle, Physiology meant the **study of nature**
“**physis** = nature; **logos** = study”
- **Galen (130–201 A.D)** began modern experimental physiology by studying body parts of animals like blood vessels and their functions

Definition Cont...

- By the **sixteenth century** in Europe, physiology had been formalized as the study of the vital functions of the human body
 - Today the term is again used to refer to the study of animals and plants
- ❖ **Physiology is the study of how living organisms function (**modern def.**)**

Subfields of Physiology

- Physiology has many subfields:
 - Viral physiology
 - Bacterial physiology
 - Plant physiology
 - Mammalian physiology
 - Medical physiology
 - Others

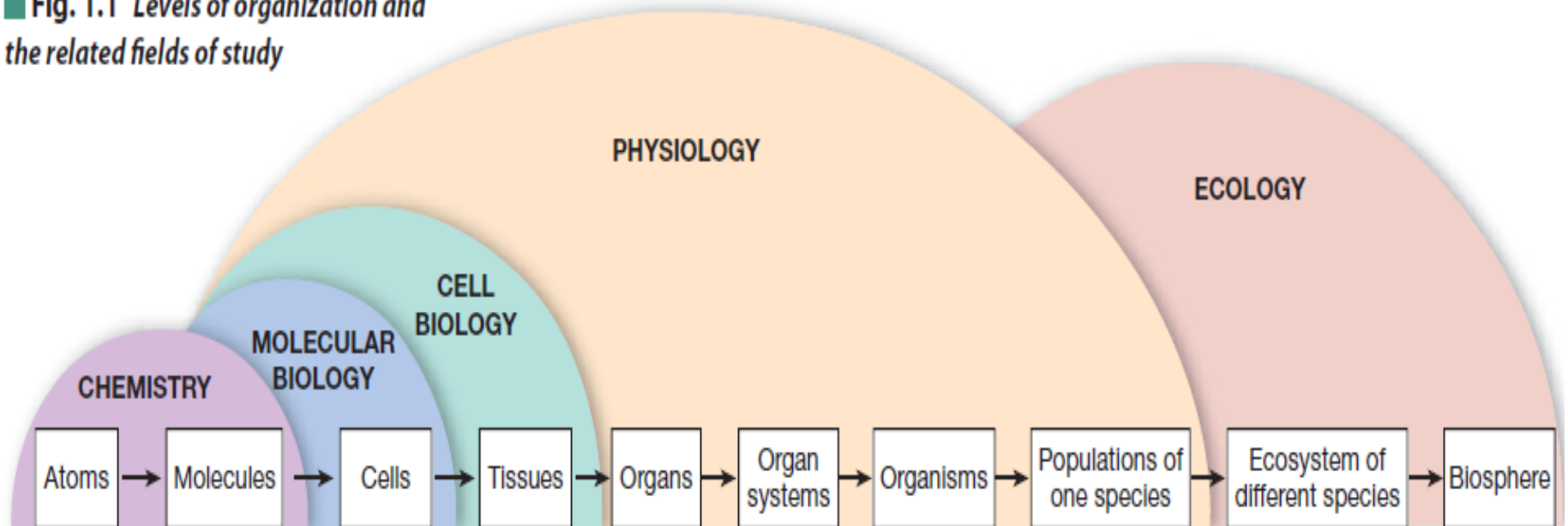
Medical physiology

- The study of how human body function

Scope of Physiology

The scope of physiology ranges from the activities or functions of individual molecules and cells to the interaction of our bodies with the external world

■ Fig. 1.1 *Levels of organization and the related fields of study*



Introduction Cont...

- Relationship b/n physiology and other sciences
 - Physiology has a strong link with other disciplines
 - Highly related to anatomy, biochemistry, pathology, pharmacology, etc
- Physiology is a quantitative science

Levels of the Organization of the Human Body

Chemical level → Cell → Tissue → Organ → Organ system → Organism

Levels of the Organization

Cont...

- The basic living unit of the body is the cell
- Each human being begins as a single cell, a **fertilized egg**
- The fertilized egg divides to create two cells, each of which divides in turn to result in four cells, and so on
- Multiplication is followed by cell differentiation

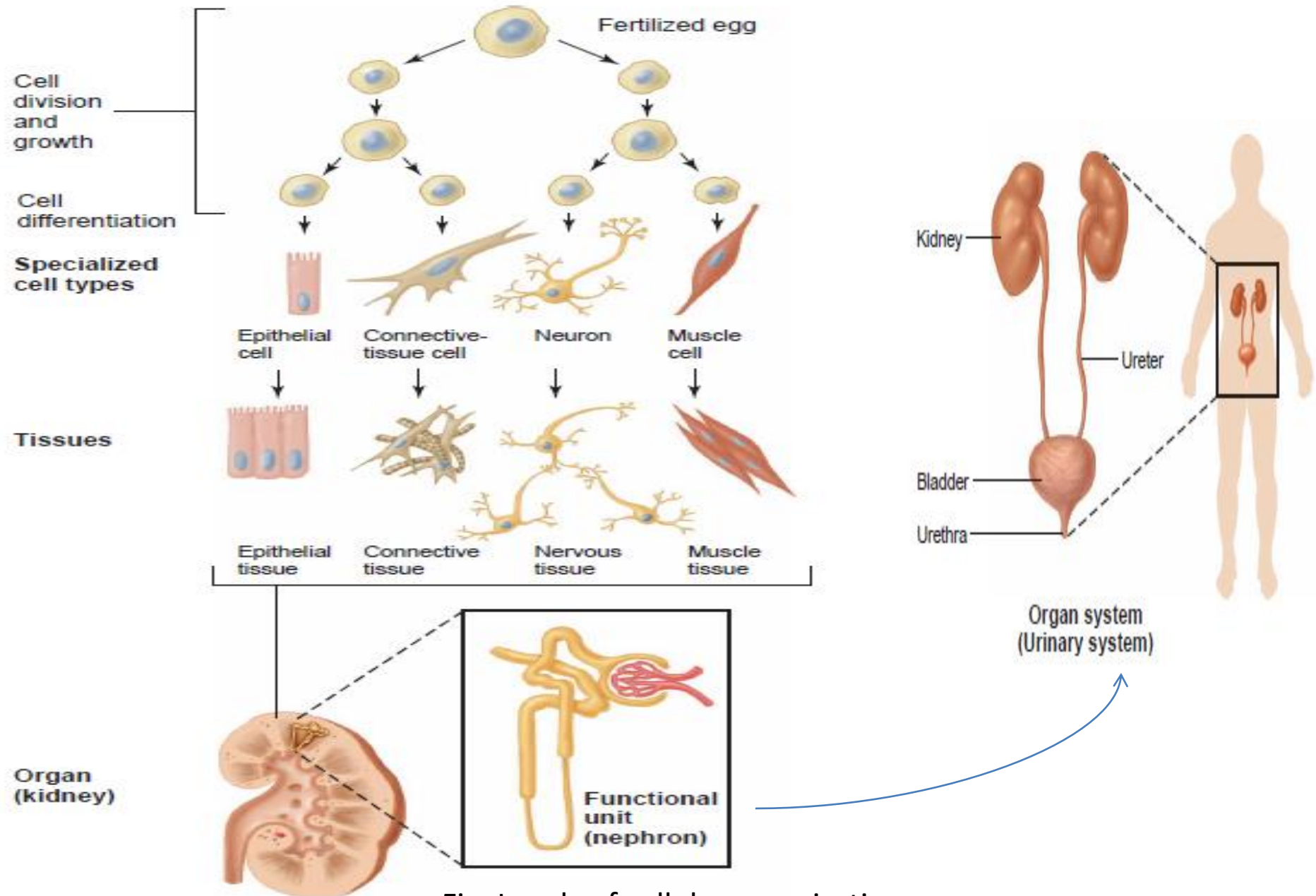


Fig. Levels of cellular organization

Body Systems

- There are 10 body systems, each with **unique contributions** to body function
- However, it is the **integration of the body systems** that allows the creation of a stable internal environment in which cells are able to function

Body Systems cont...

Table: Major Components and Functions of the Body Systems

Body System	Component(s)	Major Function(s)
Cardiovascular	Heart, blood vessels, blood	Transport of materials throughout the body
Digestive	Gastrointestinal tract, liver, pancreas	Assimilation of nutrients; elimination of some wastes
Endocrine	Endocrine glands	Coordination of body functions through release of regulatory molecules
Immune	Thymus, spleen, lymphatic system, white blood cells	Defense against pathogens
Integumentary	Skin	Protection against external environment

Cont.....

Body Systems cont...

Musculoskeletal	Skeletal muscle and bones	Movement and support
Nervous	Brain, spinal cord, peripheral nerves	Coordination of body functions through electrical signals and release of regulatory molecules; cognition
Reproductive	Gonads, penis, vagina, uterus	Procreation
Respiratory	Lungs	Oxygen and carbon dioxide exchange with external environment
Urinary	Kidneys, bladder	Homeostasis of ion concentrations in internal environment; elimination of wastes

Source- Kibble & Halsey, 2009

Composition of Human Body

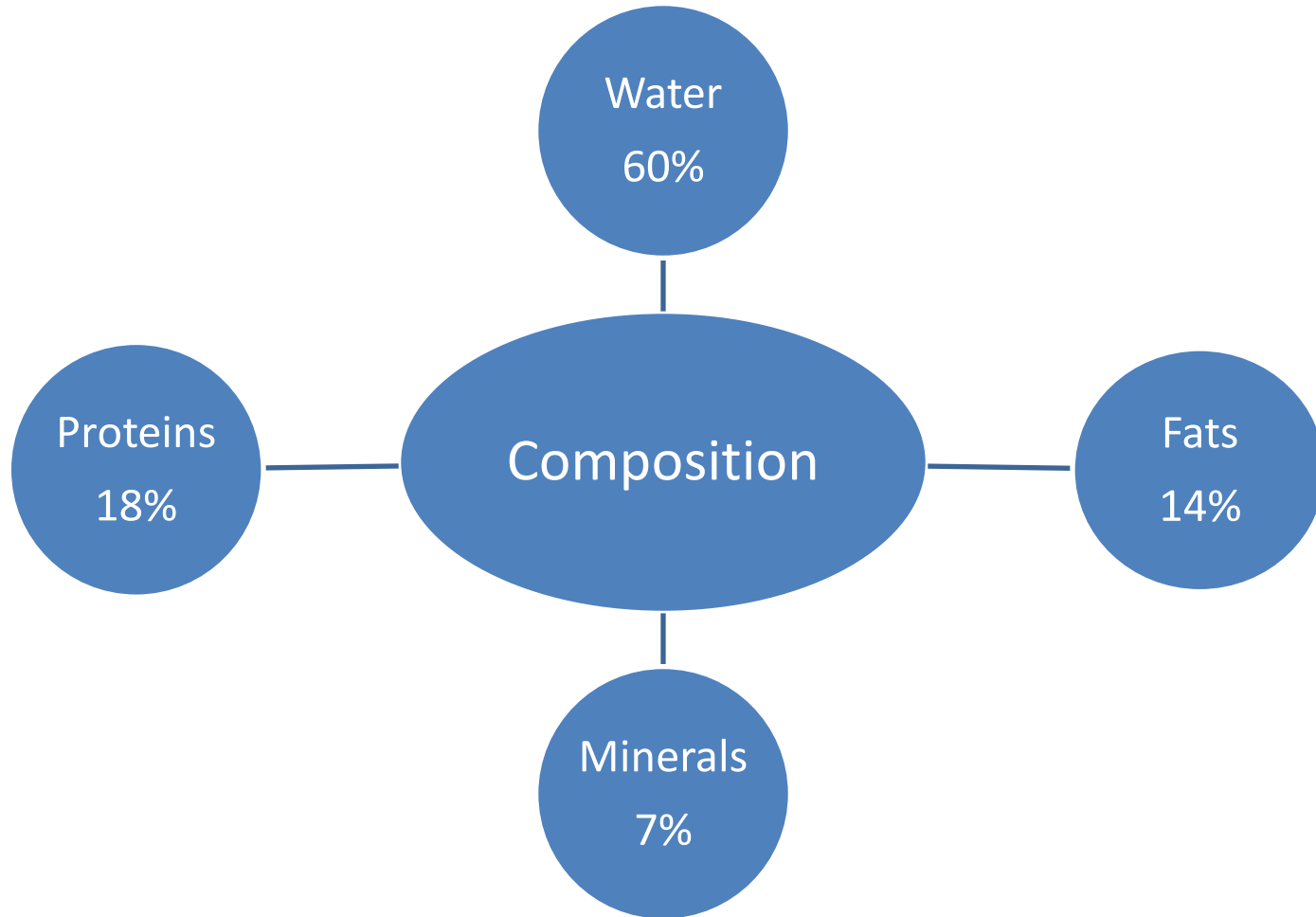


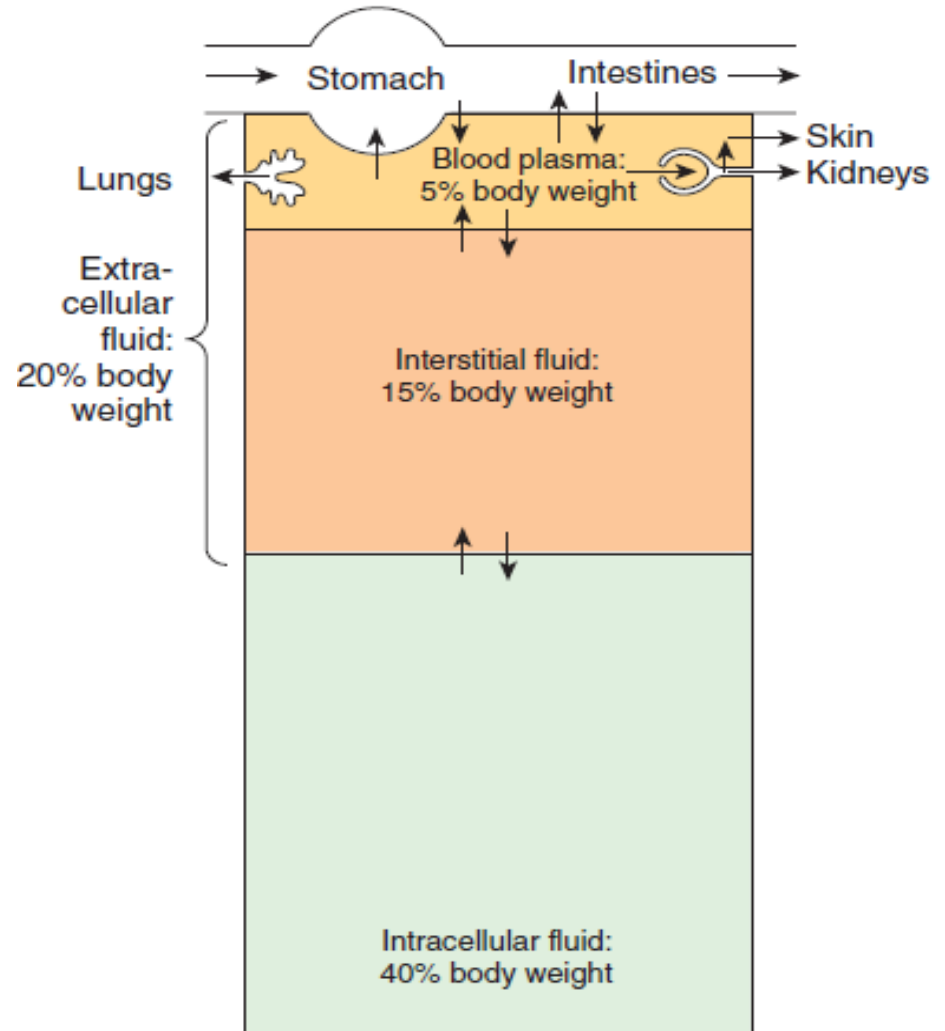
Fig. The approximate composition of an average adult human per body weight

Body Fluid Compartments

- About 60% of total body water is ICF and 40% is ECF.
- Approximately 80% of ECF is interstitial fluid and the remaining 20% is blood plasma

ICF- intracellular fluid
ECF- extracellular fluid

ECF is also called internal environment



Body Fluid Cont...

- Transcellular fluid is part of the ECF and includes epithelial secretions such as CSF and extraocular fluids
- Electrolytes and proteins are **unequally distributed** among the body fluids
- This uneven distribution is crucial to physiology

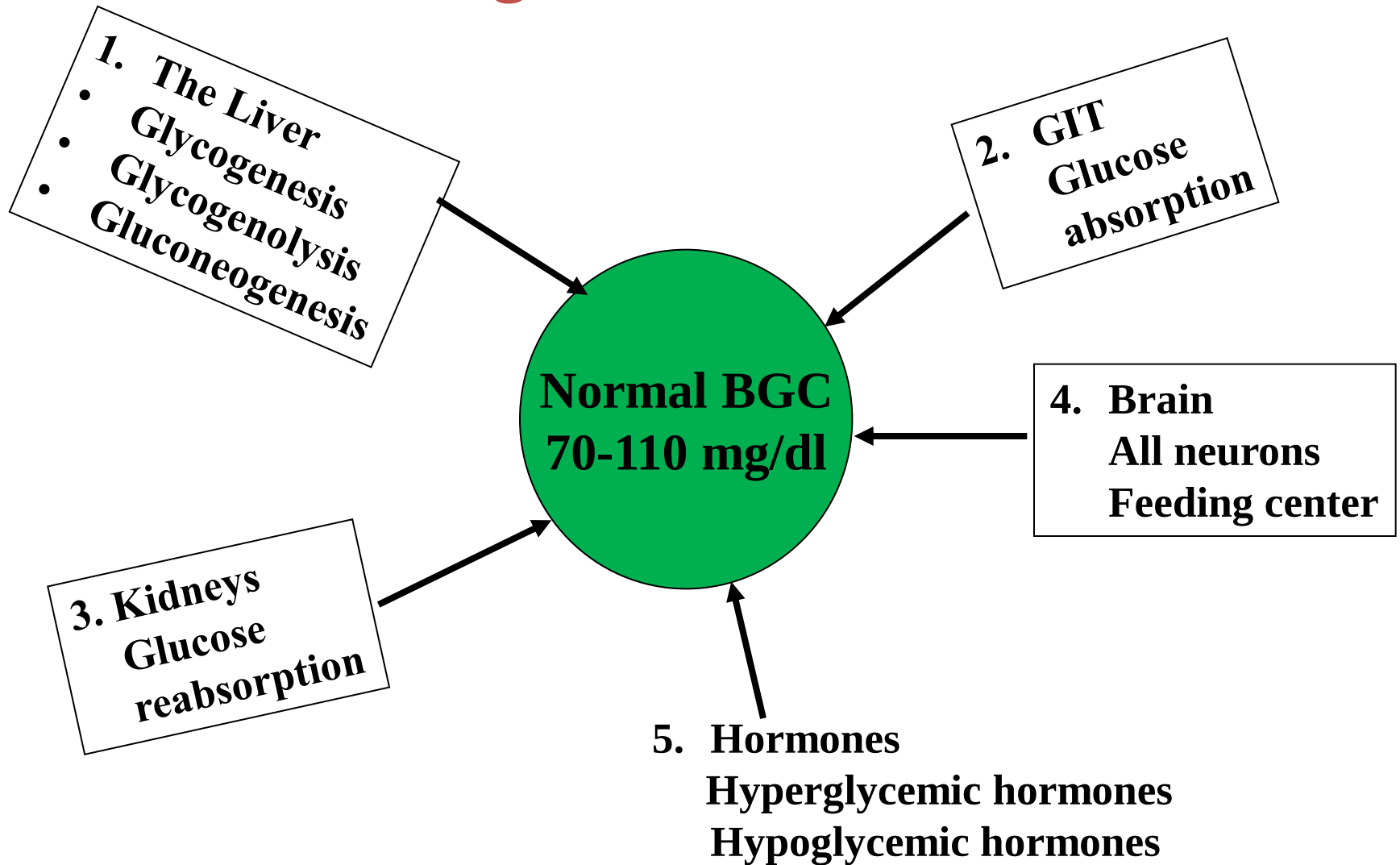
Table: Important components of extracellular and intracellular fluid compartments

	Extracellular ^a	Intracellular ^b
Ca ²⁺ (mmol/L)	2.5	1×10^{-4}
Cl ⁻ (mmol/L)	110	≈10
HCO ₃ ⁻ (mmol/L)	20	≈10
K ⁺ (mmol/L)	4	120
Na ⁺ (mmol/L)	140	14
Osmolarity (mOsm/L)	295	295
pH	7.4	7.1–7.2

Homeostasis

- Maintenance of constant conditions in the internal environment (ECF)
- Essentially all organs of the body perform their functions to maintain constant conditions in the ECF
- E.g.
 - Lungs provide oxygen
 - Kidneys maintain constant ion concentrations
 - GIT provides nutrients to ECF

Blood glucose homeostasis



Homeostasis Cont...

An organism is said to be in homeostasis when its internal environment contains an optimum amount of;

- Nutrients
- Gases
- Electrolytes
- Water
- Hormones
- Enzymes
- Temperature

Regulatory systems of Homeostasis

- Homeostasis is maintained by two general categories of regulatory mechanisms

1. Intrinsic

- Built into the organs being regulated
e.g molecules produced in the walls of blood vessel cause vessel dilation or constriction

2. Extrinsic

- Regulation of an organ by the nervous and endocrine systems

Regulatory systems Cont...

1. Nervous regulatory mechanism

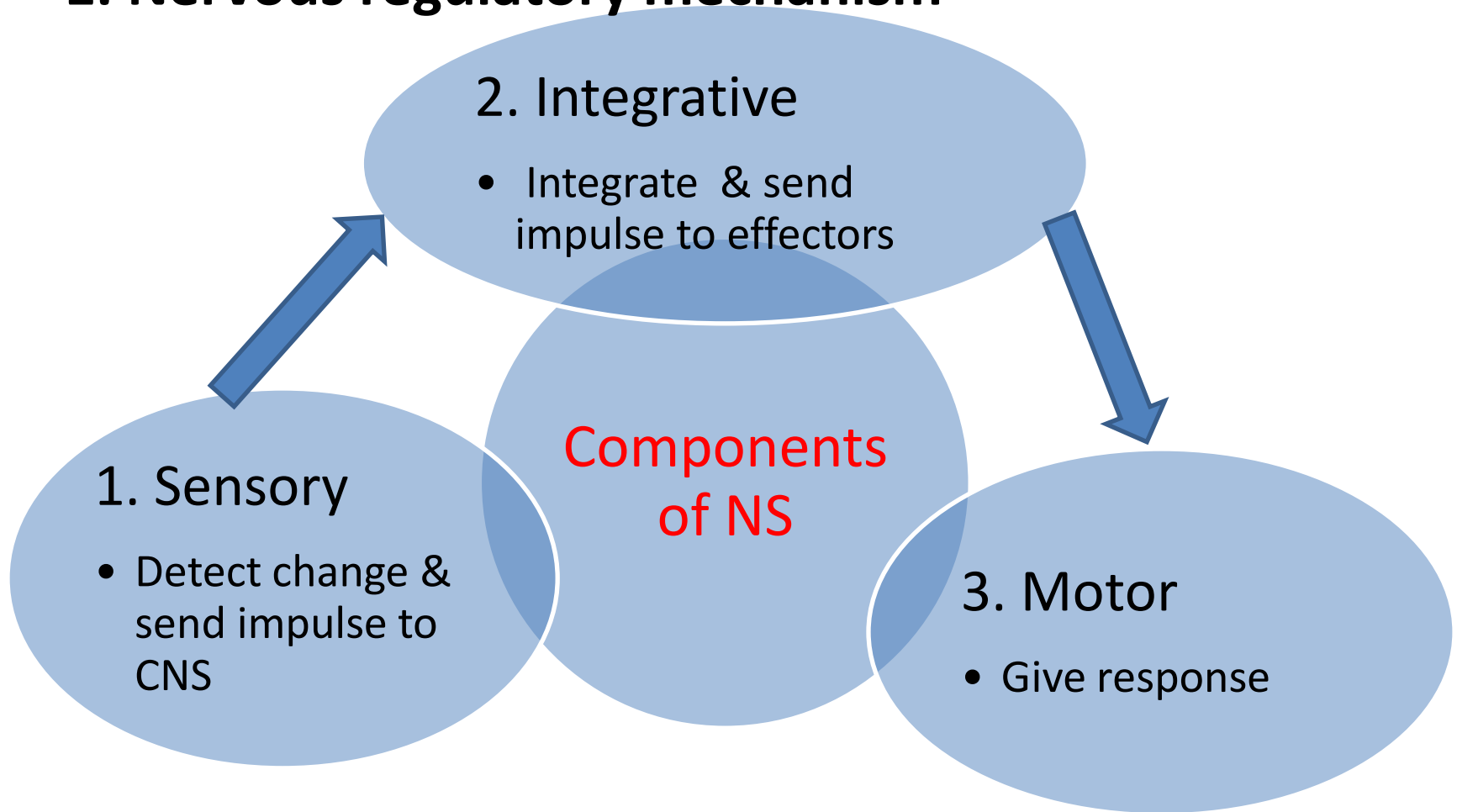


Fig: Three major components nerve system

Regulatory systems Cont...

2. Hormonal regulatory mechanism

- Regulation is done by action of hormones on target organs

Examples:

- PTH → act on the kidney, bone, and intestine = $\uparrow[\text{Ca}^{2+}]$
- ADH controls water electrolyte balance

PTH – parathyroid hormone

ADH – antidiuretic hormone

Feedback control mechanisms of the homeostasis

There are two types of feed back mechanisms:

- a. Negative Feedback Mechanism (NFM)
- b. Positive Feedback Mechanism (PFM)

Negative Feedback Mechanism (NFM)

- It works by producing an effect which opposes the previous condition (the initiating stimulus) of the organ
- Most homeostatic values of the body are controlled by NFM

Components of a Negative Feedback

1. Set point value:

- The value at the center of the normal range and is treated by the control system as the target value

2. Sensors

- Continuously monitor the controlled variable

Components Cont...

3. Comparator

- Interprets input from the sensors to determine when deviations from the set point have occurred
- Initiates a counter response

4. Effectors

- Mechanisms that restore the set point to its normal level

Components Cont...

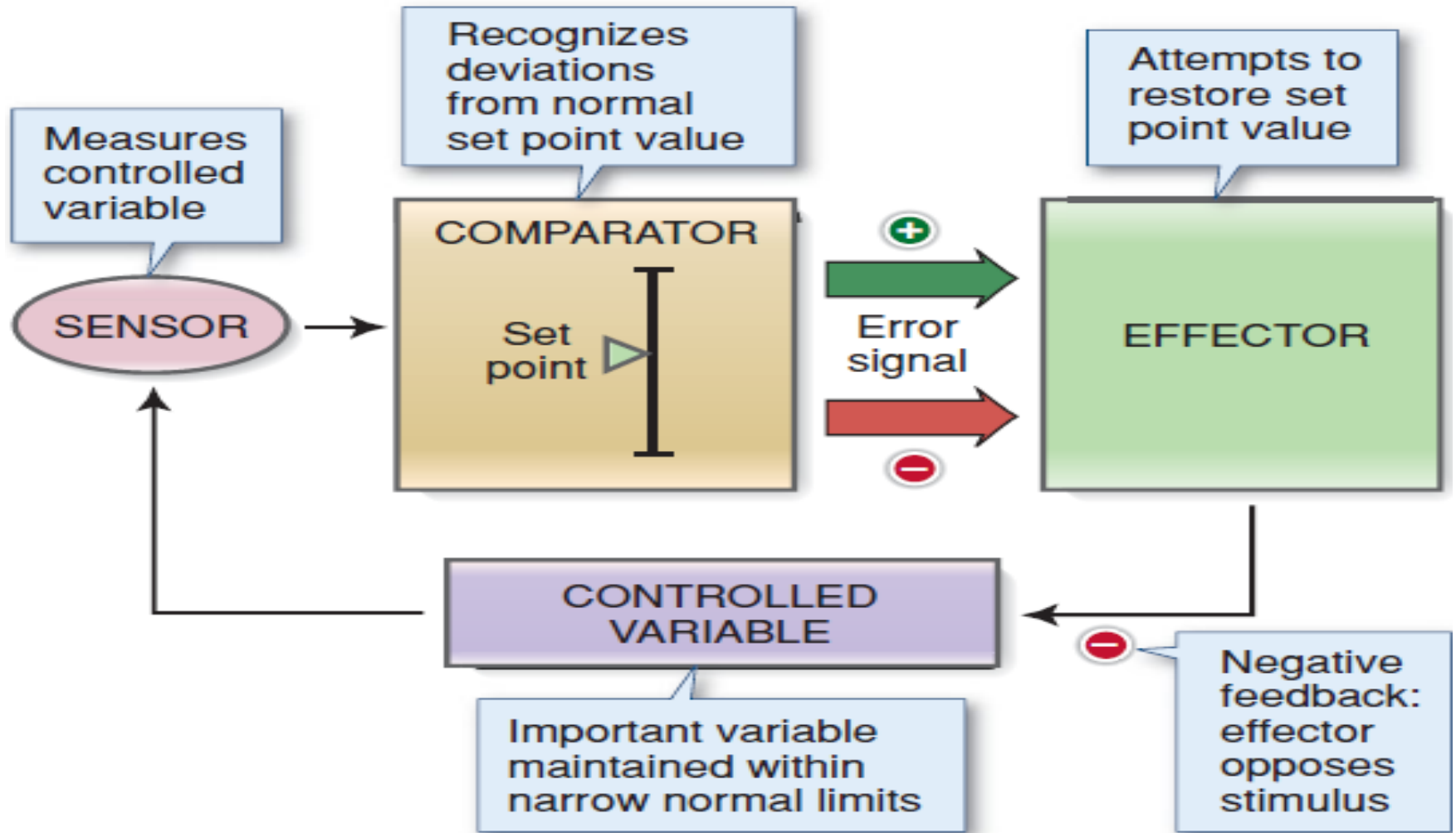


Fig. Components of a negative feedback control system ((Kibble & Halsey, 2009)

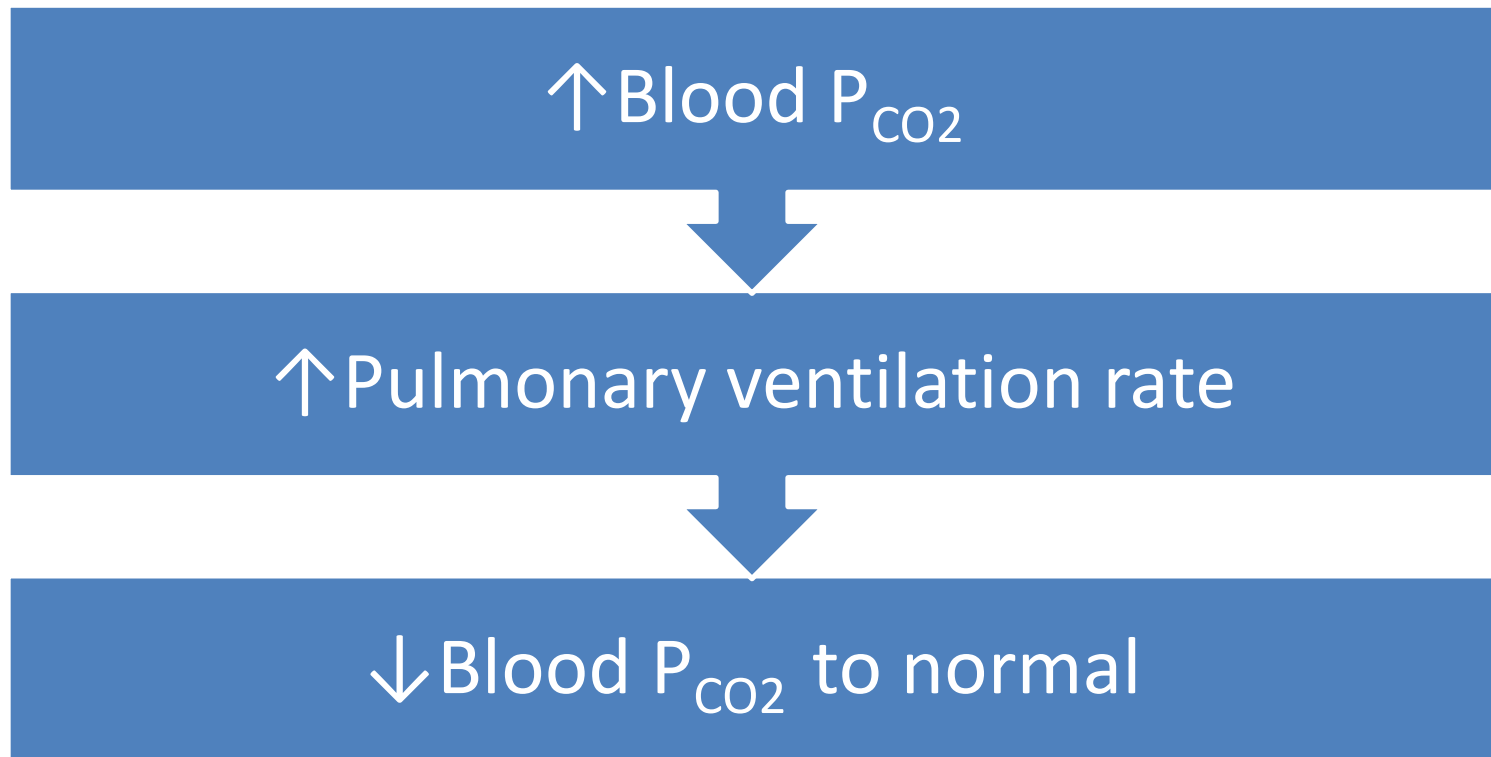
Table: Some examples of physiologic controlled variables

Controlled Variable (Arterial Blood Sample)	Typical Set Point Value
Arterial O ₂ partial pressure	100 mm Hg
Arterial CO ₂ partial pressure	40 mm Hg
Arterial blood pH	7.4
Glucose	90 mg/dL (5 mM)
Core body temperature	98.4°F (37°C)
Serum Na ⁺	140 mM/L
Serum K ⁺	4.0 mM/L
Serum Ca ²⁺	2.5 mM/L
Mean arterial blood pressure	90 mm Hg
Glomerular filtration rate	120 mL/min

(Kibble & Halsey, 2009)

NFM Cont...

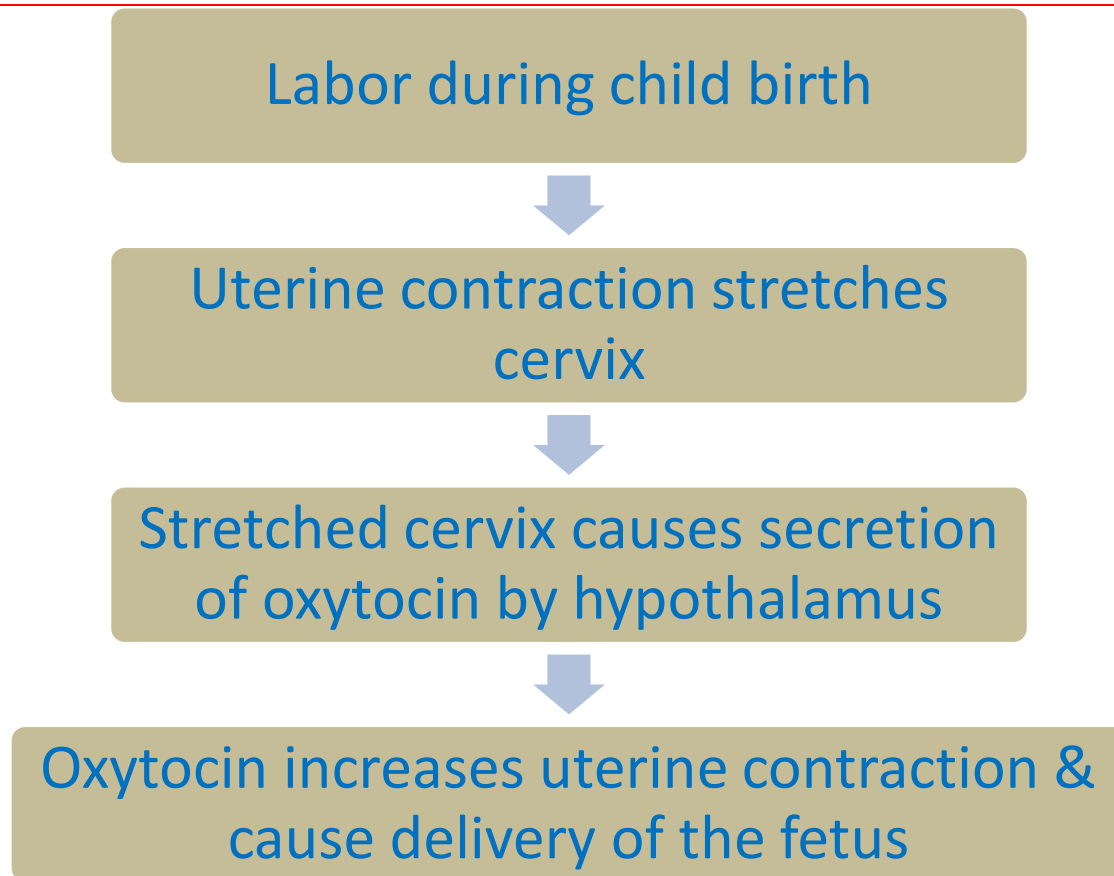
E.G. The body responds negatively for abnormally high level of blood CO₂ as follows:



Positive Feedback Mechanism (PFM)

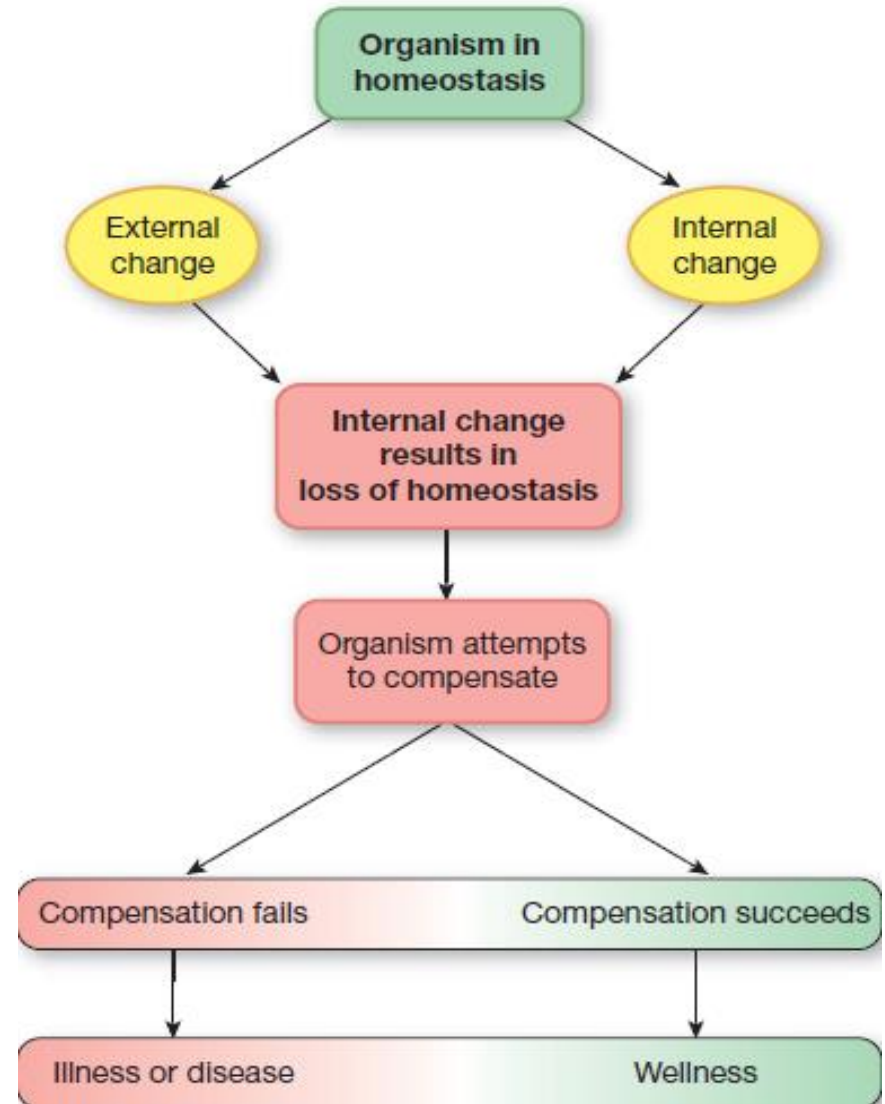
- Produce an effect which enhances or repeats the action of the starting stimulus

Example



Summary

- When homeostasis is disturbed, the body attempts to compensate
 - Compensation successful
→ homeostasis is restored
 - Compensation fails → illness or disease



Pathophysiology -- study of body functions in a disease state

Unit One

CELL PHYSIOLOGY

Objectives

At the end of this unit, you are expected to explain:

- The nature of the cell membrane
- The different organelles of the cell and their function
- Mechanism of transport across the cell membrane
- Membrane potential
 - Resting membrane potential
 - Action potential

Introduction

- All the living things are composed of cells
- A single cell is the smallest unit that has all the characteristics of life
- Cell is defined as the structural and functional unit of the living body

Cells

Two fundamental types:

Prokaryotic cell

No Nucleus

No organelles

Small 100nm-5um

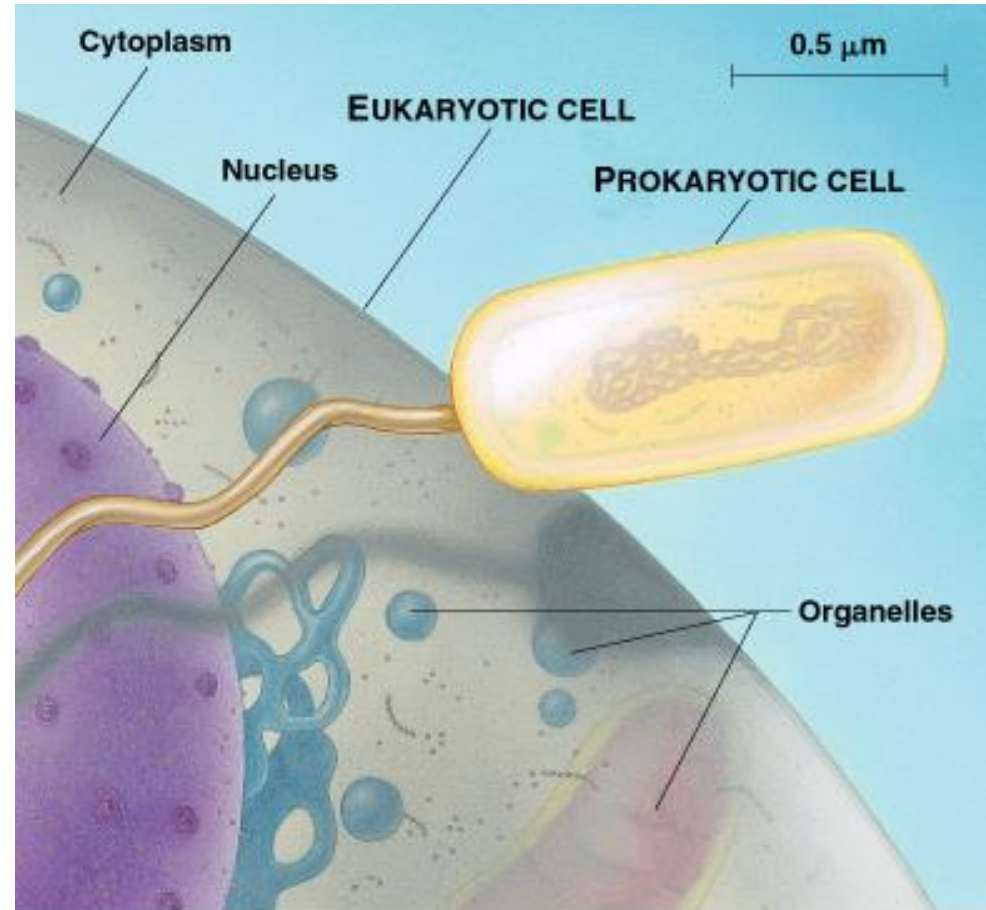
Eukaryotic cell

True Nucleus

Membrane bound
organelles

10-100um

Some are larger



Cell Cont...

- About 100 trillion cells
- About 200 distinct kinds of cells in terms of differences in structure and function

Cell cont...

- Four groups of cells according to the broad types of function
 1. muscle cells
 2. neurons
 3. epithelial cells
 4. connective-tissue Cells

Cell cont...

Components of cells

- A typical cell has two parts: **nucleus** and **cytoplasm**
- The nucleus is separated from the cytoplasm by a **nuclear membrane**
- The cytoplasm is separated from the surrounding fluid (ECF) by the **plasma membrane**

Protoplasm:- the living part of a cell, including the **cytoplasm**, **nucleus**, and **other organelles**

Cytoplasm

- Includes all materials inside the cell membrane except the nucleus
- Has **four** components:
 1. **Cytosol**
 2. **Inclusions**
 3. **Insoluble protein fibers**
 4. **Organnels**

2. Inclusions

- Particles of **insoluble materials**
- Some are **stored nutrients**
- Others are responsible for specific cell functions
- Sometimes called the **nonmembranous organelles**

3. Insoluble protein fibers

- Form the cell's internal support system, or cytoskeleton

4. Organelles—“little organs”

- **Membrane-bounded** compartments that play **specific roles** in the overall function of the cell

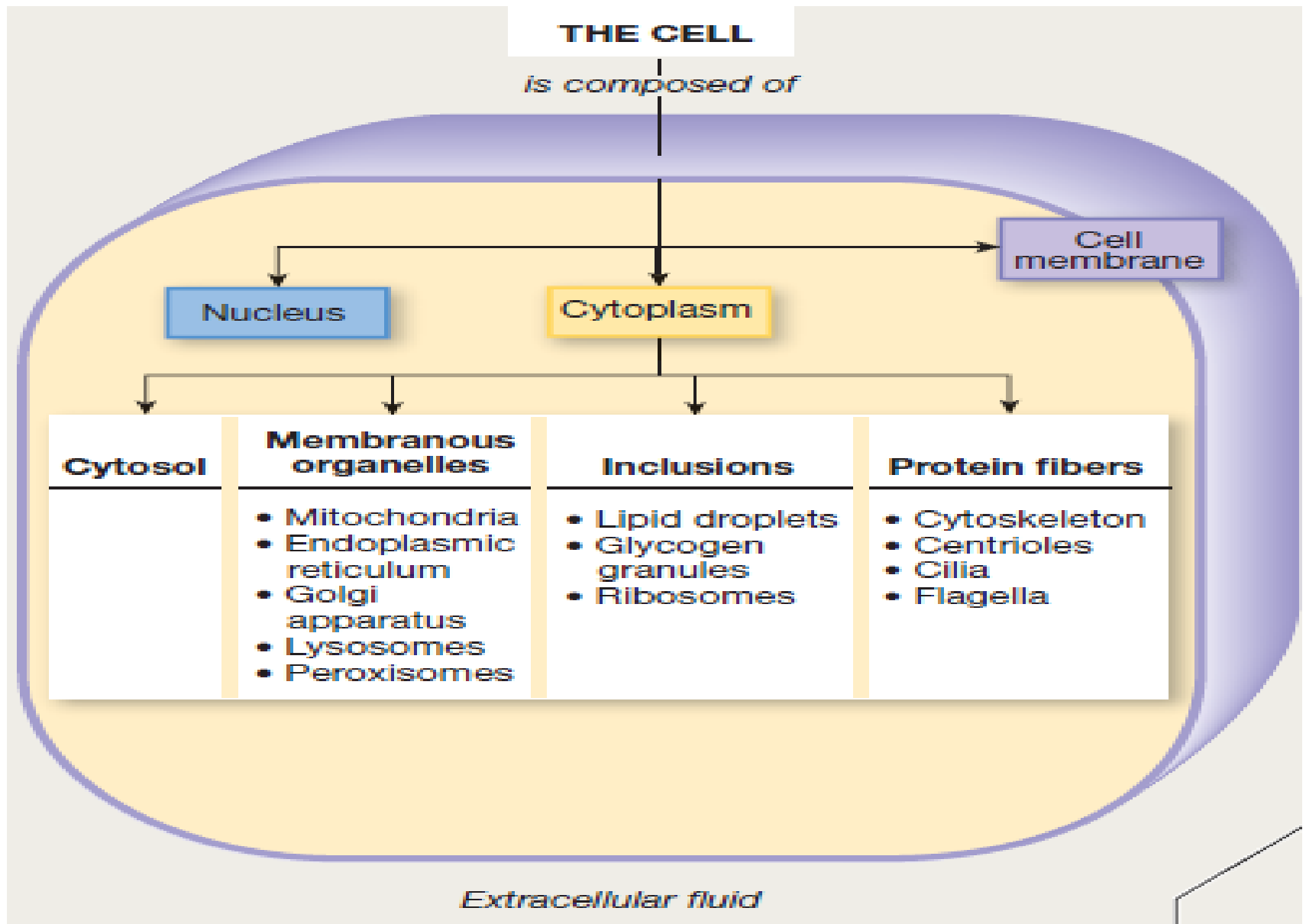


Fig. Overview map of cell structure

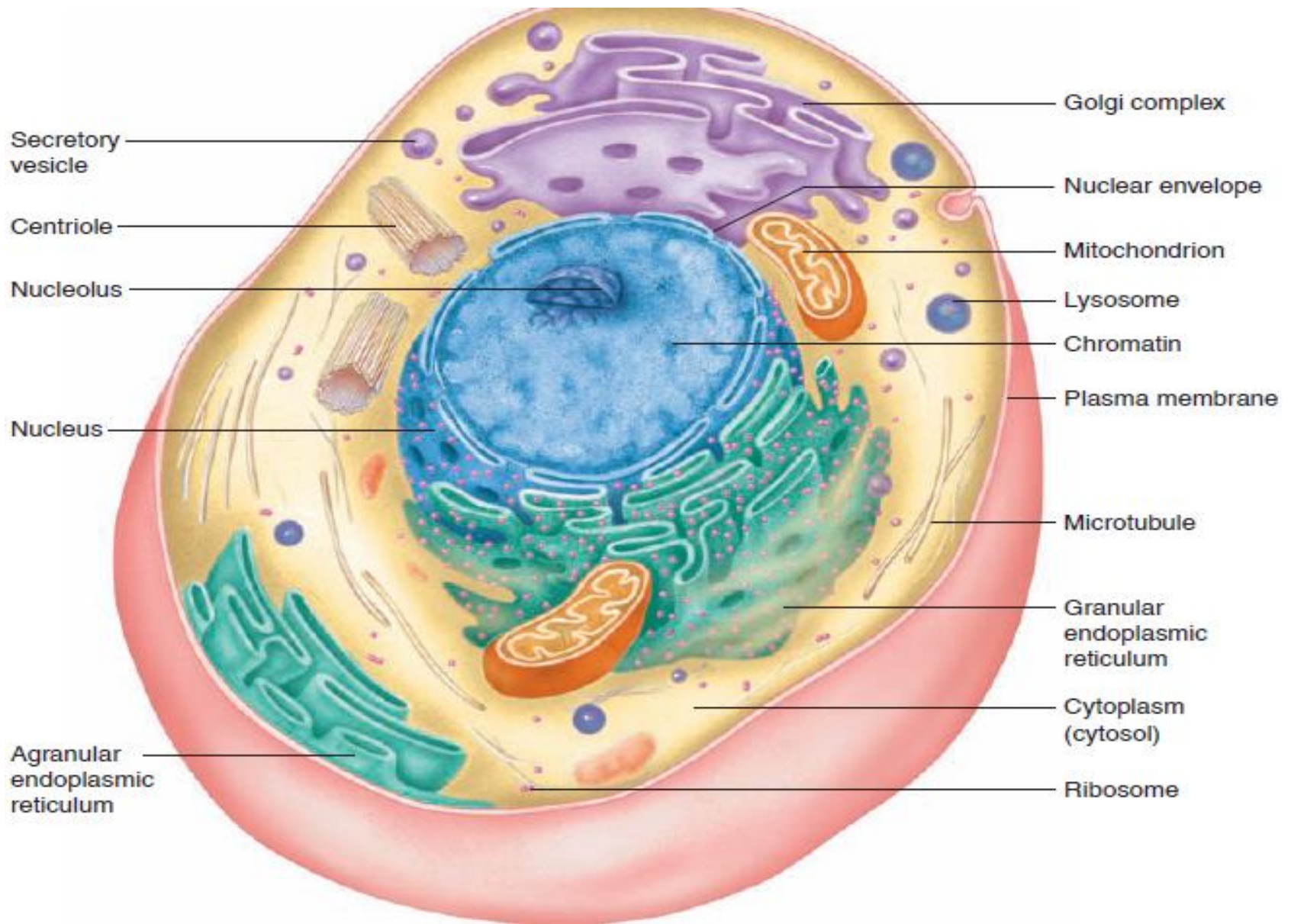


Fig. Principal organelles of cell, (Human physiology, 12th edition)

Plasma membrane

- A sheet-like structure that surround the cell
- Separating the cellular contents from the ECF
- It is entirely composed of proteins, lipids and carbohydrates

Percent proportion:

1. Proteins:	55 %	→ {	Phospholipids	25 %
2. Lipids:	42 %		Cholesterol	13 %
			Neutral fats	4 %
3. Carbohydrate:	3 %			

Plasma Membrane Cont...

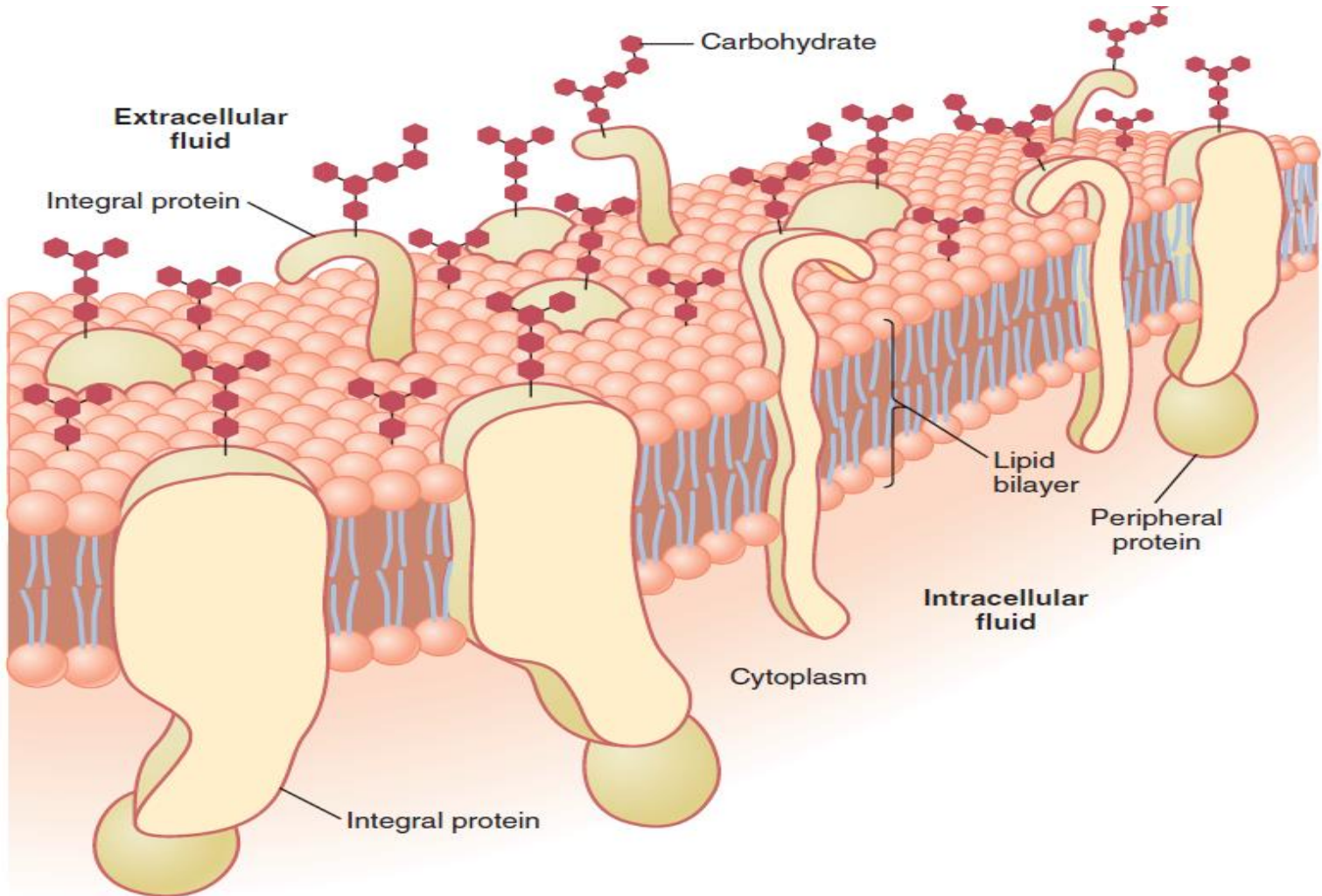
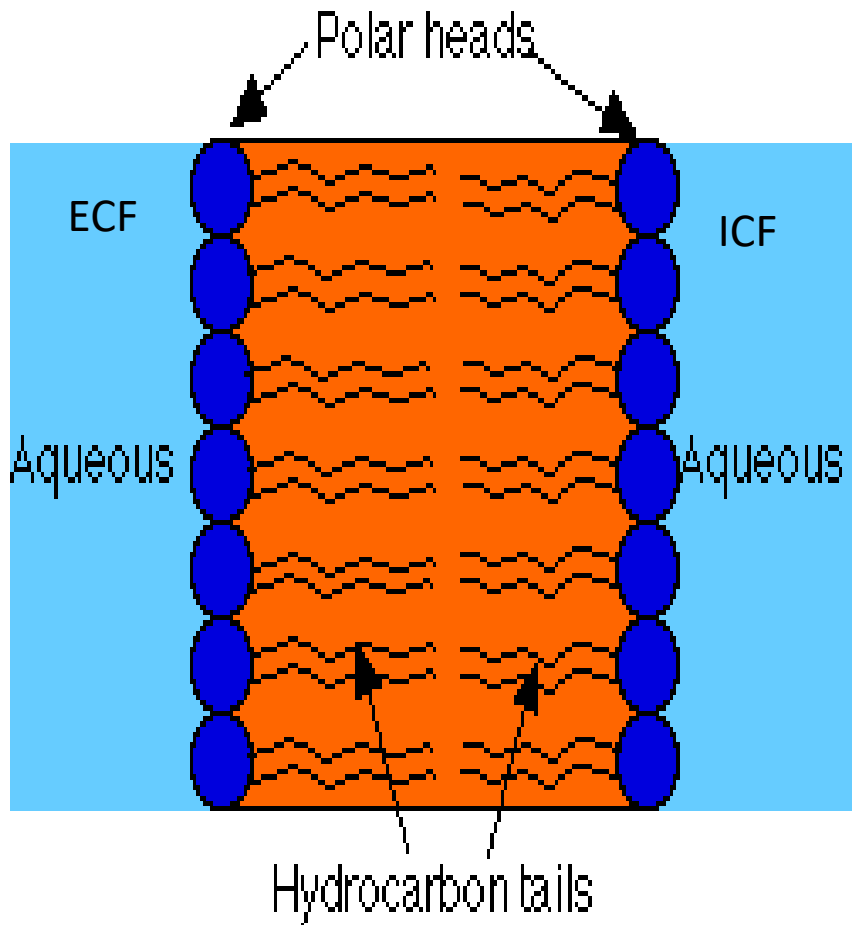


Fig. Structure of the cell membrane (Guyton & Hall, 13th edition)

Lipid Component of Cell Membrane



- Lipids form the **basic structure of the membrane**
- The lipid molecules are arranged in two parallel rows, forming a **lipid bilayer**
- **Polar phosphate heads** are **hydrophilic** and face the ICF and ECF
- **Non-polar tails** are **hydrophobic** and face each other in the interior of the bilayer

Lipid Cont...

- The lipid bilayer portion of the cell membrane is impermeable to water and water soluble substances
 - Includes ions, glucose, urea and others
- Fat soluble substances can cross cell membrane easily
 - Includes O_2 , CO_2 , alcohol, drugs and others

Membrane proteins

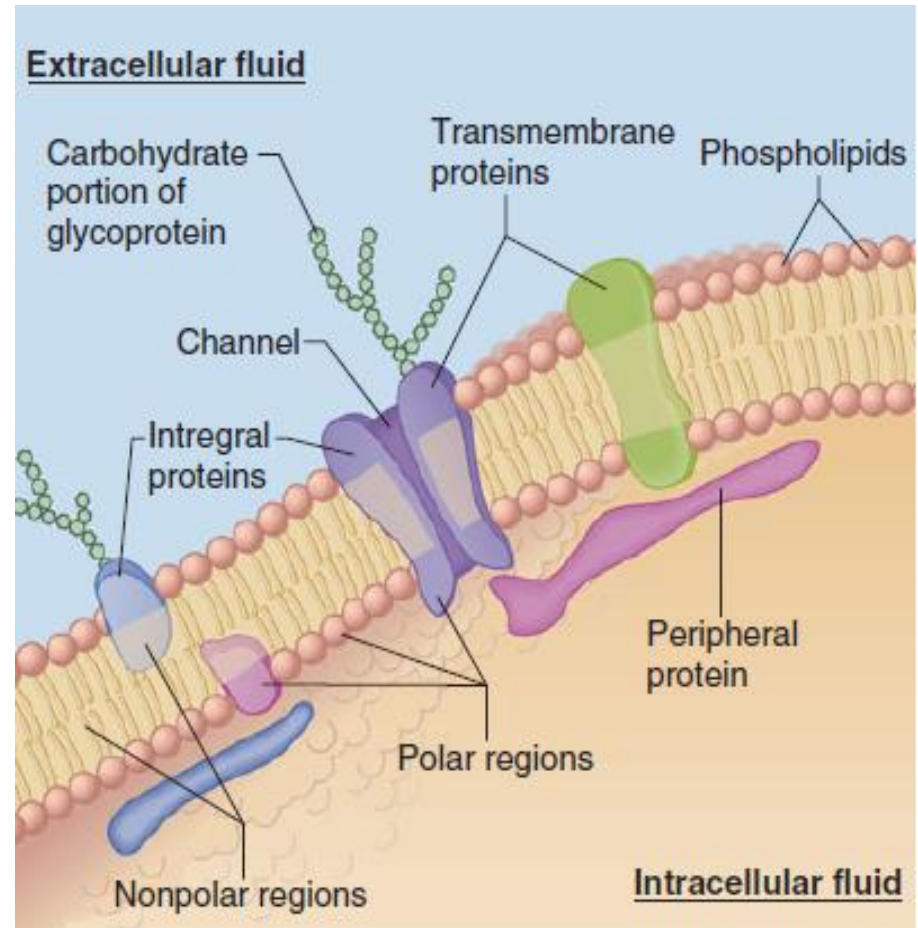
Two types

A. Integral (intrinsic) proteins:

- Interdigitated in the hydrophobic center of the lipid bilayer
- Transmembrane proteins are integral proteins that span the entire bilayer.

B. Peripheral (extrinsic) proteins:

- Bind to the hydrophilic polar heads of the lipid or on integral proteins



Membrane protein cont...

- Transmembrane proteins serve as:
 - **Channels** through which ions pass
 - **Carriers** which transports materials across the bilayer e.g. glucose
 - **Pumps** which actively transport ions
 - **Receptors** for neurotransmitters and hormones
- Peripheral proteins serve as:
 - **Enzymes**
 - Contribute to the cytoskeleton on the **intracellular surface**
 - Contribute to the **glycocalyx** (a cell coat) on the extracellular surface

Membrane Carbohydrates

- Attached on the outside surface of the membrane, binding with protruded **integral proteins** and **lipid**
→ form **glycoproteins** and **glycolipid**
- **Function**
 - It is the site of **hormonal receptors** (act as receptors for NTs, hormones and drugs) and
 - **antigenic activity** in ABO blood groups (immune reaction , antigenical importance),
 - Cell to cell attachment

General Functions of Cell Membrane

1. Physical isolation

A physical barrier that separates ICF from ECF

2. Regulation of exchange with the environment

Controls:

- entry of ions and nutrients into the cell
- elimination of cellular wastes
- release of products from the cell

General Functions Cont...

3. Communication between the cell and its environment

- Contains proteins that enable the cell to recognize and respond to molecules or to changes in its external environment

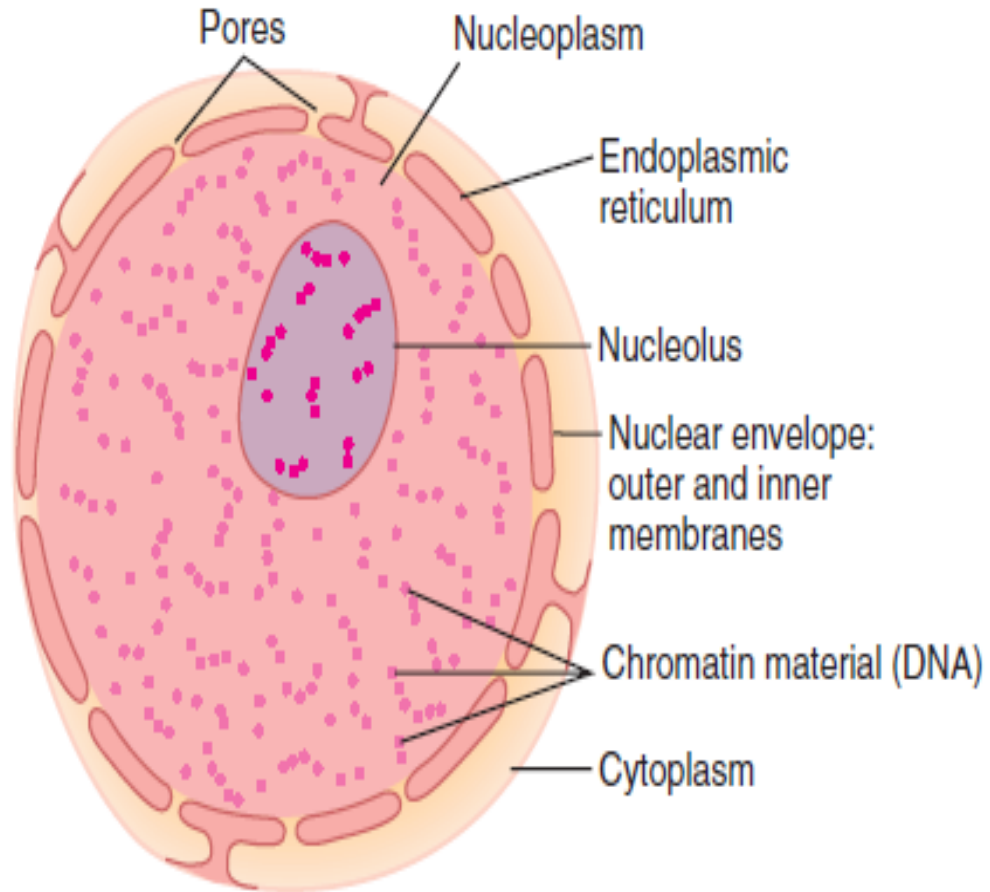
4. Structural support

- Proteins in the cell membrane hold the cytoskeleton in place to maintain cell shape

5. Enzymatic activity

Nucleus

- The **control center** of cell
- Contains large quantities of **DNA**, which comprise the genes (units of heredity)
- The genes determine the characteristics of the cell's proteins, including the structural proteins, as well as the intracellular enzymes that control cytoplasmic and nuclear activities



Nucleus cont...

- With the exception of mature human red blood cells, all cells within the body contain a nucleus
- Contains **chromatin** and **nucleoli**
- The nuclear contents are surrounded by a double walled **nuclear membrane**
- The pores present in this membrane allow fluids, electrolytes, RNA, and other materials to move between the nuclear and cytoplasmic compartments
- The nucleus is also the site of **RNA synthesis**

Nucleolus

- An accumulation of large amounts of **RNA** and **proteins**
- Does not have a limiting membrane
- One or more per cell
- Most prominent and numerous in growing cells
- The site of **synthesis of ribosomes**, the structures in the cytoplasm in which proteins are synthesized

Ribosomes

- The sites of protein synthesis in the cell
- Found in two forms: attached to the wall of ER or as free ribosomes
- Free ribosomes are found in two forms
 - scattered in the cytoplasm and
 - clustered (aggregated) to form functional units called polyribosomes

ER- endoplasmic reticulum

Endoplasmic Reticulum (ER)

- An extensive membranous structure connected with the nuclear membrane
- Two types
 - **Rough ER**- contains ribosome
 - **Smooth ER**- no ribosome

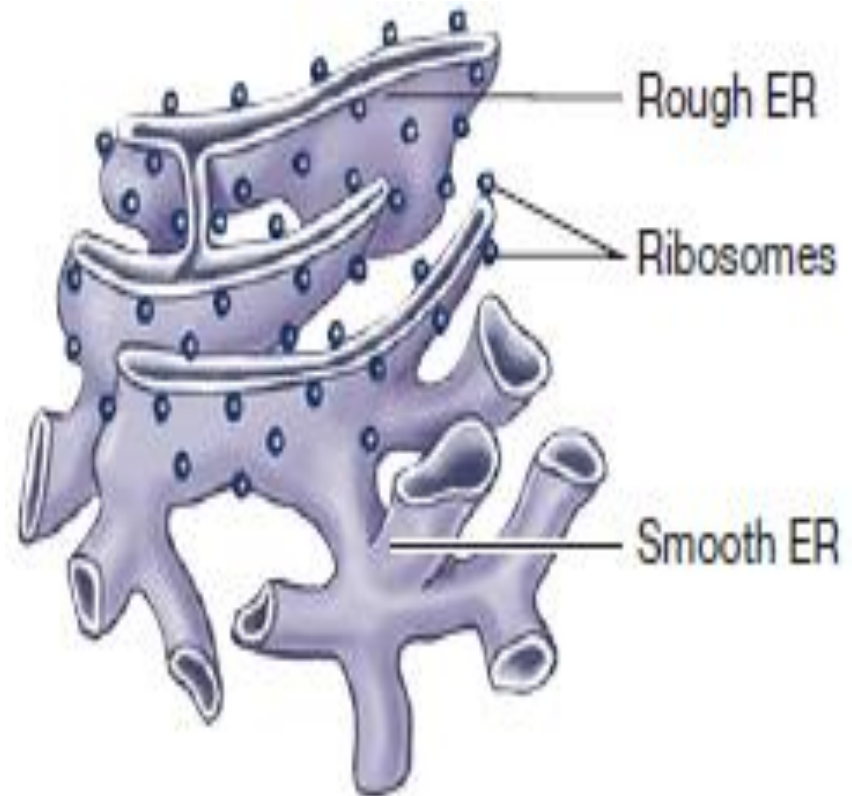


Fig. Endoplasmic Reticulum (ER)

Functions of ER

- Process molecules made by the cell and transports them to their specific destinations
- Rough ER is involved in protein synthesis
- Smooth ER Functions for:
 1. Storage:- glycogen, calcium
 2. Lipid biosynthesis
 3. Drug metabolism (detoxify)

Golgi Apparatus

- A collection of membrane-enclosed **sacs (cisternae)** that are stacked like dinner plates
- **One** or **more** golgi apparati are present in all eukaryotic cells, usually near the nucleus

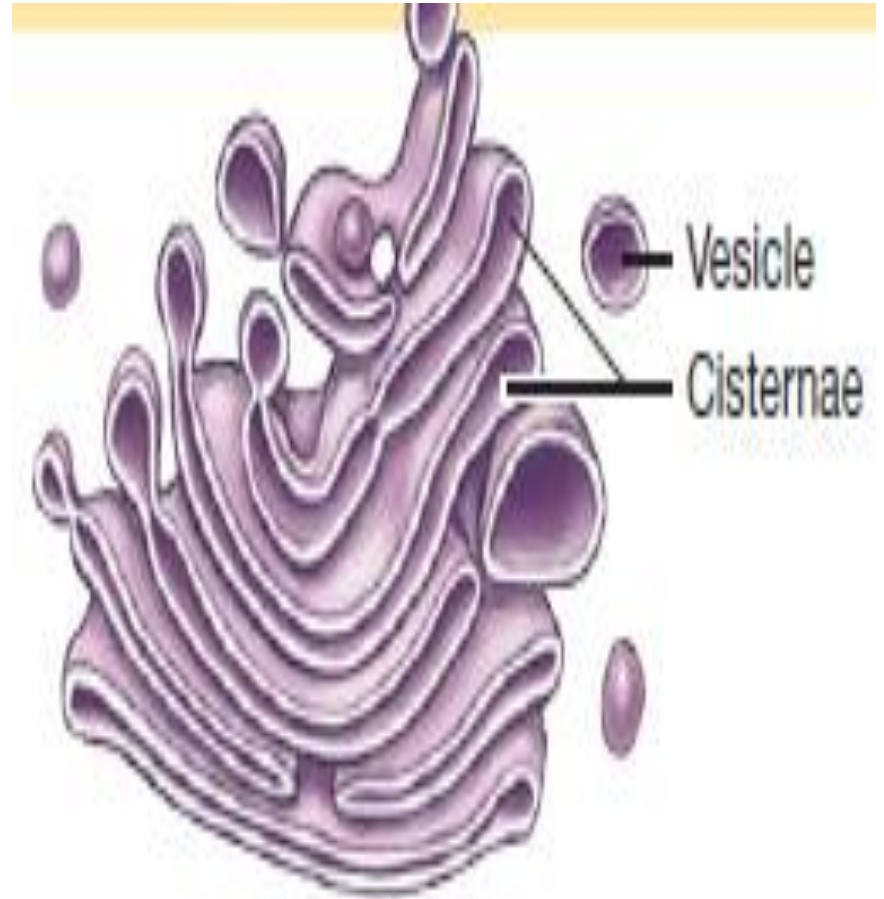


Fig. Golgi apparatus

Golgi Apparatus Cont...

- There are more than 200 enzymes that function to add, remove, or modify sugars from proteins and lipids in the golgi apparatus
- It then modifies and packages these substances into secretory granules

Golgi Complex Cont...

- Vesicles containing newly synthesized proteins bud off from the rER and fuse with the cistern on the cis side of golgi apparatus
- The proteins are then passed via other vesicles to the cistern on the trans side
- From the trans golgi, vesicles shuttle to the lysosomes and to the cell exterior

Golgi Complex Cont...

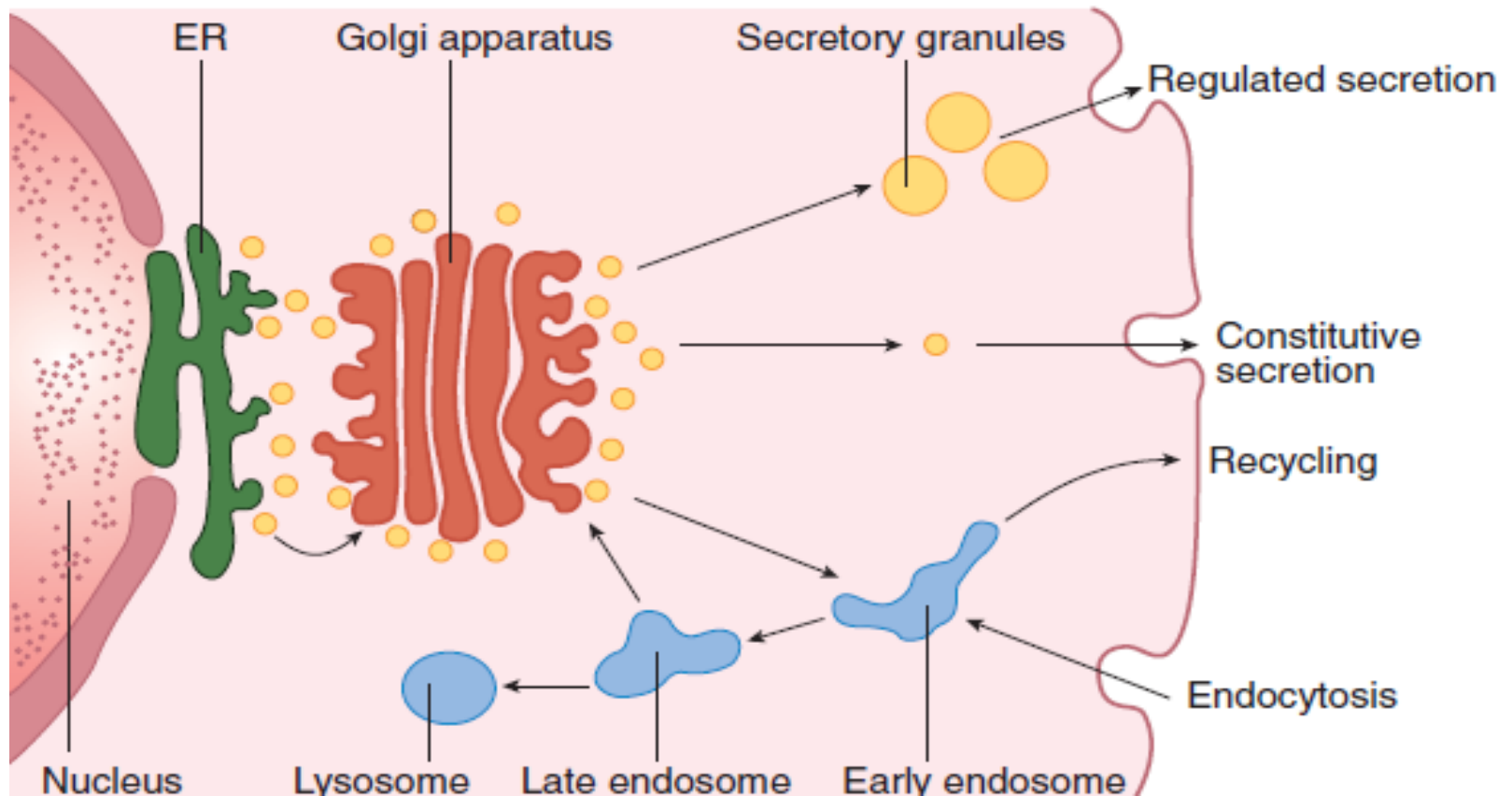


Fig. Cellular structures involved in protein processing

Lysosomes

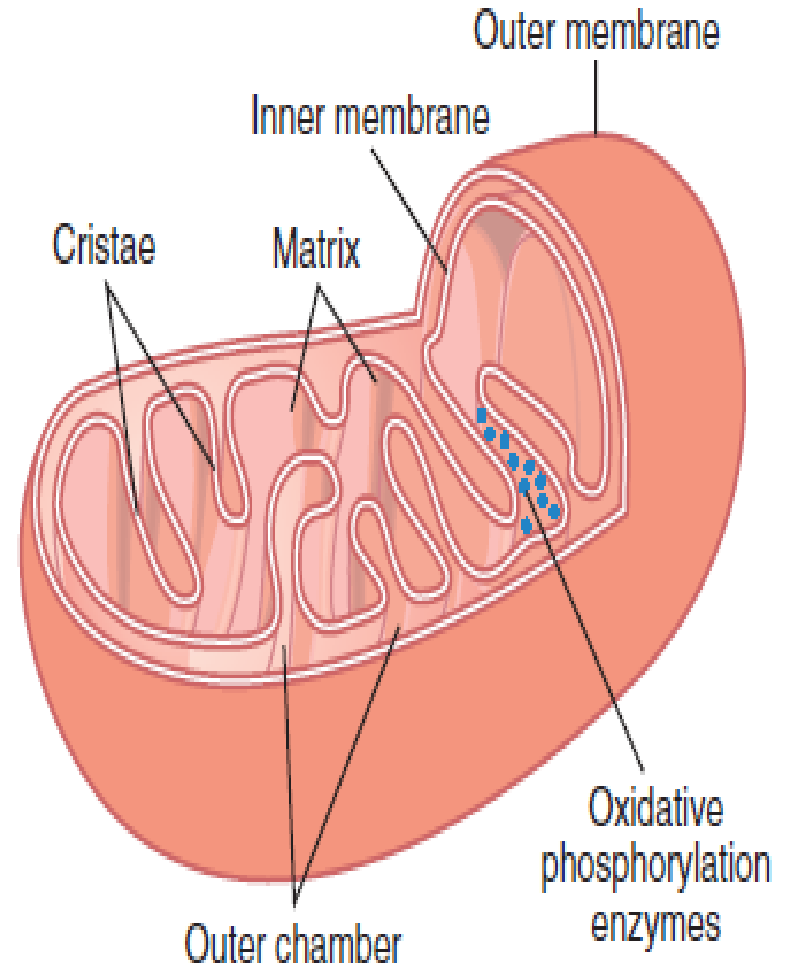
- Vesicular organelles that are formed by breaking off from the Golgi apparatus
- Contains over 40 hydrolase enzymes
- Provide an intracellular digestive system that allows the cell to digest:
 - damaged cellular structures
 - food particles that have been ingested by the cell
 - unwanted matter such as bacteria
- Deficiency of lysosomal enzymes causes lysosomal diseases

Peroxisomes

- Formed by self-replication or by budding off from sER
- Contain more than 40 oxidase enzymes, which catalyze a variety of reactions (eg, breakdown of lipids)
- Oxidases form H_2O_2 which oxidize many substances that might otherwise be poisonous to the cell

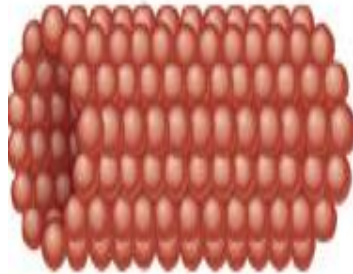
Mitochondria

- The “powerhouses” of the cell, capable of **producing** the **energy rich compound ATP**, which is required for various cellular activities.
- Total number per cell varies from less than a hundred up to **several thousand**
- Have their own genome (DNA)



Cytoskeletal System of the Cell

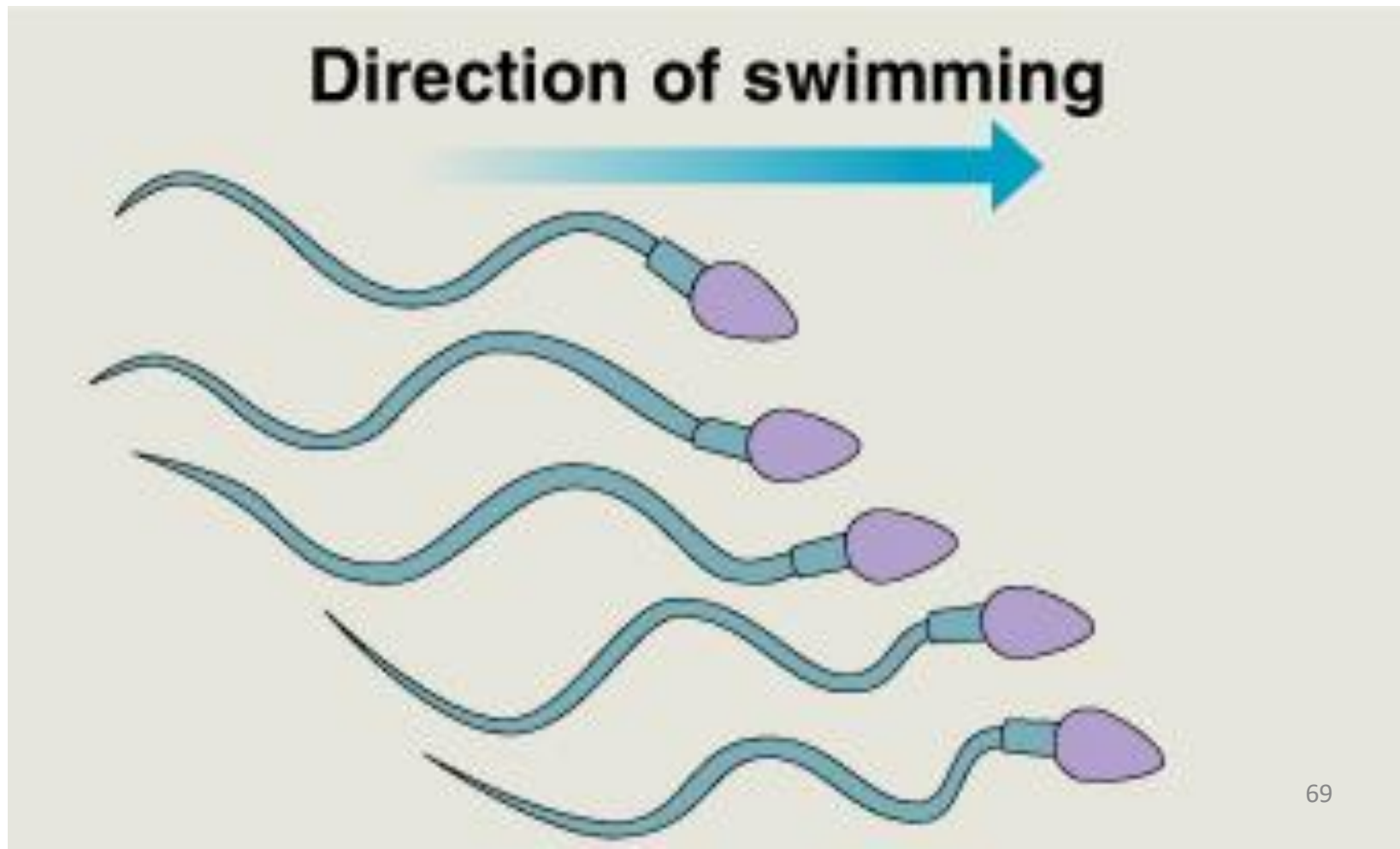
- They are **microfilament**, **intermediate filaments** and **microtubules**, rigid threadlike structures dispersed throughout the cytoplasm

	<u>Cytoskeletal filaments</u>	<u>Diameter (nm)</u>	<u>Protein subunit</u>
	Microfilament	7	Actin
	Intermediate filament	10	Several proteins
	Microtubule	25	Tubulin

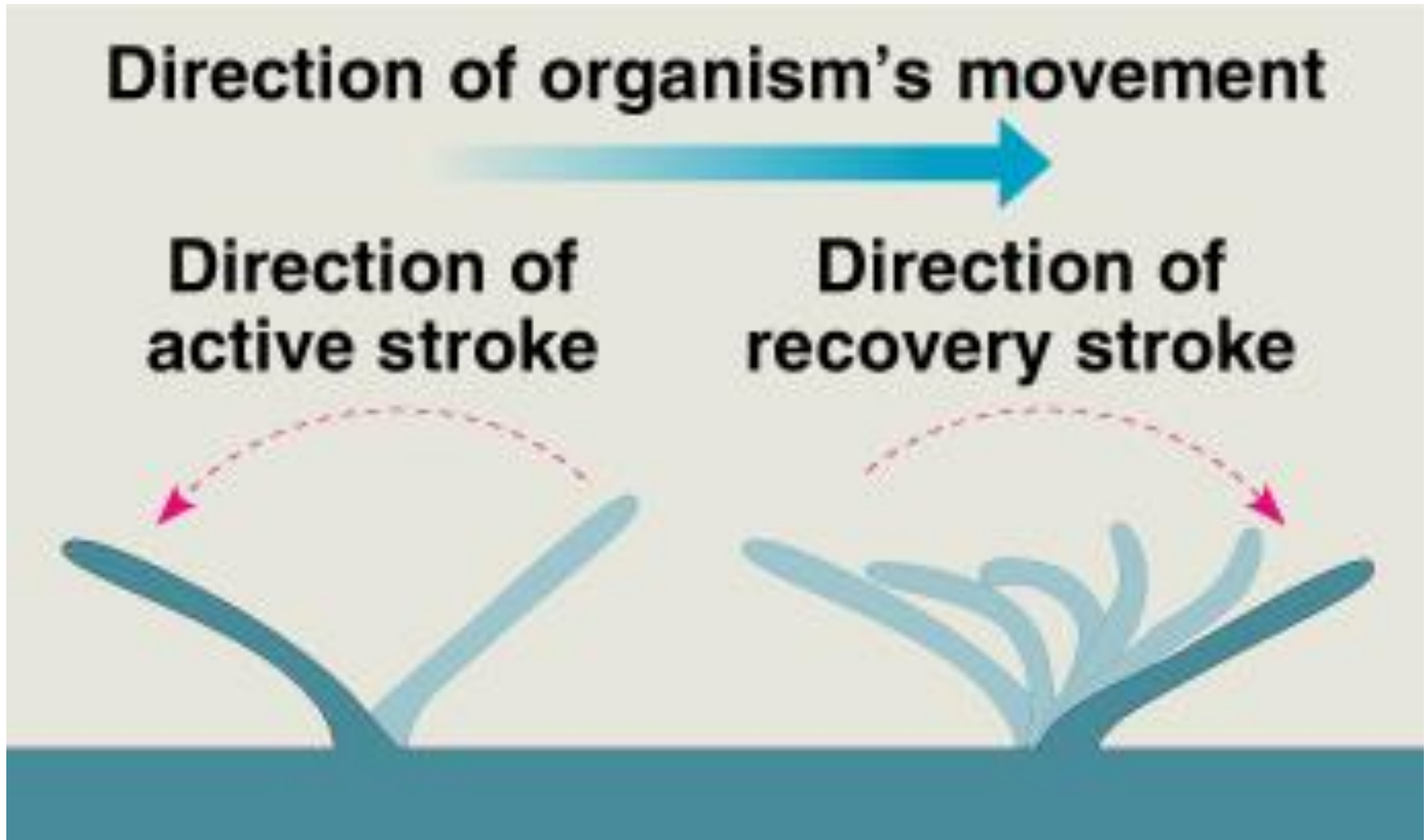
Function of Cytoskeletal System

1. Maintain shape of the cells
2. Serve as a transport system for the movement of compounds and organelles within the cell
3. Construct the mitotic spindle
4. Provide for the support and movement of cilia and flagella
5. Cell to cell contact: to fasten cell membranes together

Flagellar Movement



Ciliary Movement



Junctions between Cells

Intercellular junctions have 2 major functions

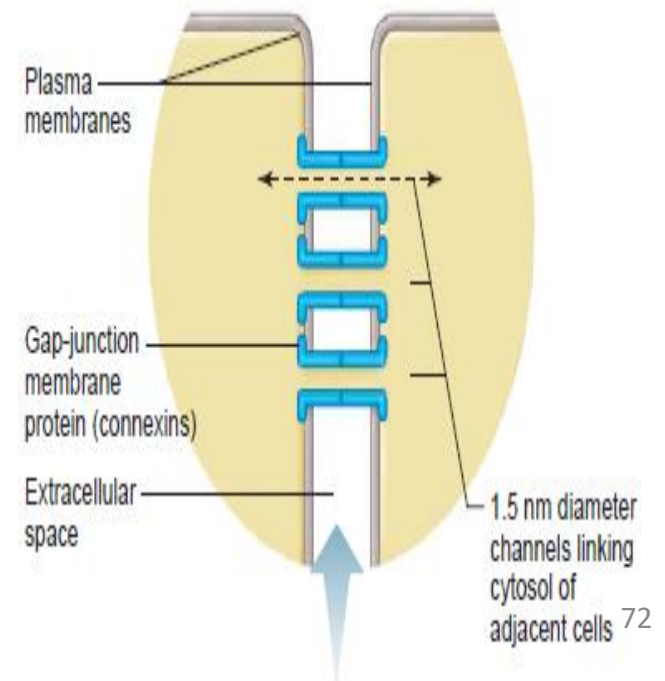
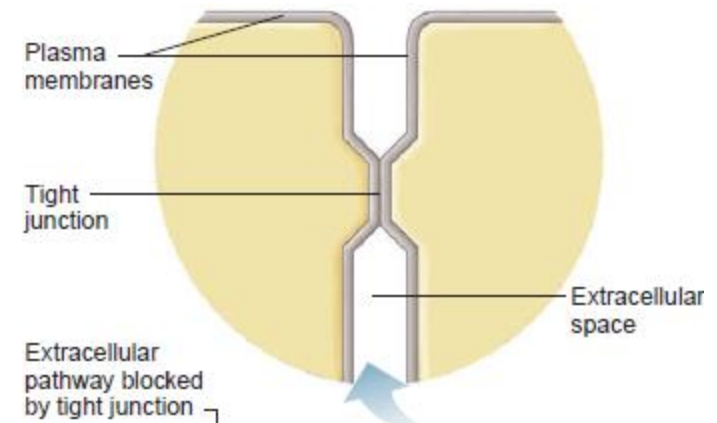
1. Fasten cells to one another and to surrounding tissues
2. Permit transfer of ions and other molecules from one cell to another

▪

Junctions Cont...

Kinds of junctions

1. Tight junctions
2. Gap junctions
3. Adherens junctions
4. Desmosomes
5. Hemidesmosomes

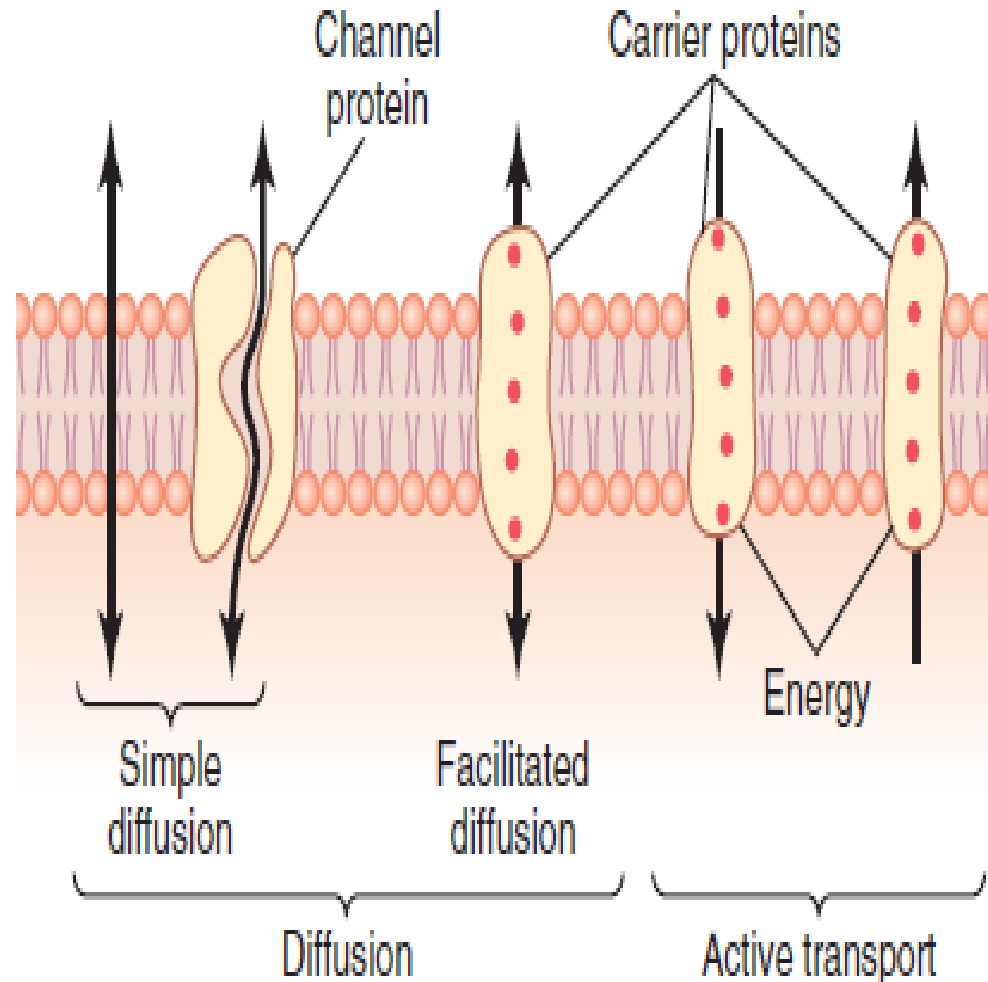


Transport of Substances across Cell Membranes

Transport across cell membrane

There are 2 forms of transport processes:

1. Diffusion- no ATP use
 - simple diffusion
 - facilitated diffusion
2. Active transport- uses ATP
 - Primary active transport
 - Secondary active transport
 - Vesicular transport



Simple Diffusion

- Diffusion is passive movement of substances down their concentration gradient
 - Example: transport of CO_2 , O_2
- Factors affecting the net rate of diffusion
 - Lipid solubility of the substance
 - Membrane permeability
 - Concentration difference or Pressure difference
 - Electrical potential difference of ions

Simple Diffusion Cont...

Membrane permeability is affected by

- Membrane thickness
- Lipid solubility
- N_o of ion channels per unit area
- Temperature
- Molecular weight of substance

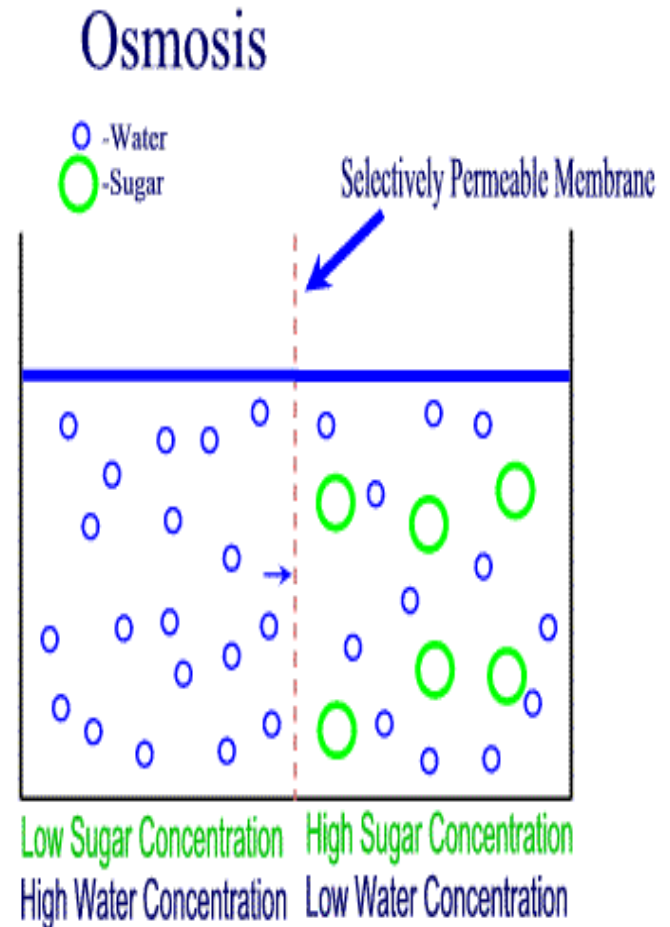
Simple Diffusion cont...

$$\text{Rate of diffusion} = \frac{S \cdot A \cdot T \cdot C}{D \sqrt{MW}}$$

Where,	C	=	Change of concentration
	S	=	Solubility in lipid
	A	=	Surface area of the membrane
	T	=	Temperature
	D	=	Distance or membrane thickness
	MW	=	Molecular wt of substances

Osmosis

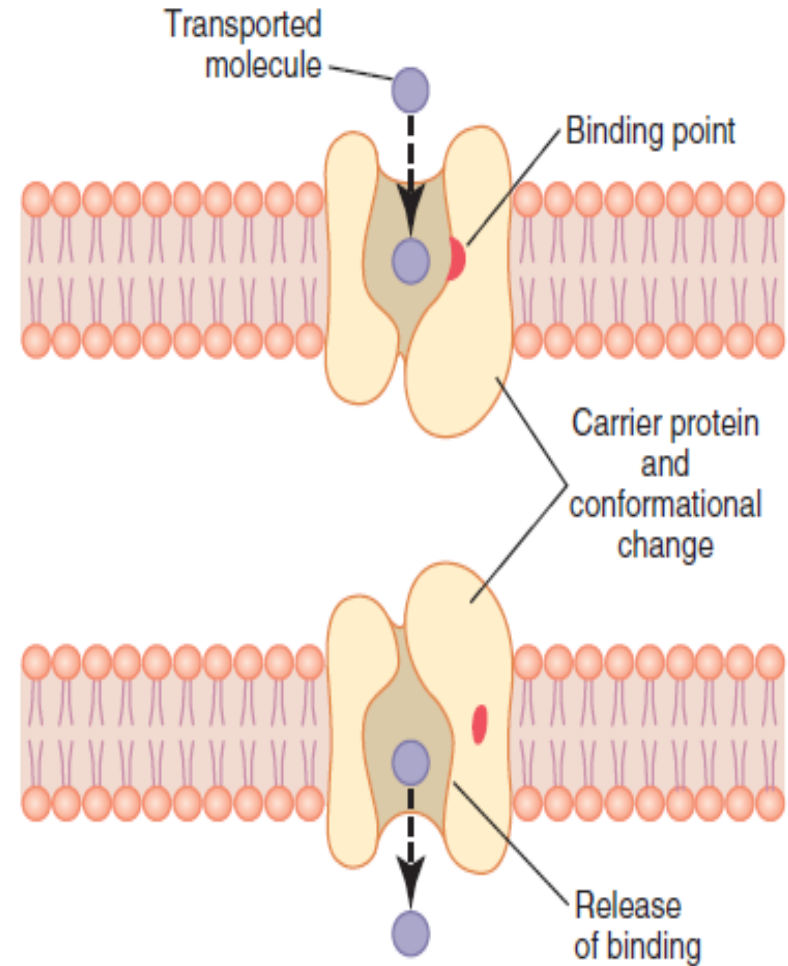
- Movement of H_2O from an area of higher amount of water to an area of lower amount of water
- H_2O molecules pass through specific water channels called **aquaporins**



N.B. Osmosis is one type of simple diffusion

Facilitated Diffusion

- Carrier mediated transport
- Do not need energy
- Transports substances **down their concentration gradient**
- Examples: transport of glucose, proteins



Active Transport

- Substances are transported **against concentration** or electrochemical gradient
- Used for the transport of substances like Na^+ , K^+ , Ca^{2+} , Fe^{2+} , H^+ , ...
- **Consumes energy** in the form of ATP

Primary Active Transport

- Carrier protein is involved
- Consumes energy from ATP directly
- Carrier protein is **anti-porter**
- Common examples
 - ✓ Na^+ - K^+ ATPase
 - ✓ H^+ - K^+ ATPase
 - ✓ Ca^{2+} ATPase

Uniport carriers: Carry single substance to one direction

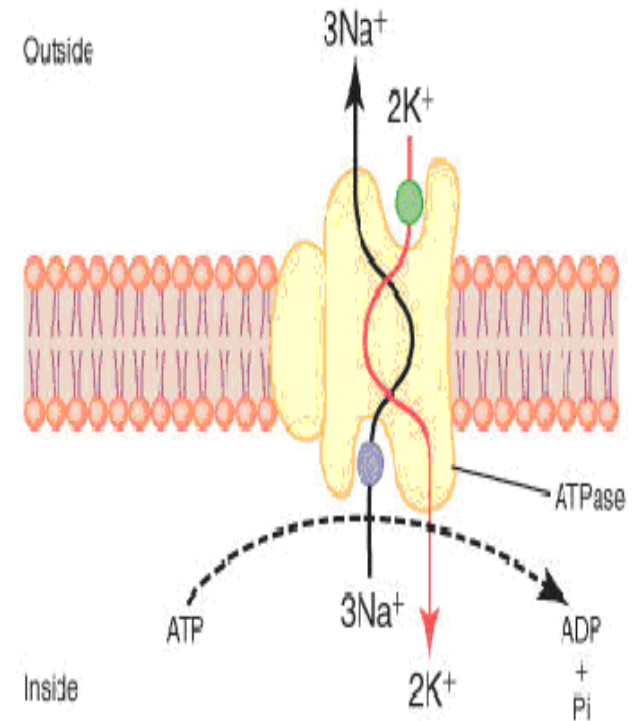
Antiport carriers: Carry two substances in opposite directions

Symport carriers: Carry two substances into the same direction

Active Transport Cont...

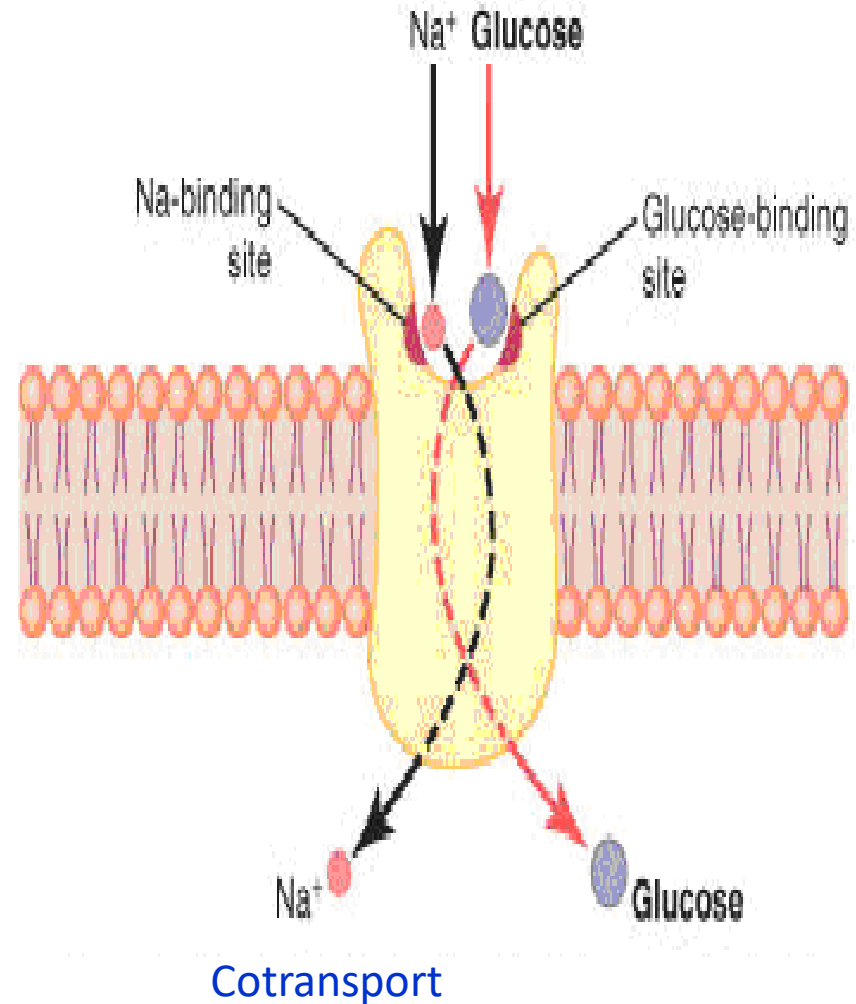
Na-K-Pump (Na^+ - K^+ ATPase)

- A carrier protein that is made up of two subunits, larger α and smaller β
- Pumps 3Na^+ outward and 2K^+ inward
- Has ATPase activity inside
- Accounts for about 24% of the energy utilized by cells, and in neurons it accounts for 70%.
- Energy brings conformational change of the pump so that Na^+ pumped outward and K^+ inward



Secondary Active Transport

- Carrier protein is involved
- Consumes energy **indirectly** from already built electrochemical gradient



Vesicular Transport

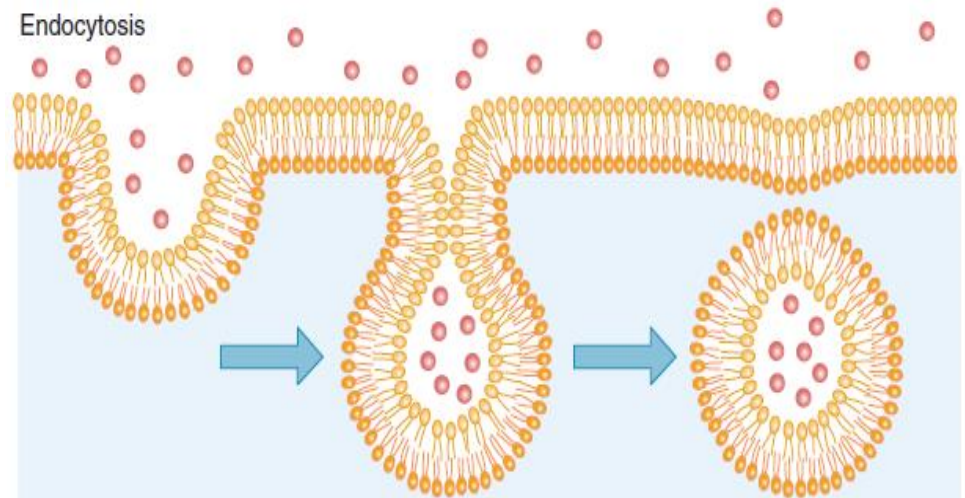
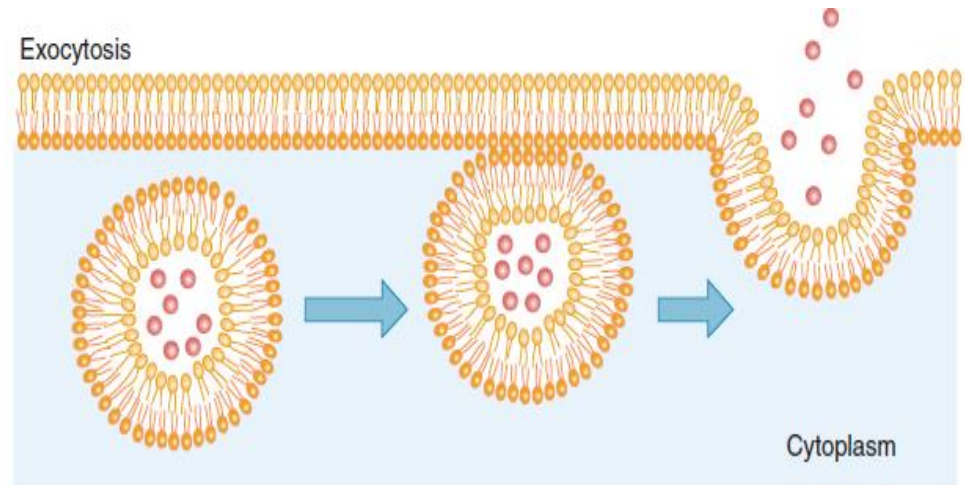
There are two types:

1. **Endocytosis**: the process in which a region of the plasma membrane is pinched off to form an endocytic vesicle inside the cell
 - a. **Phagocytosis** (“cell eating”)- **bacteria**, **dead tissue**, or other bits of microscopic material are engulfed by cells
 - b. **Pinocytosis** (“cell drinking”)- **vesicles much smaller** in size and the substances ingested are in **solution**

Vesicular Transport Cont...

2. Exocytosis

- Vesicles containing material export and fuse with the cell membrane and then breaks down, leaving the contents of the vesicle outside
- Ca^{2+} -dependent process



Membrane Potential

Membrane Potential Cont...

- Def. ~ electrical energy difference between the inside and outside the cell

$$E_m = V_{in} - V_{out}, \text{ where}$$

V_{in} = Potential on the inside of the cell

V_{out} = Potential on the outside

E_m = Membrane potential (**mV**)

Membrane Potential Cont...

- All cells have membrane potentials
- Membrane potential α charge separation across the membrane
- The range of E_m : -20 mV to -90mV (organism, cell type)
- Δ Membrane conductance $\leftrightarrow$ Δ membrane potential

Resting Membrane Potential (RMP)

- Steady transmembrane potential of a cell that is not producing an electrical signal
- No net flow of ions across the plasma membrane
(No net inward current, influx = efflux)
- Always negative in nerve & muscle cells
- Magnitude is constant for individual cell types
 - Cardiac and skeletal muscle: -90mV
 - Motor neuron: -70mV
 - Smooth muscle: -55 to -30mV

RMP Cont...

- RMP is necessary for the cell to fire an action potential
- RMP is nearly equals to that of E_K ($E_m \approx E_K$)
- Permeability $\propto$ number of open channels that allow passage of ion
- **NB.**
 - ✓ Inexcitable cells have RMP

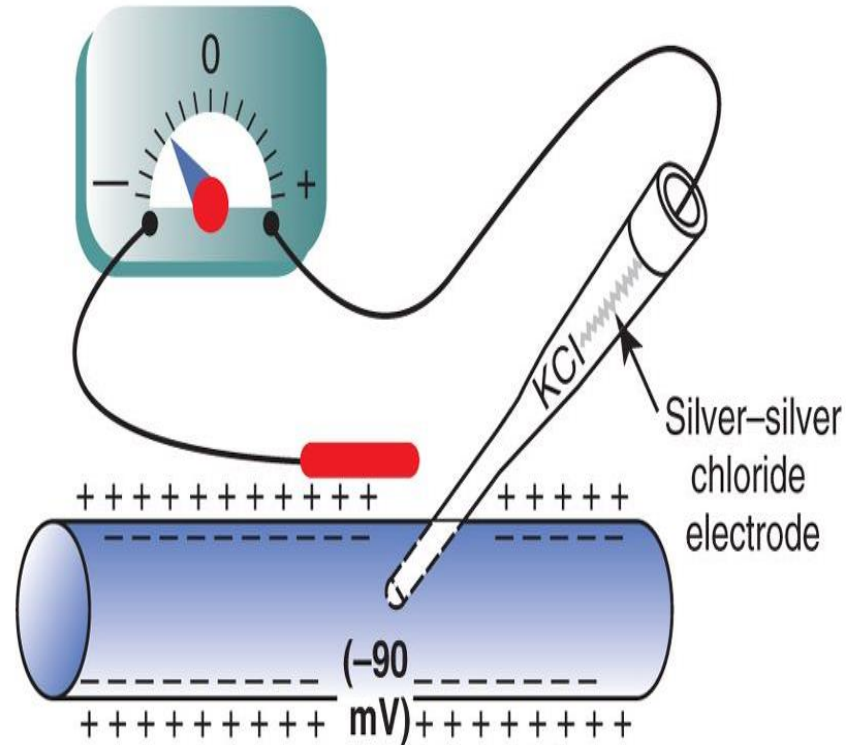


Fig. Measurement of E_m

Action Potentials

- Rapid, transient, self-propagating electrical excitation in the plasma membrane of excitable cells
- Initiation: electrical perturbation $\rightarrow \Delta E_m \rightarrow AP$
 - Sequential opening of voltage-gated channels of Na^+ and K^+

Phases and Ionic Basis of Action Potential

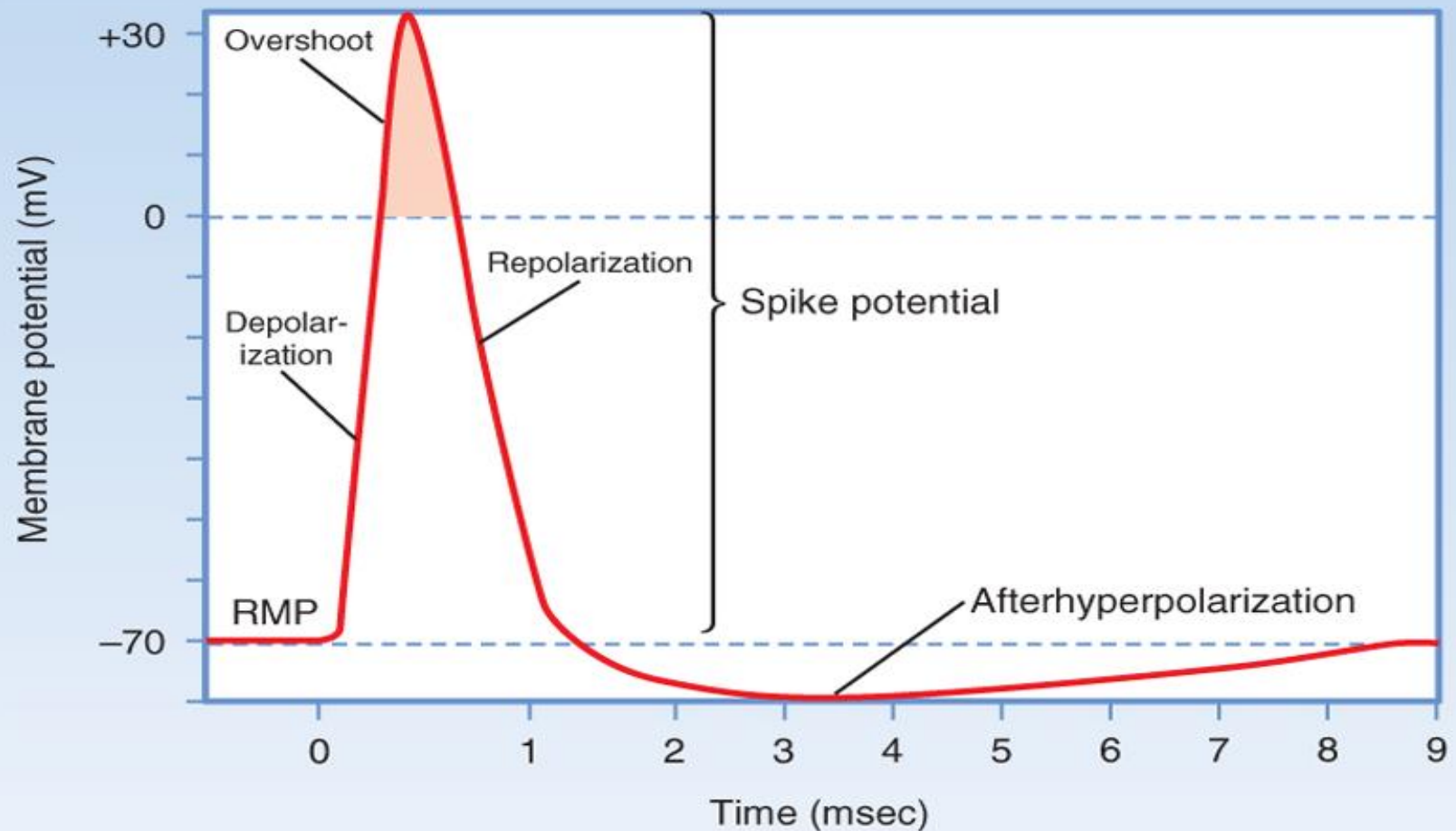


Fig. Phases of action potential

Phases Cont....

1. Resting stage

- The resting membrane potential before the action potential begins
- Membrane is “polarized”

2. Depolarization Phase/upstroke

- Caused by flow of Na^+ into the cell

3. Overshoot/peak of the action potential

- i. Portion of the AP during which the membrane is positive/reversed
- ii. Magnitude: 30 to 40mV
- iii. Approaching E_{Na^+} activation gate & ↓ Cl^- channel

Phases Cont....

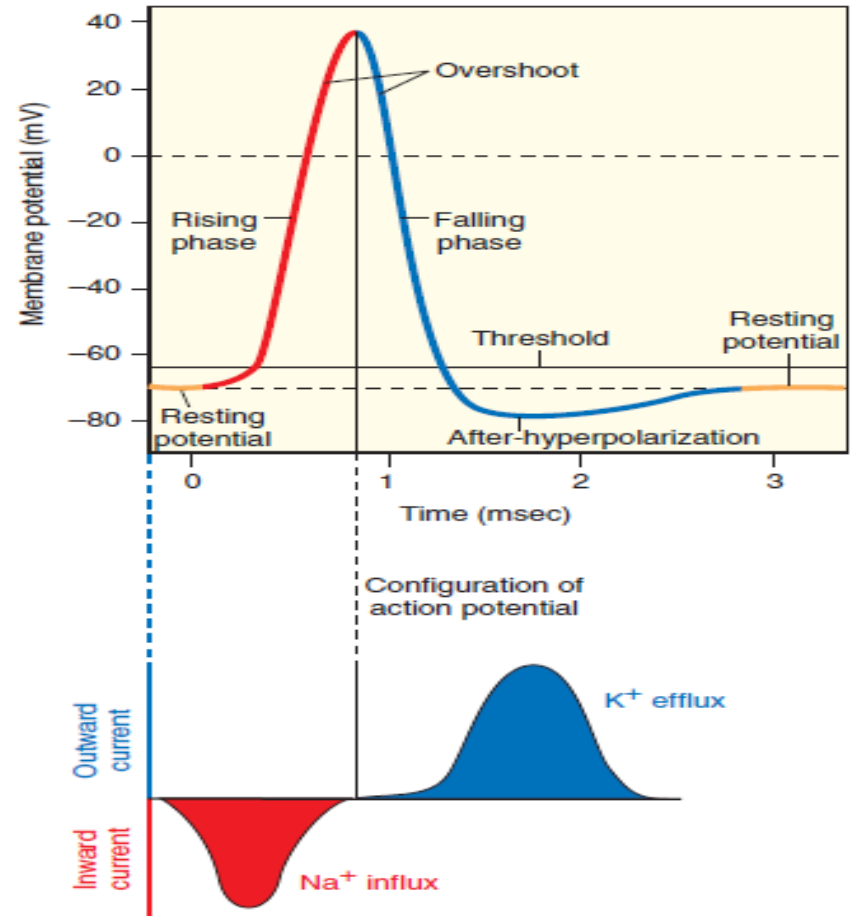
4. Repolarization (Downstroke)

- Rapid return of the membrane towards its RMP
- Reasons:
 - Time-limited nature of Na^+ permeability (g_{Na^+} is short-lived)
 - Closure of the inactivation gate of $\text{Na}^+ \rightarrow \text{Na}^+$ gate inactivation
 - $\uparrow$ gated K^+ (delayed opening of K^+ channels, **activation gate** $\rightarrow$ open, activated)

Phases Cont...

5. Afterpotentials (under shoot)

- Membrane becomes more negative than its RMP at the end of the action potential
- Due to delaying of K^+ to close



Properties of Action Potential

i. Threshold:

- Critical stimulus intensity below which no action potential (AP) occurs, above which an action potential occur
- $< \text{Threshold} \rightarrow$ no action potential
- $\geq \text{Threshold} \rightarrow$ action potential occurs
- Varies from neuron to neuron (10-20mV depolarized from resting potential)
- **Significance:** small random depolarizations of the membrane do not generate AP

Properties Cont...

ii. **All -or-none**: size of AP is independent of stimulus magnitude (**100-110mV**)

iii. **Refractoriness**:

ARP: another action potential can't be produced at all

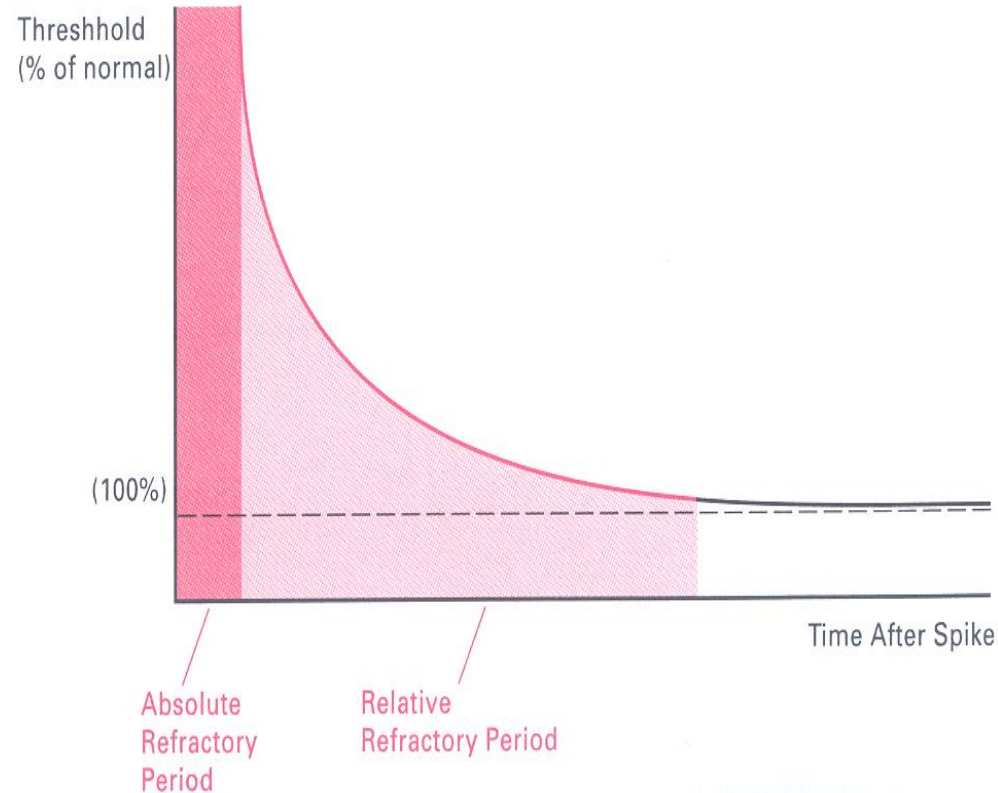
RRP: AP can be produced but threshold is larger than normal

NB.

ARF- absolute refractory period

RRP- relative refractory period

AP- action potential



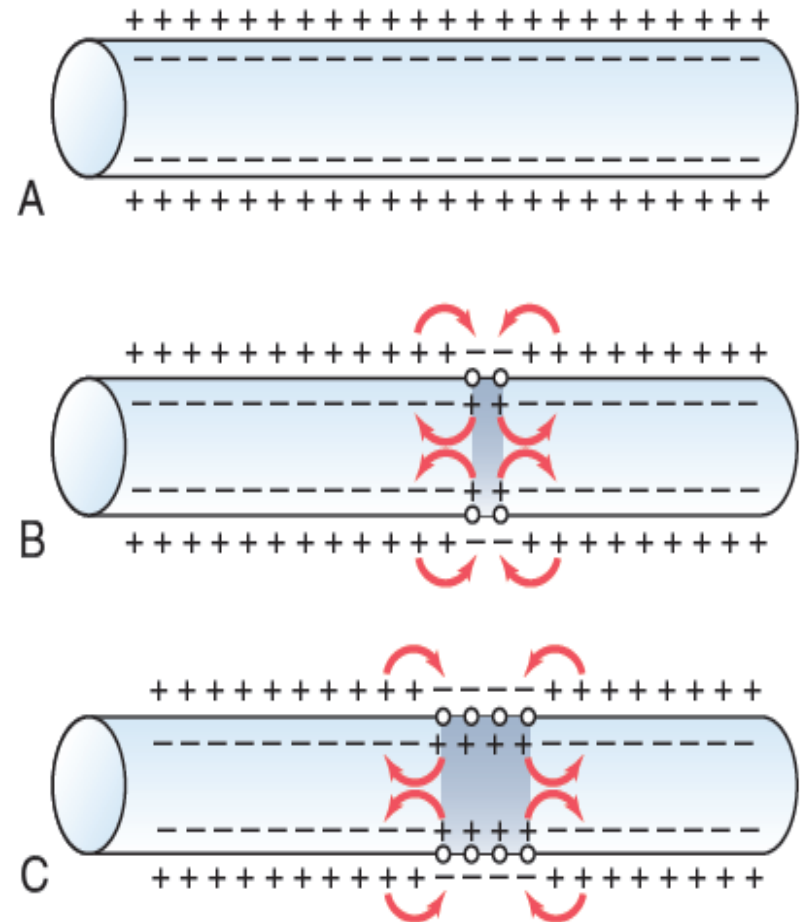
Properties Cont...

iv. Strength-latency relation

- Latency: the time delay from the onset of stimulus to the peak of action potential
- The stronger the stimulus the shorter the delay between stimulus and AP (stronger stimulus produces action potential more rapidly than weaker stimulus)

Propagation of Action Potential

- Midportion increased permeability to Na^+ → Na^+ diffuses to nearby areas inside membrane → increase the voltage above the threshold voltage value
- Na^+ channels in new areas immediately open → explosive action potential spreads



Propagation Cont...

Types:

1. Cable /continuous/sweeping conduction
 - Occurs in unmyelinated nerve
 - Speed of AP $\propto \sqrt{\text{diameter of the fiber}}$
2. Saltatory Conduction
 - Occurs in myelinated nerve
 - Speed of AP = 6 x diameter of fiber

Unit Two

Excitable Tissue

Objectives

- Describe the function of the different neuroglial cells
- Describe the major functions of the components of a neuron
- Explain the mechanism of synaptic transmission
- Explain the mechanism of skeletal muscle contraction
- Explain the mechanism of smooth muscle contraction

Introduction

- Excitable tissue is a tissue whose membrane potential can be altered in a manner that results activation of that cell's function
- Includes:
 - Nerve tissue (neurons)
 - Muscle tissue

Nerve Tissue

- The NS is made up of two principal cell types:
neurons and **neuroglial cells**
- Neurons are functional units of the NS:
 - Specialized for the generation and transmission of nerve impulse
 - About 100 billion neurons in human CNS

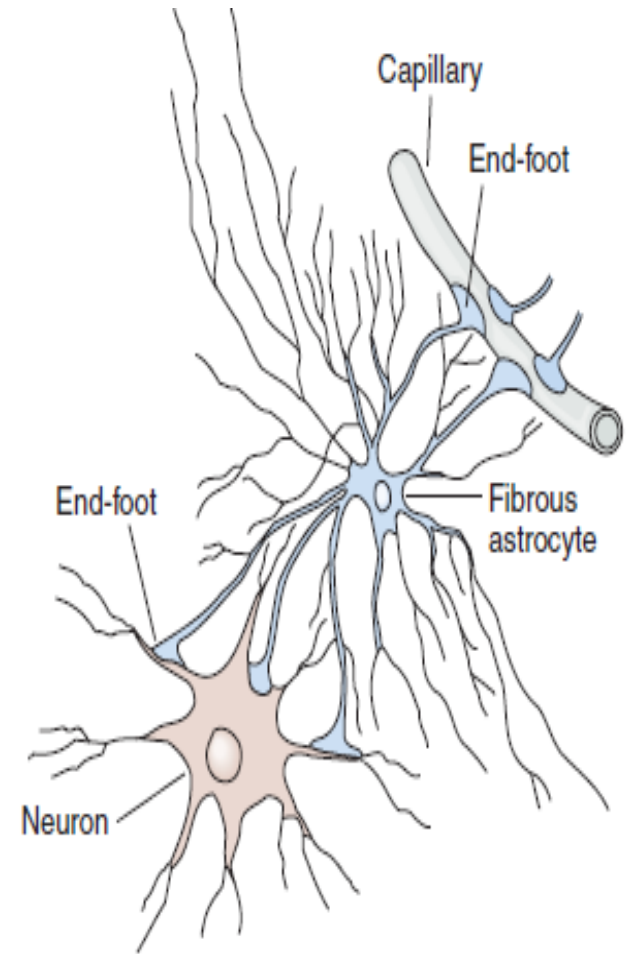
Neuroglia

- The neuroglia are **non excitable cells** found in association with neurons
- Not directly involved in signal processing (electrically inexcitable)
- Morphologically different from the neurons (**no axon, no dendrites**)
- Provide supportive functions to the neurons
- Outnumber neurons by about **20x**
- **There are 5 types:**

Neuroglia Cont...

1. Astrocytes

- Formation of BBB
- Nutrient transfer
- Spatial buffering effect [K^+]
- Re-uptake of NTs (Glutamate, GABA,...)
- Neurogenesis & detoxification (e.g. free radicals)



Neuroglia Cont...

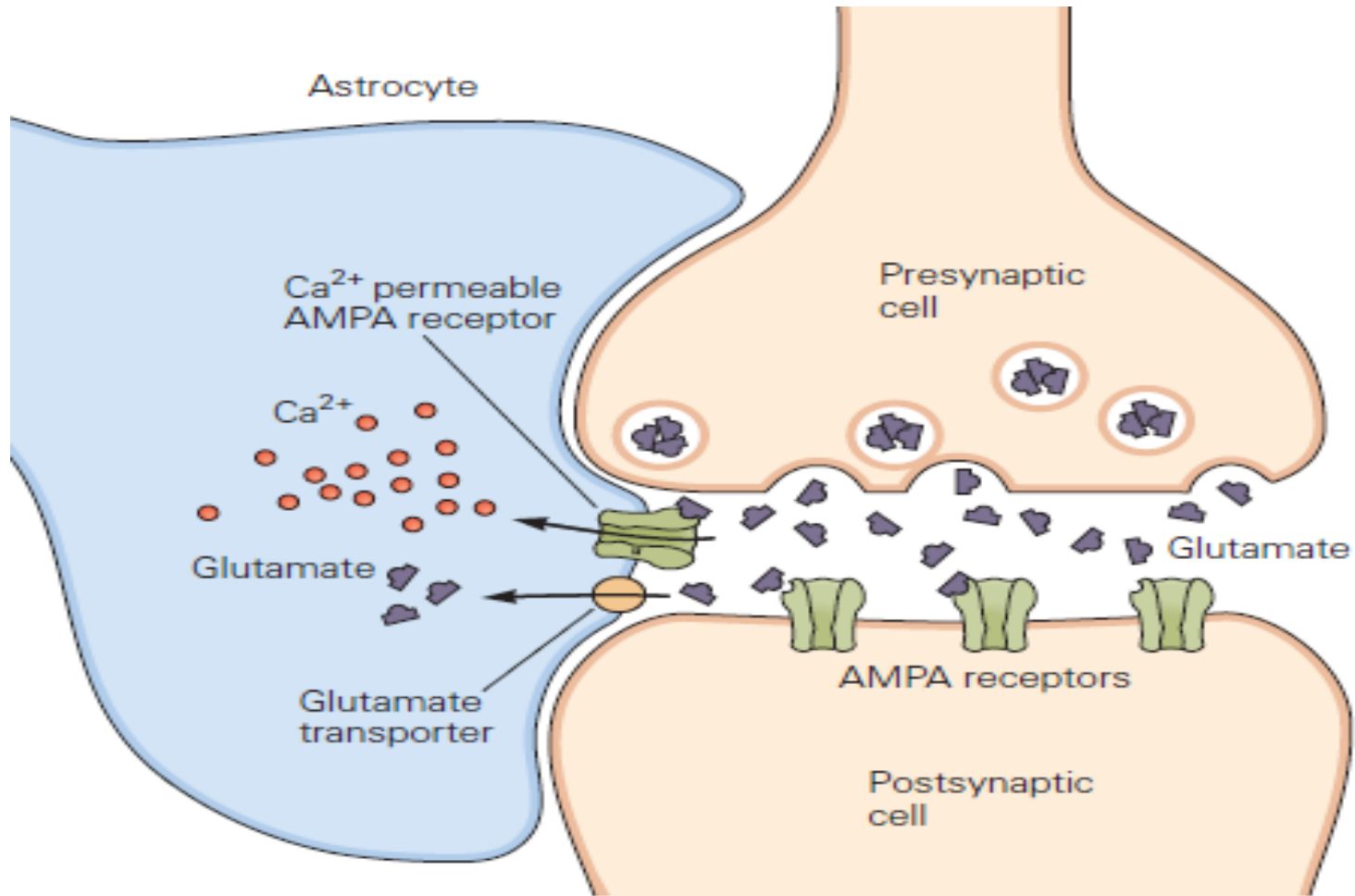


Fig. Astrocyte processes are intimately associated with synapses

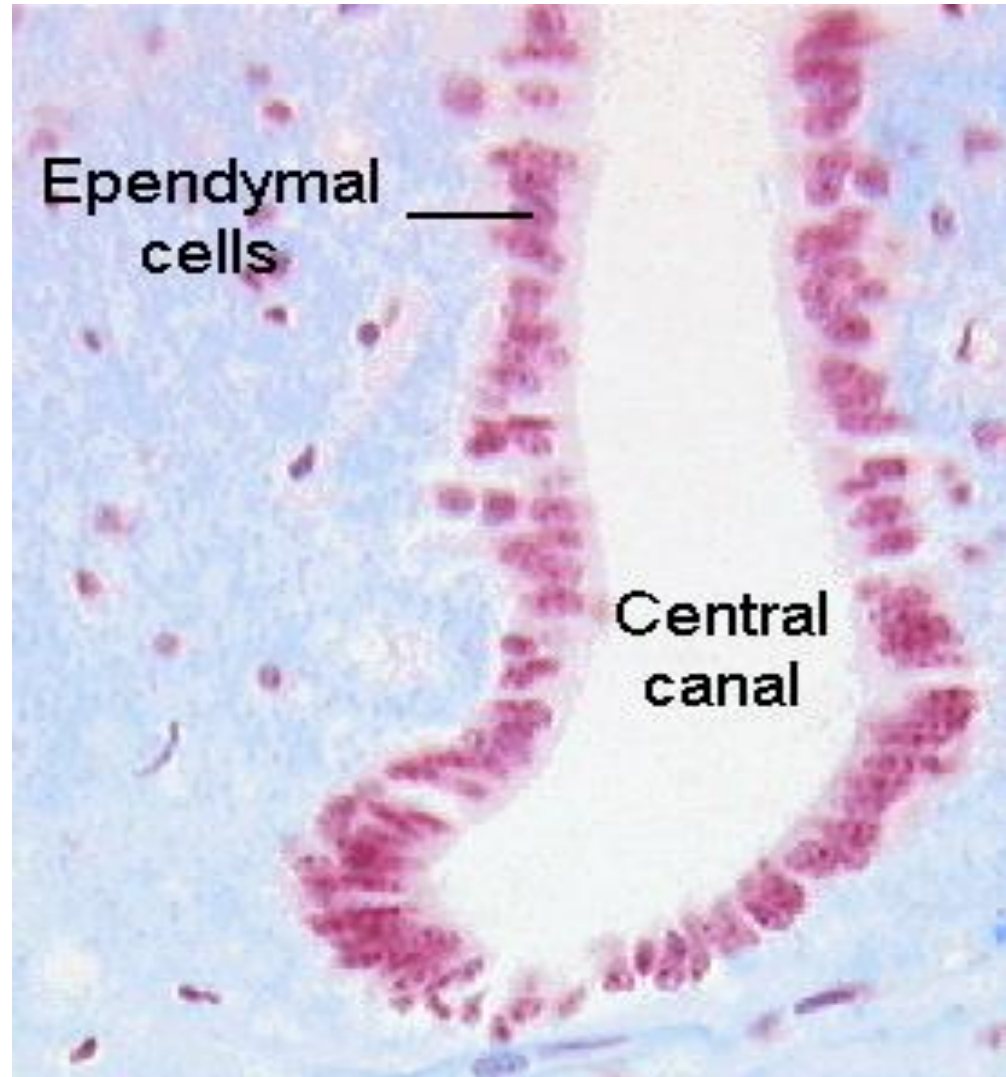
Neuroglia cont...

2. Microglia

- Macrophages of the CNS

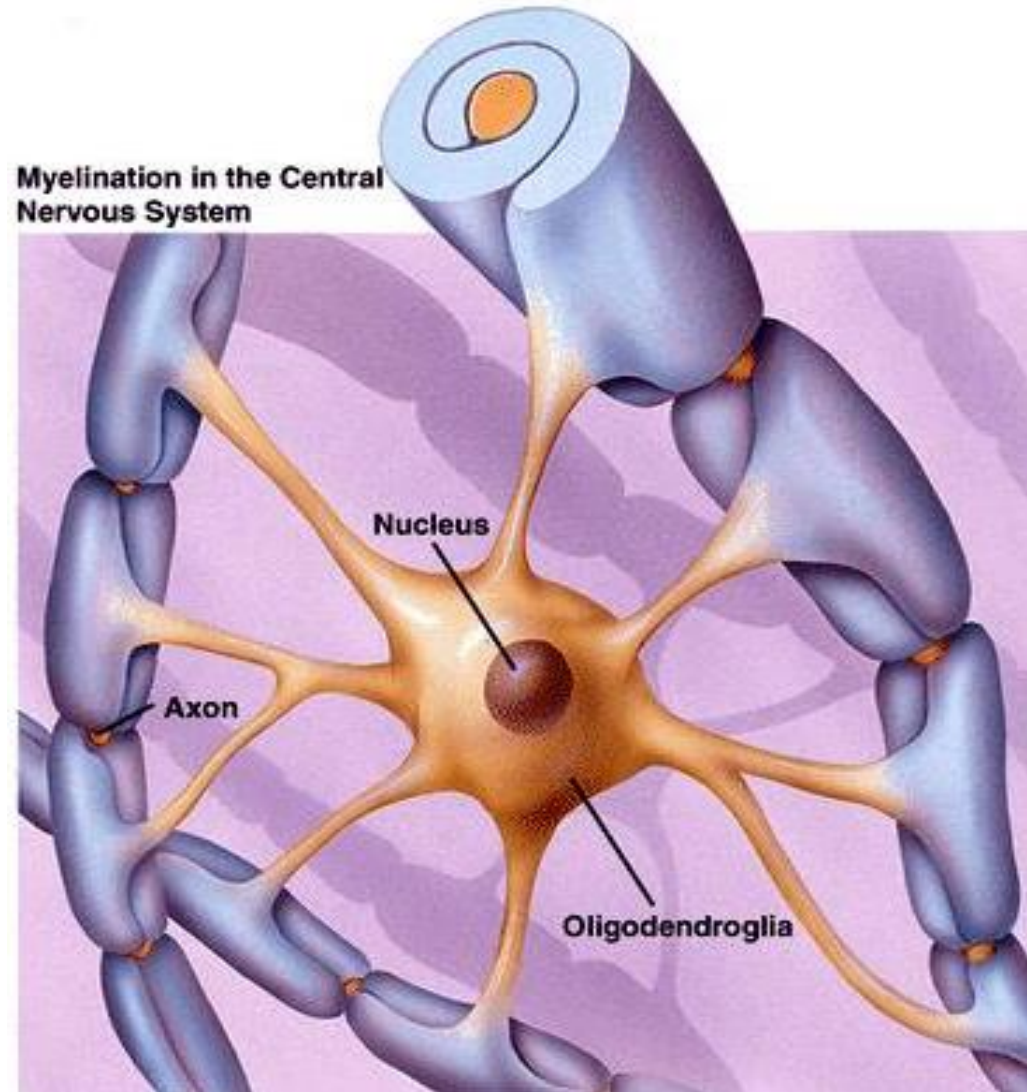
3. Ependymal Cells

- Make up the walls of the ventricles
- Secrete & absorb CSF



Neuroglia Cont...

- 4. Oligodendrocytes
 - Produce the **myelin sheath** in the CNS

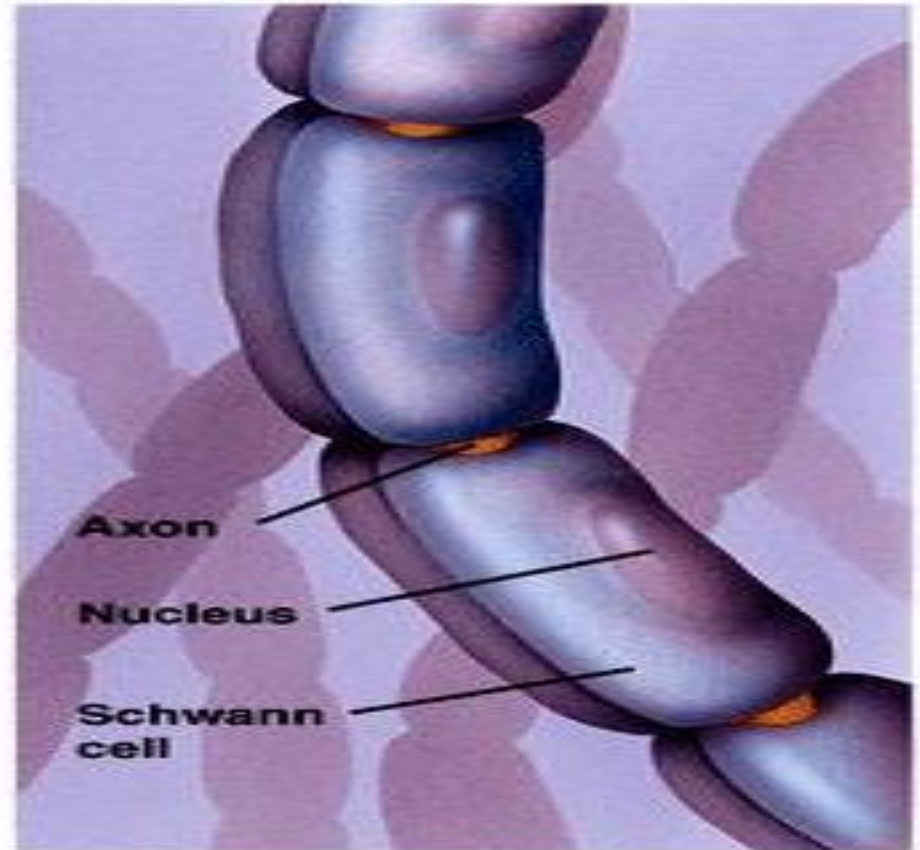


Neuroglia Cont...

5. Schwann cells

- Form myelin sheaths around the larger nerve fibers in the PNS

Myelination in the Peripheral Nervous System



Neuroglia Cont...

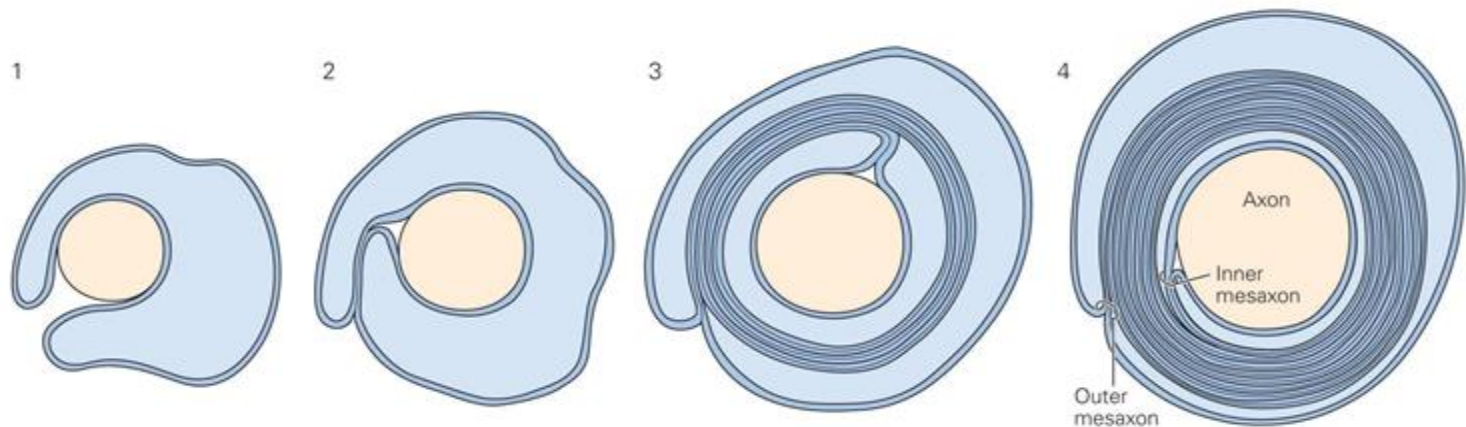
Myelin sheath

- Made up of lipids (70%) & proteins (30%)
- Envelope only one internode
- Function:
 - Insulation (↑speeds of impulse conduction)
 - Protection
 - Neuronal regeneration

Neuroglia Cont...

Myelin sheath...

- No. of layers of myelin $\propto$ diameter of the axon
 - The larger axons have thicker sheaths
 - Very small diameters axons $\rightarrow$ not myelinated



Neuroglia Cont...

Multiple Sclerosis

- Patches of demyelination/plaques in the white matter of the CNS (Brain, optic nerve + spinal cord)
- Attack of myelin by antibodies → degeneration of myelin sheath → myelin removed → conduction of impulses in the axons is impeded

Neuroglia Cont...

Guillain-Barré Syndrome

- Antibodies against the proteins in the myelin sheath of the peripheral nervous system
- Demyelination → conduction of impulse is impaired → weakness and paralysis

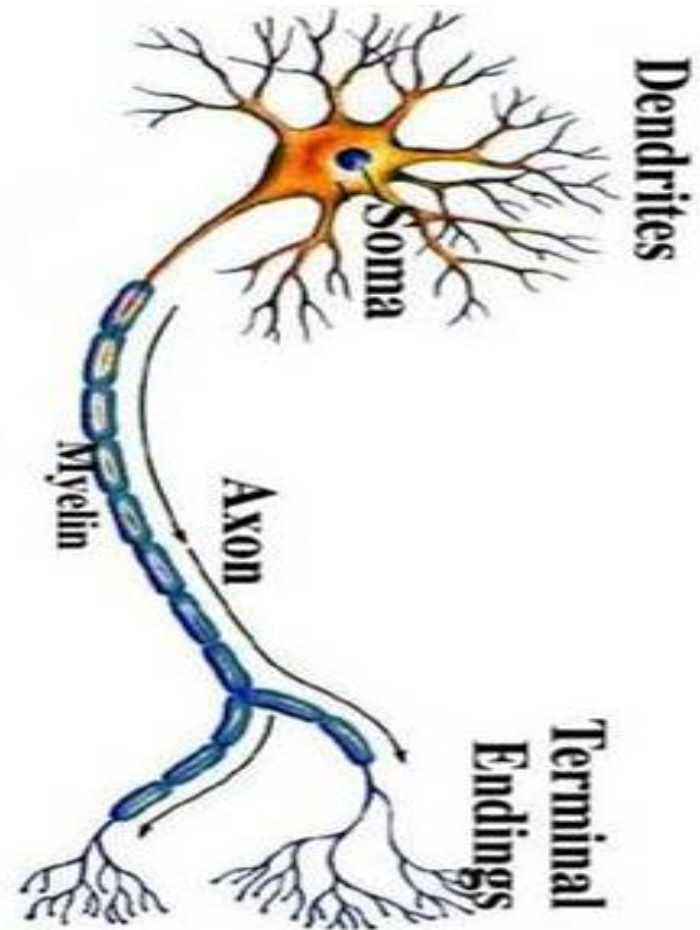
Neuron

Neurons

- Functional and structural units of the nerve system
- Significance:
 - Reception, transduction & integration of signal from internal & external environment
 - Signal conduction: chemical + electrical...
 - Information processing: learning, memory, emotion, thought...

Neurons Cont...

- Structural components of a neuron:
 - Soma/cell body
 - Dendrite
 - Axon
 - Presynaptic terminals



Soma (Cell Body)

- Gives rise to axon and dendrites
- Contains nucleus & other membranous organelles like mitochondria, ER, golgi apparatus, lysosome, cytoskeleton,...
- Clusters of soma in the CNS are known as nuclei
- Clusters of soma in the PNS are known as ganglia

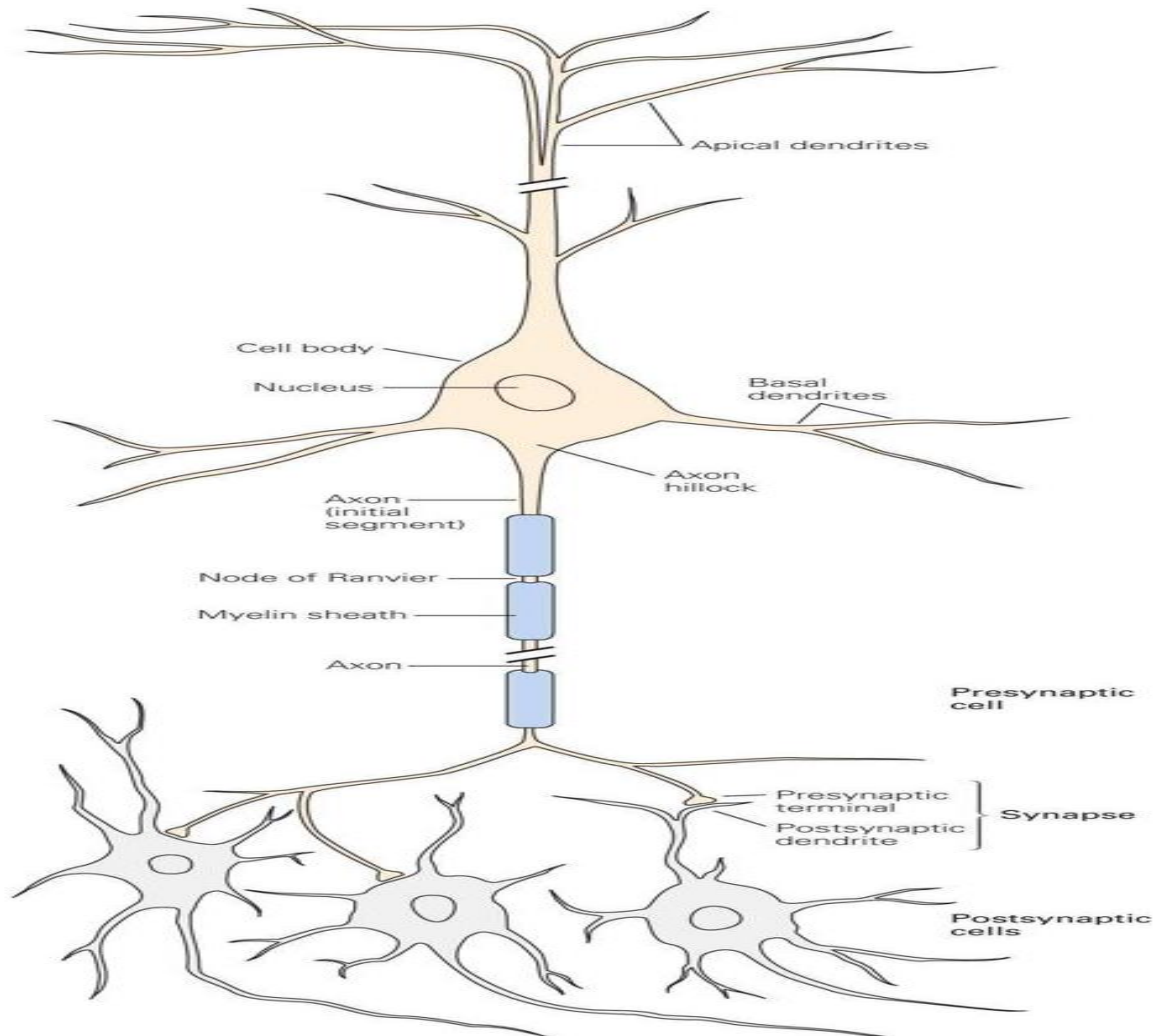
Soma Cont...

Functions of soma:

- ✓ Metabolic center of the neuron:- synthesize:
 - Synaptic vesicle membrane components
 - NT biosynthetic enzymes
 - Neurotransmitters, ...
- ✓ Reception & integration of input signals

Dendrite

- Origin: apical or basal
- Contains organelles
- Spines - $\uparrow$ SA



Dendrite Cont...

Functions

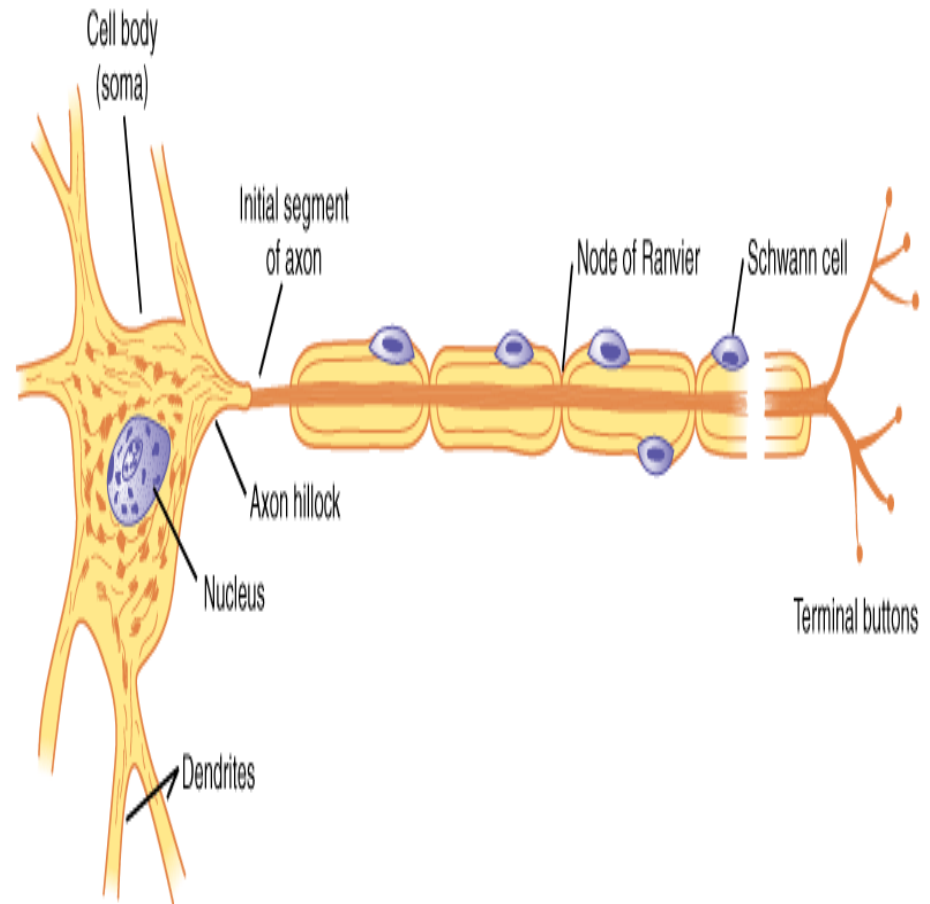
- a. Receive input signal from other neurons
 - Synaptic contacts: 10^4 - 4×10^5 /neuron
 - Important for intelligence
 - **loss of dendritic spines causes** mental retardation
- b. Integration of signal

Axon

- Originate from soma
- Only one per neuron
- Length = 0.1mm - 2m
- Uniform diameter

Special features

- Axon hillock
- Myelin sheath
- Nodes of Ranvier



Axon Cont...

Functions:

- a. Initiation of action potential at the axon hillock
 - ✓ High density of voltage-gated ion channels of Na^+ , K^+ , $\text{Ca}^{2+} \rightarrow \downarrow$ threshold
- b. Impulse conduction

Axoplasmic Transport

- Transport synaptic vesicles, enzymes, NTs,...
- Bidirectional:
 - Anterograde: Cell body → Nerve terminal
 - Retrograde: Cell body ← Nerve terminal

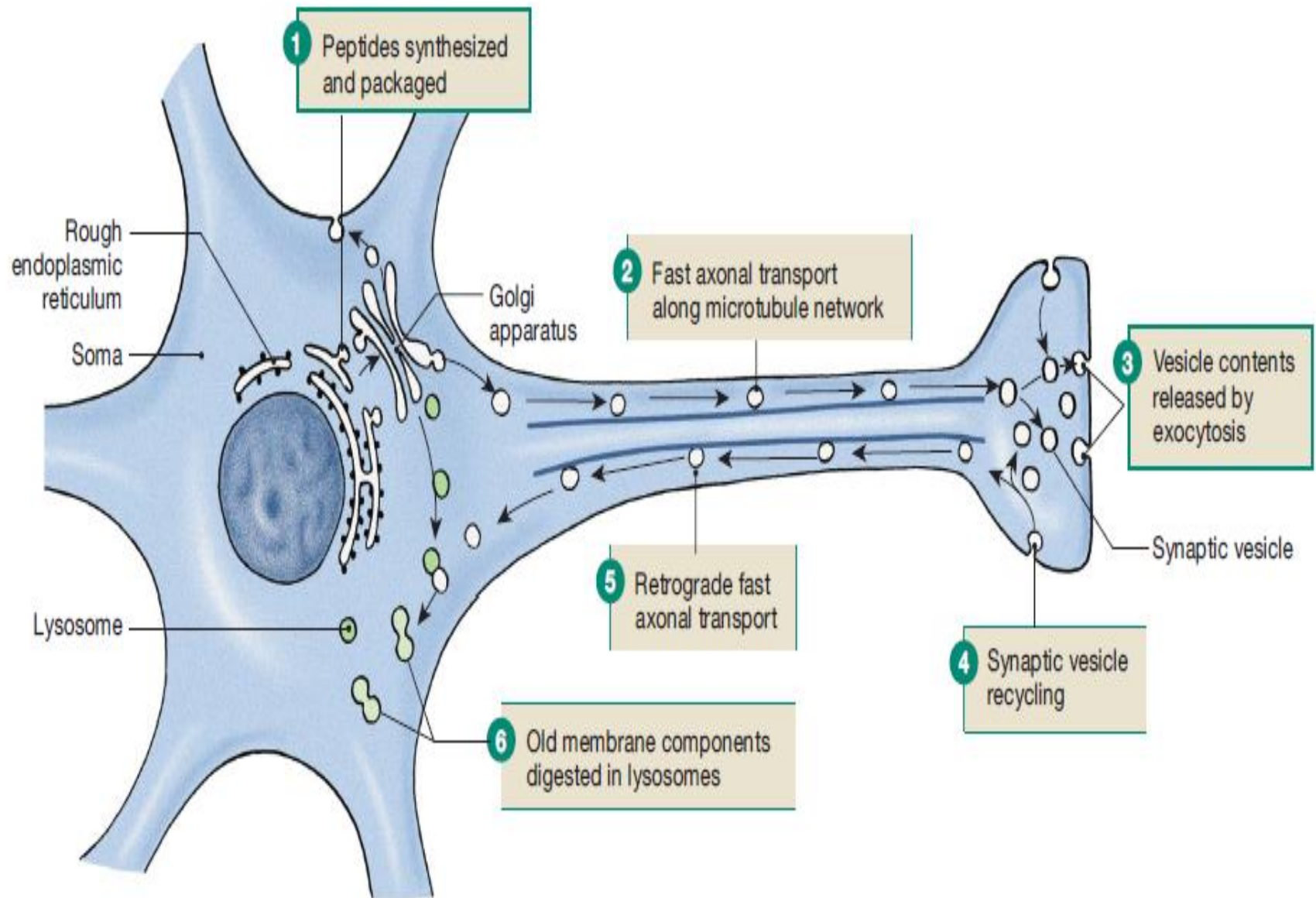


Fig. Membrane trafficking in the neuron

Presynaptic Terminal

- Contains synaptic vesicles & high number of mitochondria
- Cell sending out information is called **presynaptic cell**
- Cell receiving the information is called **postsynaptic cell**

Presynaptic Cont...

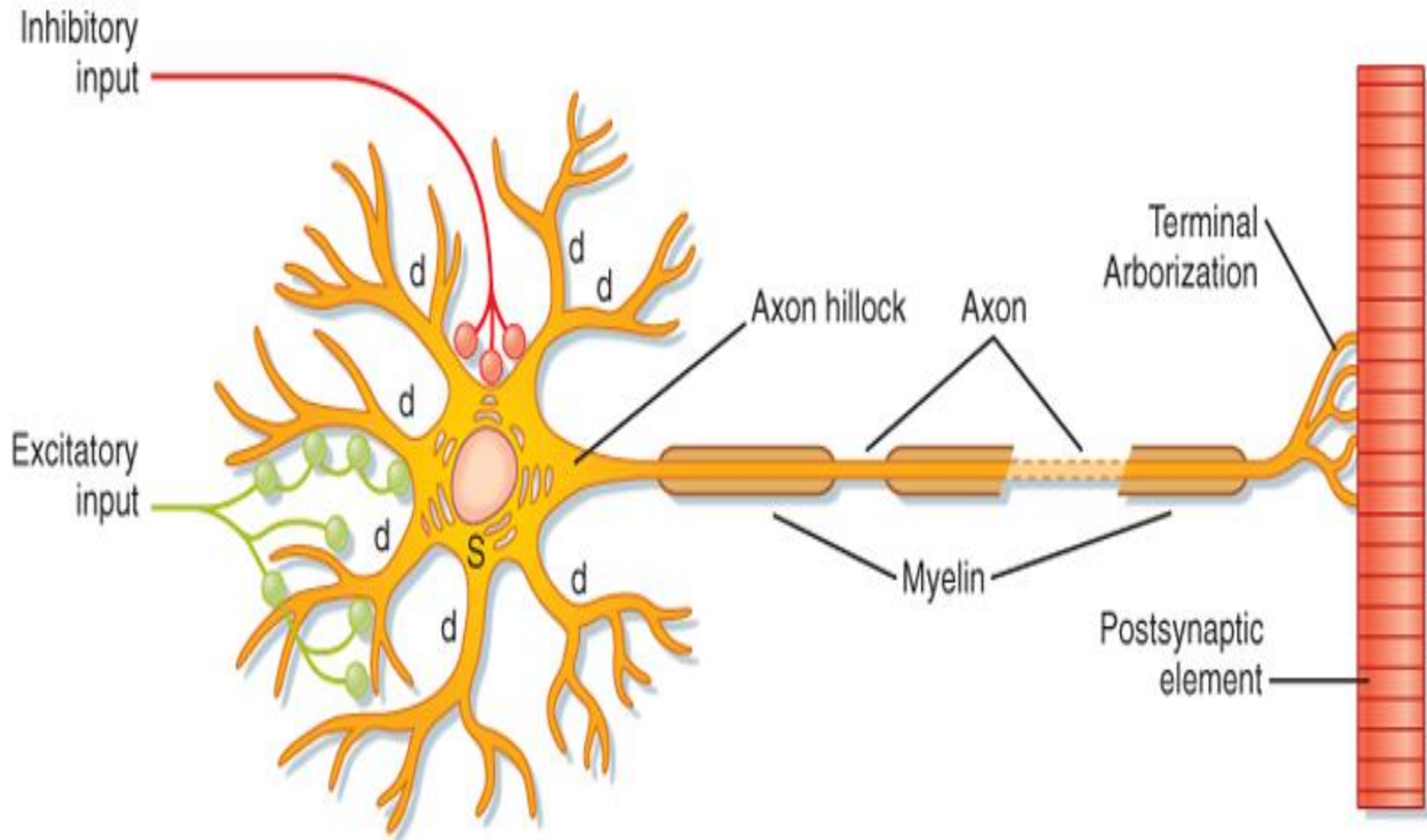


Fig. A neuron structure, showing presynaptic vesicle

Classification of Neurons

➤ Many bases of classification

➤ On the basis of function:

a. Sensory (afferent) neurons

- Transmit information into the CNS from receptors at their peripheral endings (perception)
- Do not receive inputs from other neurons
- Cell body & long peripheral processes are outside the CNS
- Only the short central process enters the CNS

Classification Cont...

b. Motor neurons (efferent neurons)

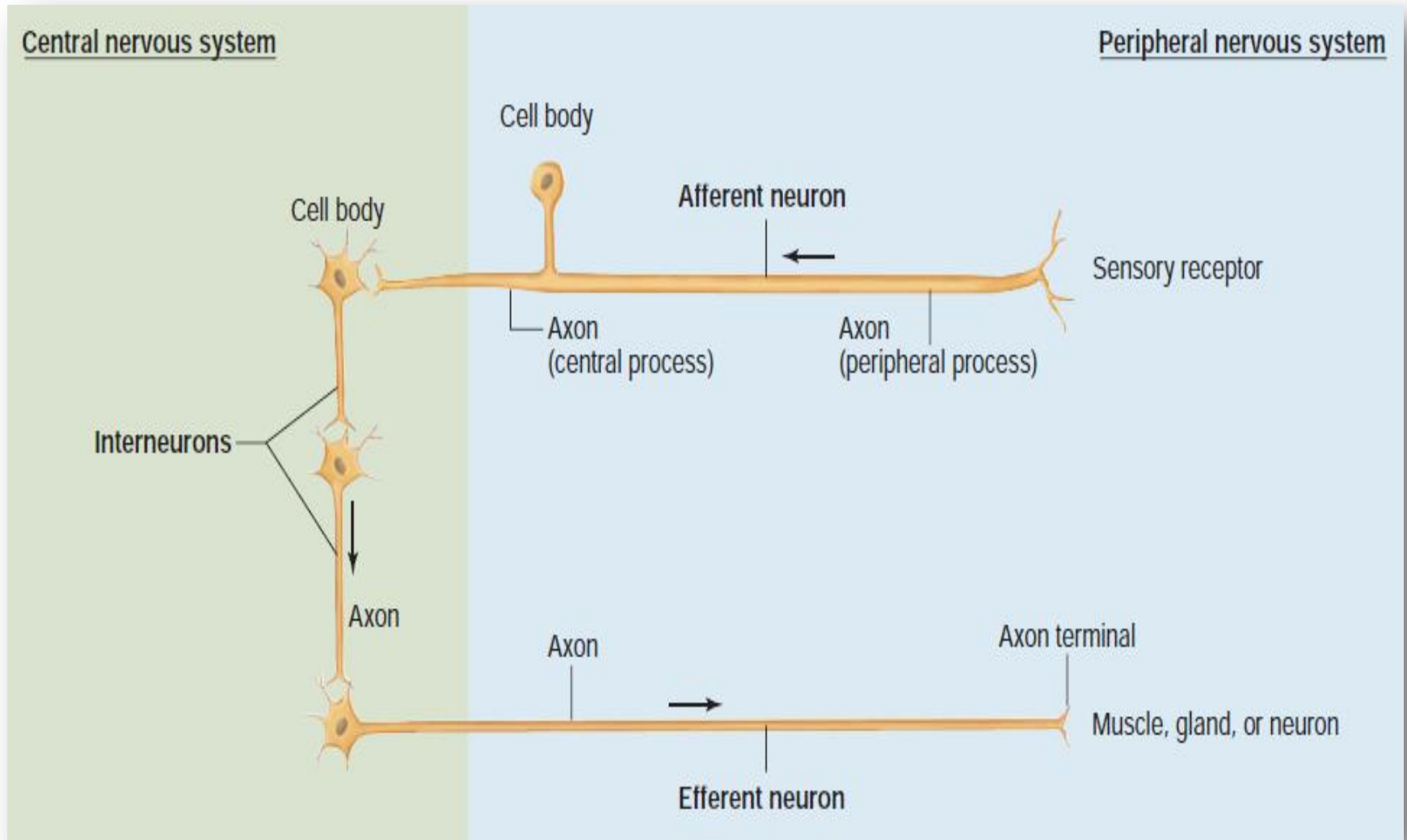
- Transmit information out of the CNS to effectors (neurons, muscles or glands)
- Cell body, dendrites & small segment of the axon in CNS
- Most of the axon is outside the CNS

Classification Cont...

c. Interneurons (association neurons)

- Function as integrators & signal changers
- Integrate groups of afferent & efferent neurons into reflex circuits
- Lie entirely within CNS
- Account for 99% of all neurons

Classification Cont...



Classification Cont...

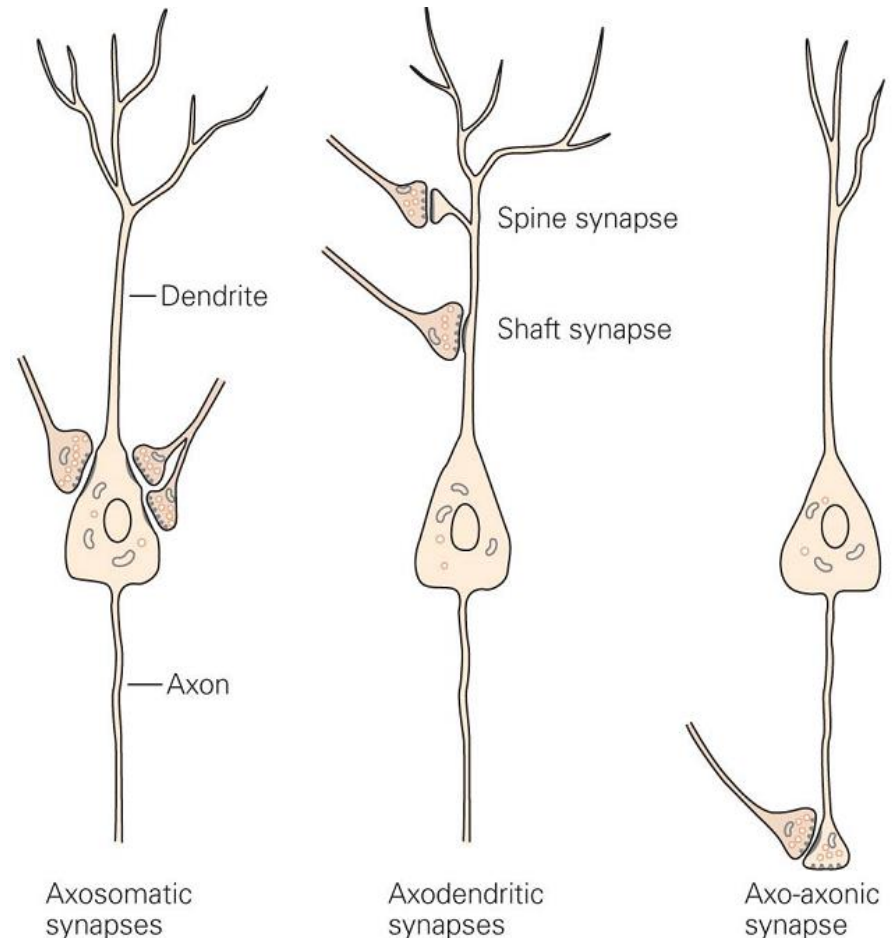
- Based on diameter of fibers and velocity of conduction of impulses:
 - A, B & C fibers
- Velocity $\propto$ thickness of the fiber
- C fibers $\rightarrow$ not myelinated

Classification Cont...

Type	Diameter (μ)	Velocity of conduction (meter/second)
A alpha (Type I)	12 to 24	70 to 120
A beta (Type II)	6 to 12	30 to 70
A gamma	5 to 6	15 to 30
A delta (Type III)	2 to 5	12 to 15
B	1 to 2	3 to 10
C (Type IV)	< 1.5	0.5 to 2

Synaptic Transmission

- Synapse is the junction b/n two cells in which at least one must be a neuron
- Synapse can be:
 1. Neuroneuronal
 - ✓ Axodendritic synapse (98%)
 - ✓ Axosomatic (2%)
 - ✓ Others
 2. Neuromuscular
 3. Neuroglandular



Synapse Cont...

- There are two major types of synapses: **chemical** and **electrical**
- Most of the synapses used for signal transmission in the CNS of the human being are chemical synapses
- The first neuron secretes a neurotransmitter (NT)
- The NT acts on receptor proteins in the membrane of the next neuron

Chemical Synapse

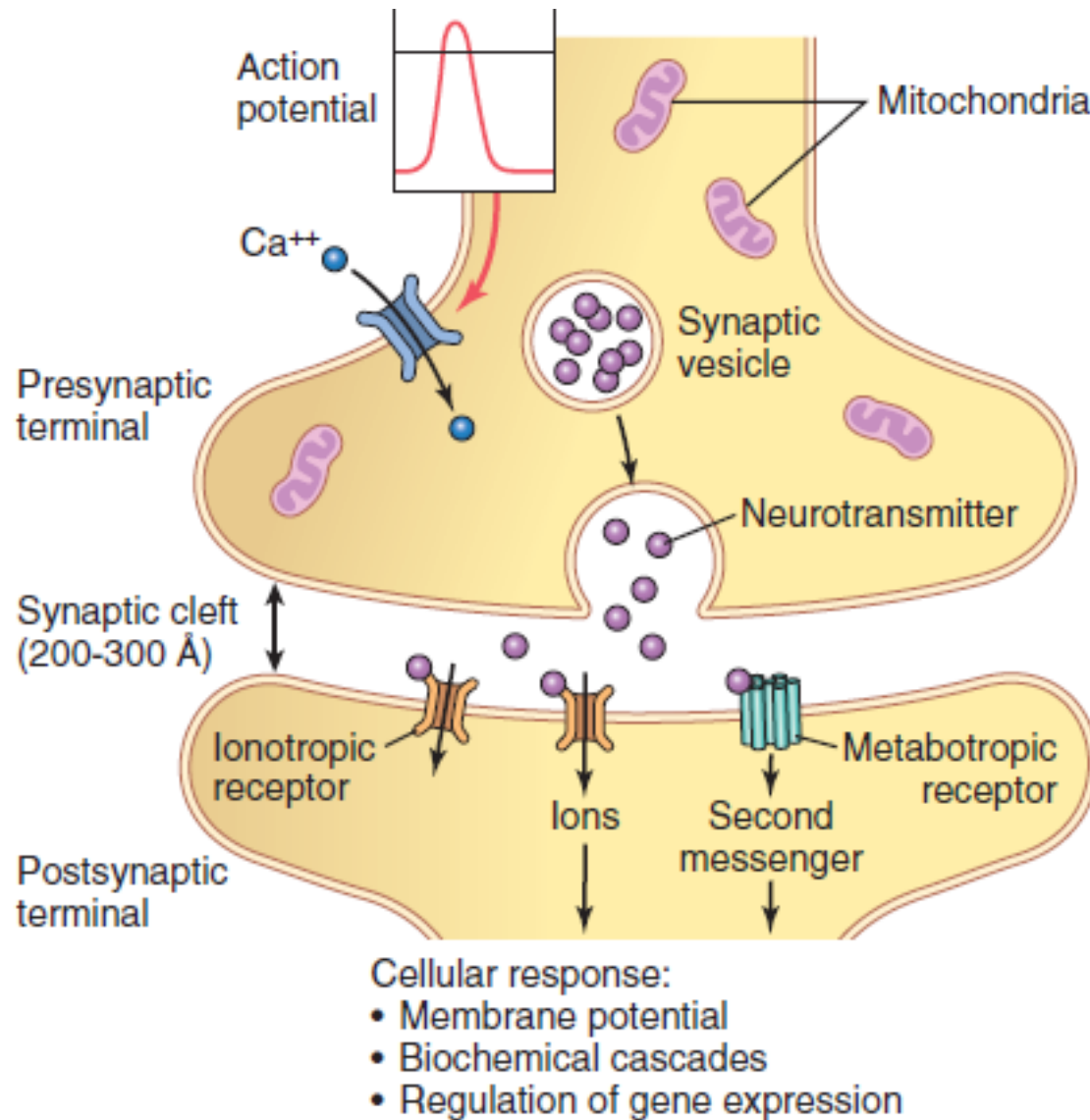


Fig. Chemical Synapse

Chemical synapse Cont...

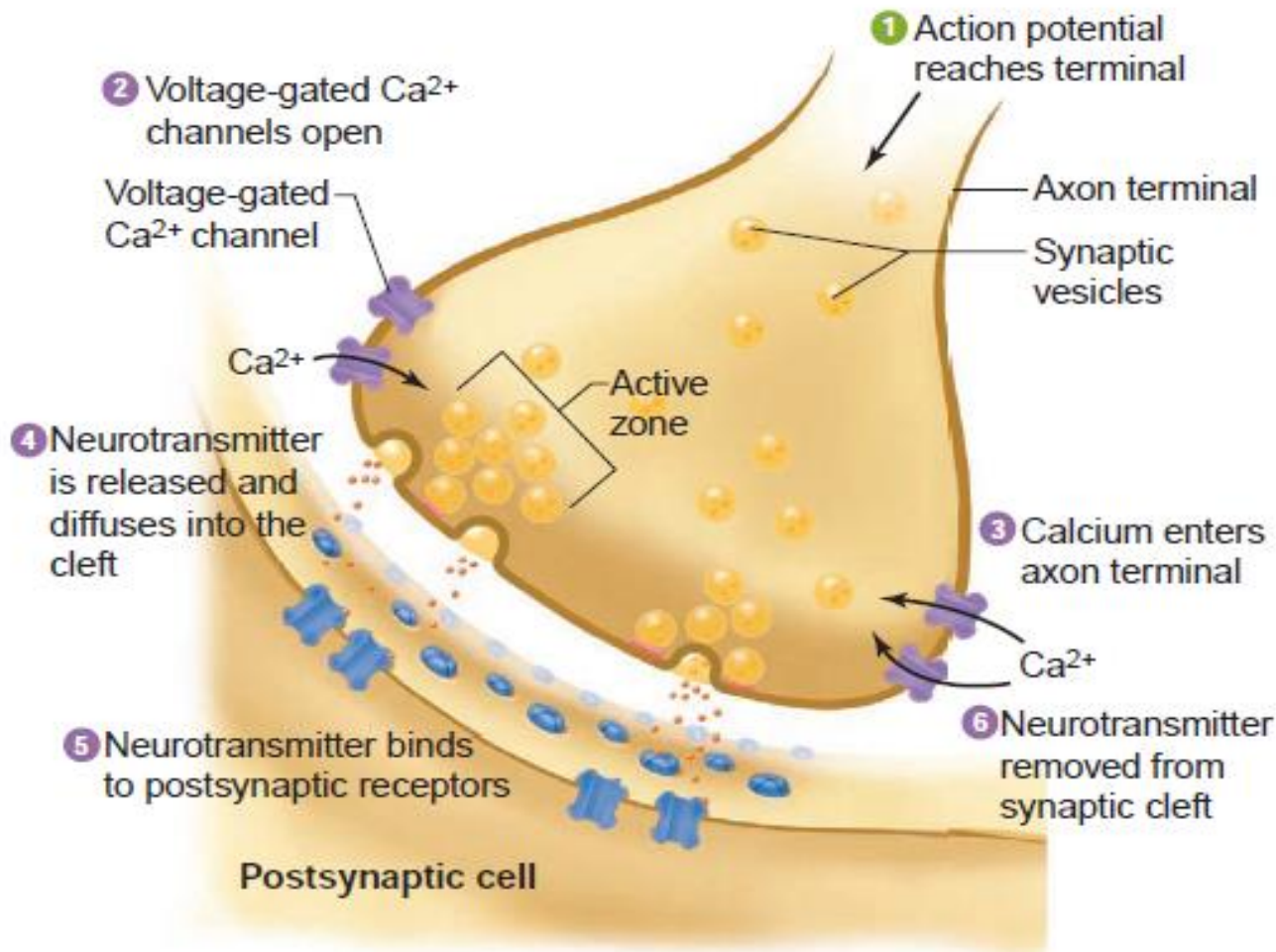
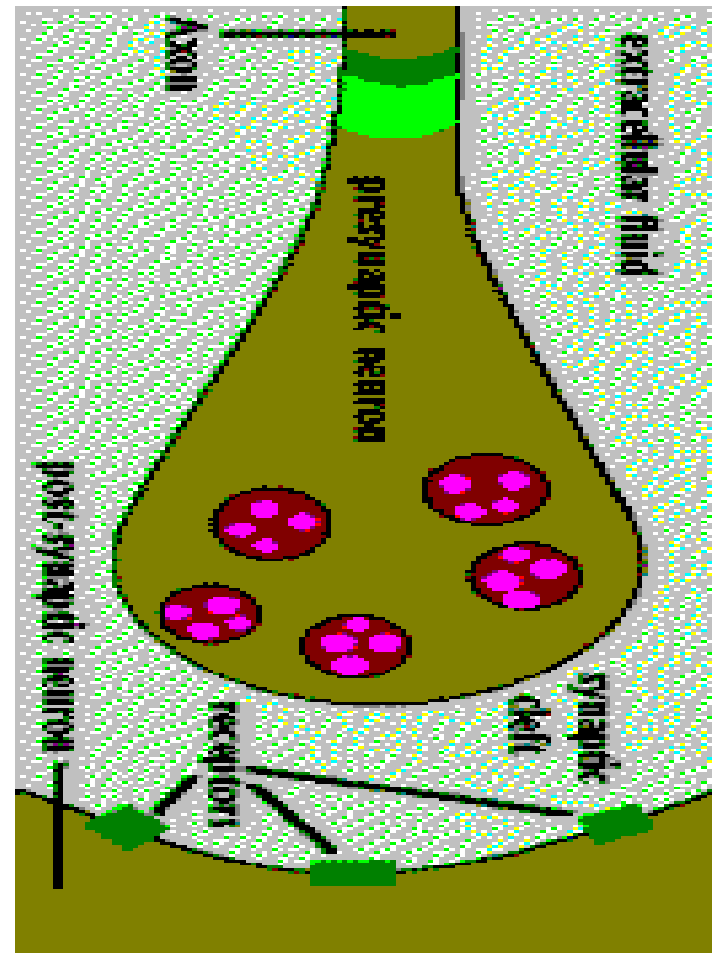


Fig. Sequence of events at chemical synapses

Chemical synapse Cont...

- More than 40 important NTs have been discovered thus far
- Neurotransmitter is a chemical:
 - present in the terminals of a neuron
 - liberated upon stimulation of the neuron
 - diffuses across the synaptic gap to stimulate or inhibit the postsynaptic membrane
- E.g. acetylcholine, dopamine, glutamate, ...



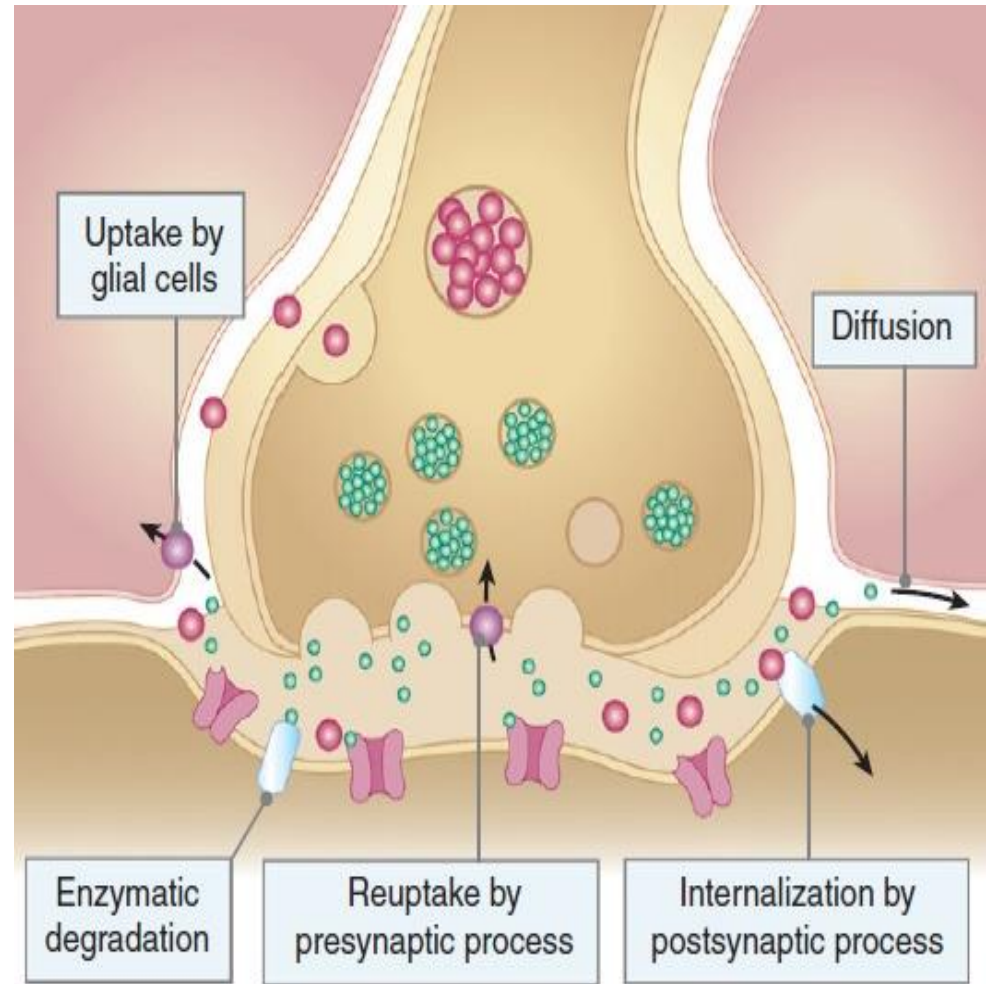
Classes of neurotransmitters

Classes	Neurotransmitters
I	Acetylcholine (Ach)
II Amines	Adrenaline, nor-adrenaline Dopamine Histamine
III Amino Acids	GABA (γ -amino butyric acid) Glycine Aspartate Glutamate
IV Polypeptides	Hypothalamic hormones, pituitary hormones, ANG-II
V	Nitric oxide

Neurotransmitter Removal

NTs are removed from the synaptic cleft via:

- Enzymatic degradation
- Diffusion
- Reuptake



Electrical Synapses

- By gap junctions
- Allow free movement of ions

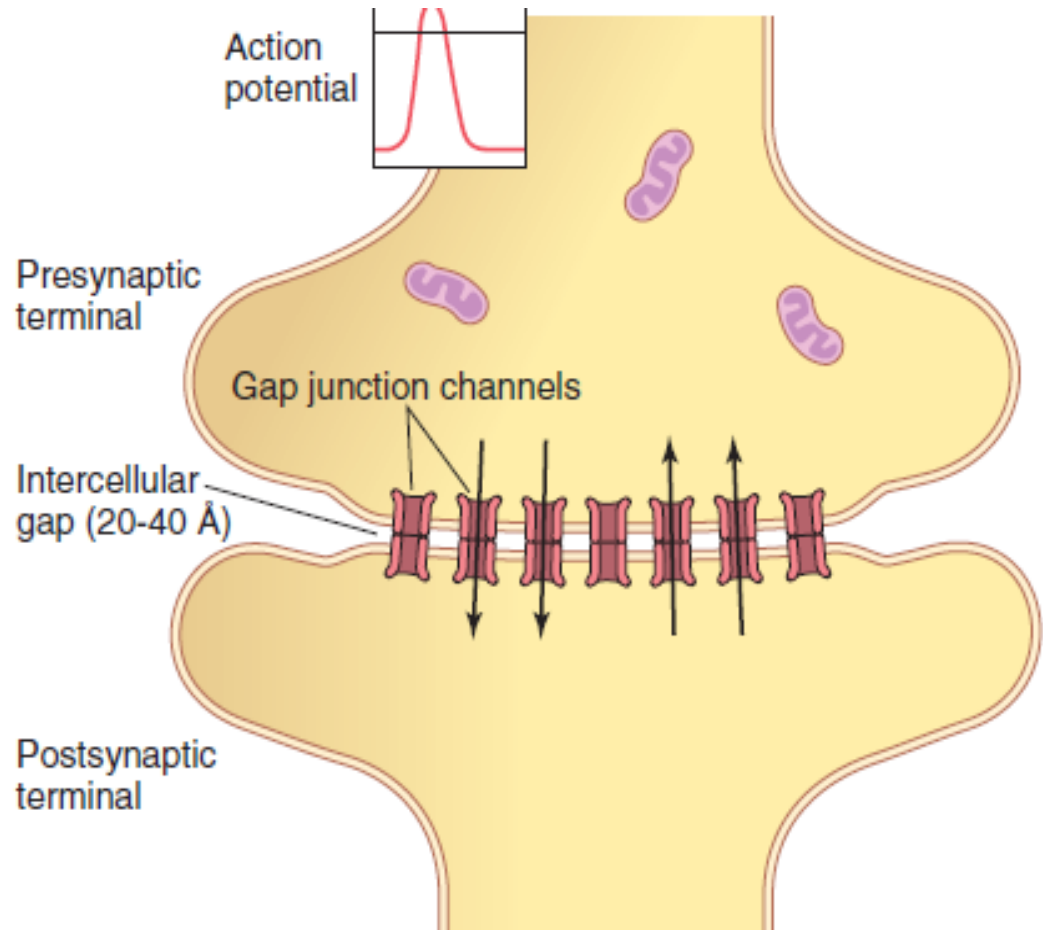


Fig. Electrical synapse

Chemical Vs electrical synapses

Property	Chemical synapse	Electrical synapse
a. Distance between presyn - postsyn	30-50nm	3-4nm
b. Cytoplasmic continuity	No	yes
c. Ultrastructural components	Presynaptic active zones, vesicles, postsynaptic receptor	Gap junctions
d. Agent of transmission	Chemical transmission	Ionic current
e. Synaptic delay	0.3ms (1-5ms)	Virtually no
f. Direction of transmission	Unidirectional	Bidirectional

Excitable Tissue

Muscle

Muscle

- **Fleshy** organ of the body that converts potential energy of food into mechanical energy
- **40-50%** of the body wt ($\approx$ **600** muscles)
 - **40%** skeletal muscles + **10%** cardiac and smooth muscles
- Consumes **25%** total bodily O_2 at rest
 - $\uparrow$ **10-20 times** during strenuous exercise

Muscle Functions

1. Production of Movement

- Movement of body parts and of the environment
- Movement of blood through the heart and the circulatory vessels.
- Movement of lymph through the lymphatic vessels
- Movement of food (and, subsequently, food waste) through the GI tract
- Movement of bile out of the gallbladder and into the digestive tract
- Movement of urine through the urinary tract
- Movement of semen through the male reproductive tract and female reproductive tract
- Movement of a newborn through the birth canal

Muscle Functions Cont...

2. Maintenance of posture

- Muscle contraction is constantly allowing us to remain upright.
- The muscles of your neck are keeping your head up right now.
- As you stand, your leg muscles keep you on two feet.

3. Thermogenesis

- Generation of heat. Occurs via shivering – an involuntary contraction of skeletal muscle

Muscle Functions Cont...

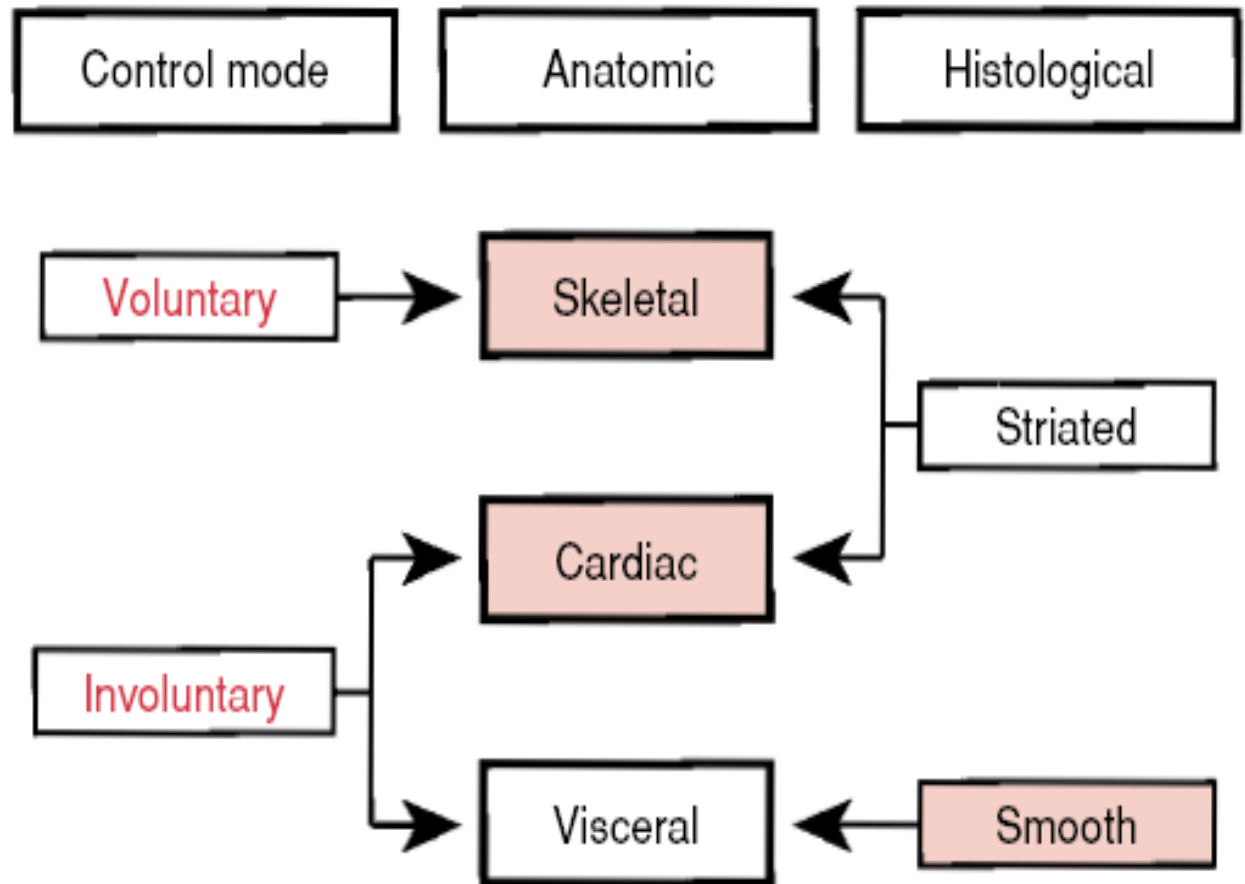
4. Stabilization of joints

- Muscles keep the tendons that cross the joint nice and taut. This does a wonderful job of maintaining the integrity of the joint



Muscle Cont...

- Muscles can be divided based on different criteria



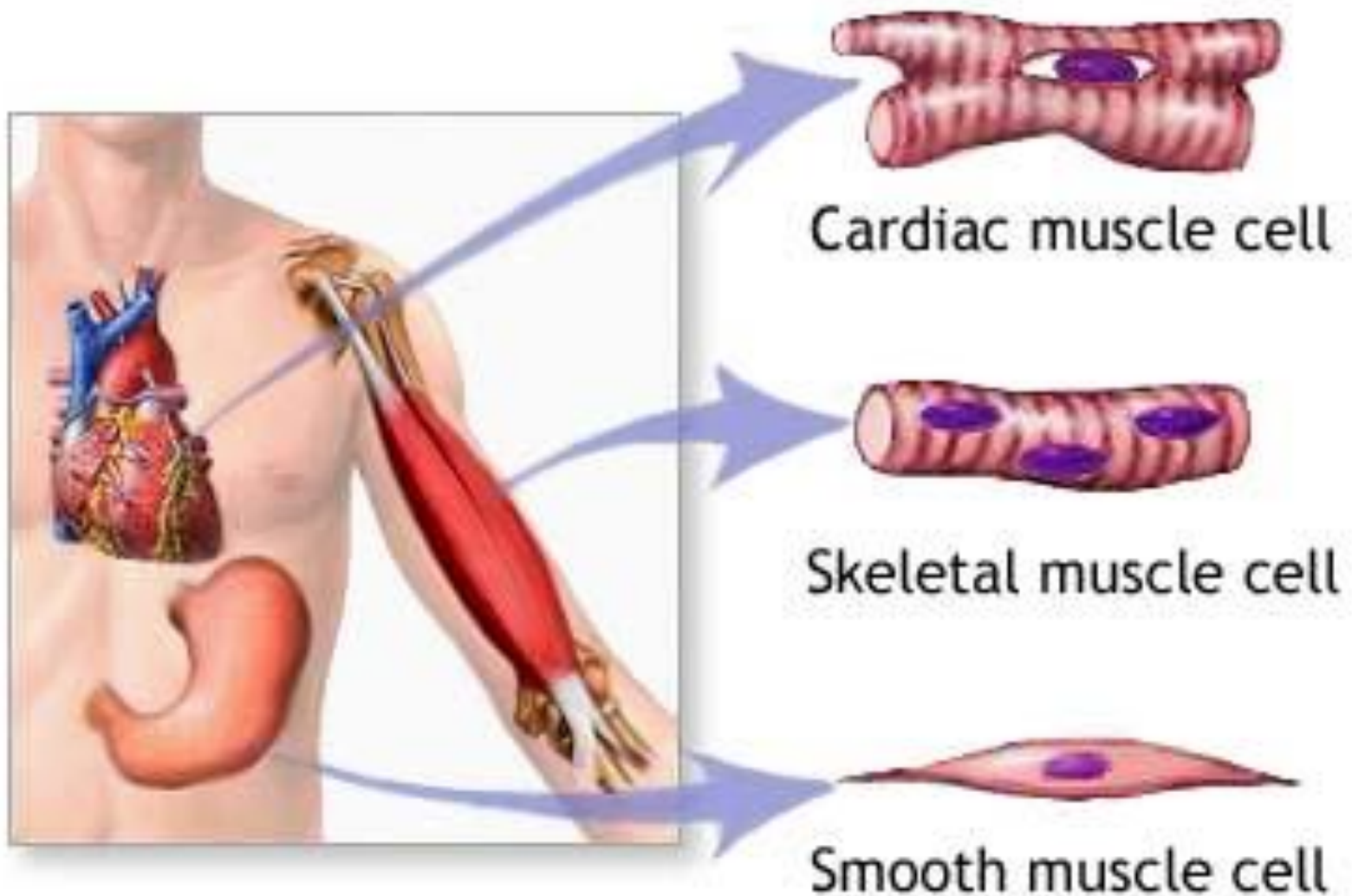


Fig. Types of muscle based on anatomical location

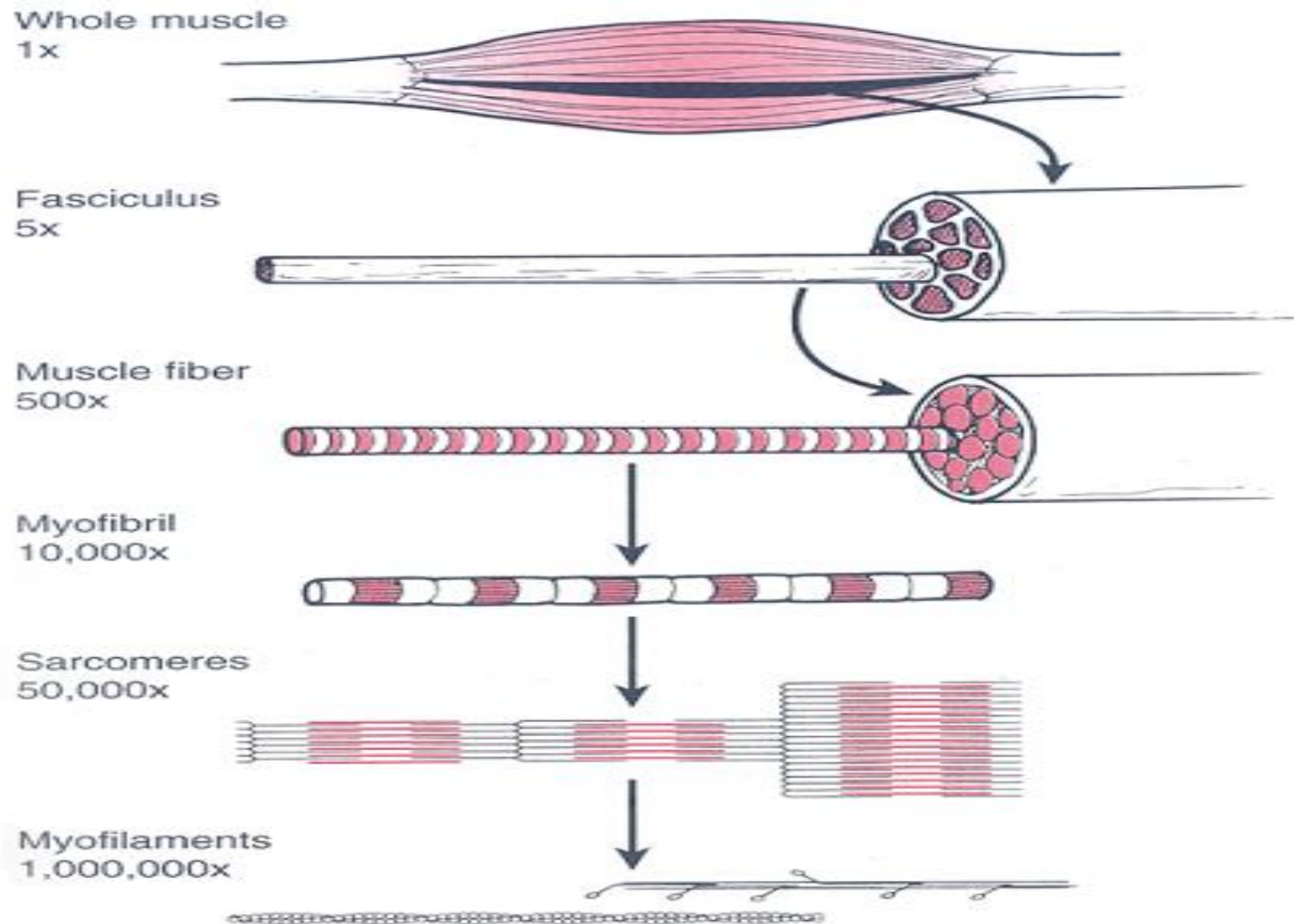
Characteristics of Muscle

- **Excitability** - responds to stimuli
- **Contractility** - able to shorten in length
- **Extensibility** - stretches when pulled
- **Elasticity** - tends to return to original shape & length after contraction or extension

Skeletal Muscles

- Located attached to bones & moves skeleton
- Elongated, cylindrical and multinucleated cells
- Striated muscle
- Voluntary muscle- controlled by somatic NS

Structural Organization of Skeletal Muscle



NB. Each muscle fiber is a single cell

Structure of Skeletal Muscle

Cont...

Terms

- **Sarcolemma**- cell membrane of muscle
- **Sarcoplasm**– cytoplasm of muscle
 - Contains myoglobin, glycogen, creatine-PK
- **Sarcoplasmic reticulum** (SR)- sER of muscle
- Creatine phosphokinase: an enzyme that transfers the phosphate group from phosphocreatine to ADP → maintains adequate ATP concentration in working muscle fibers.

Muscle fibers store energy for contraction in **phosphocreatine**

Structure of Skeletal Muscles

Cont...

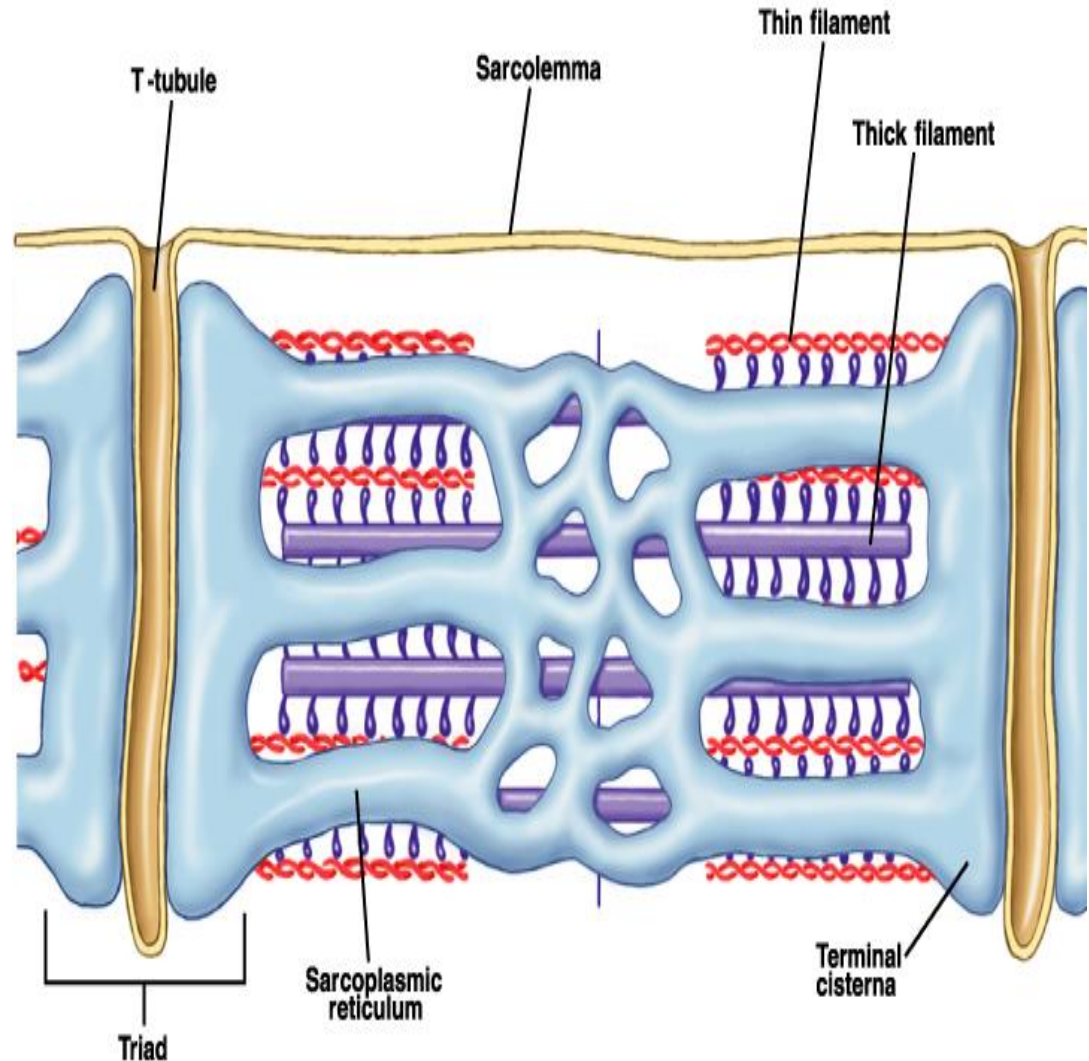
A muscle cell has two tubular structures:

a. Transverse tubules (T-tubules)

a. Function:
conduction of
depolarization

b. Longitudinal tubules (sER)

Function: Ca^{2+}
storage in terminal
cisternae



Myofilaments

- 2 types- **thick** & **thin**
- Thick myofilaments are made from **myosin**
- About **300** myosin molecules are joined together to form a single thick filament

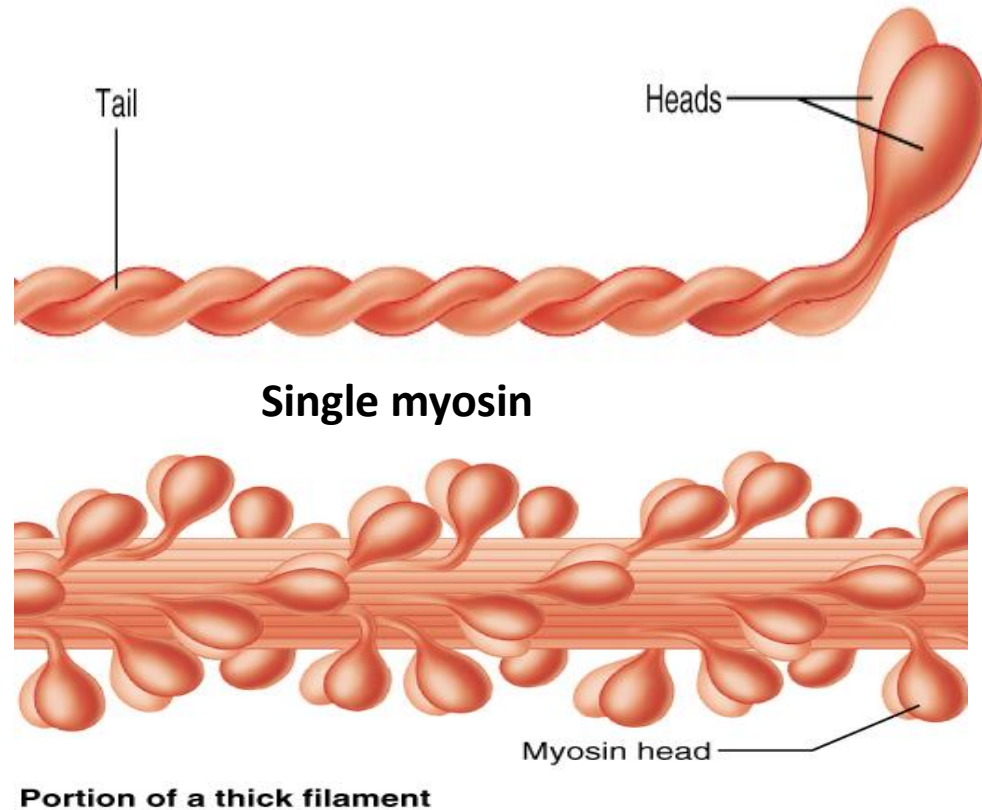
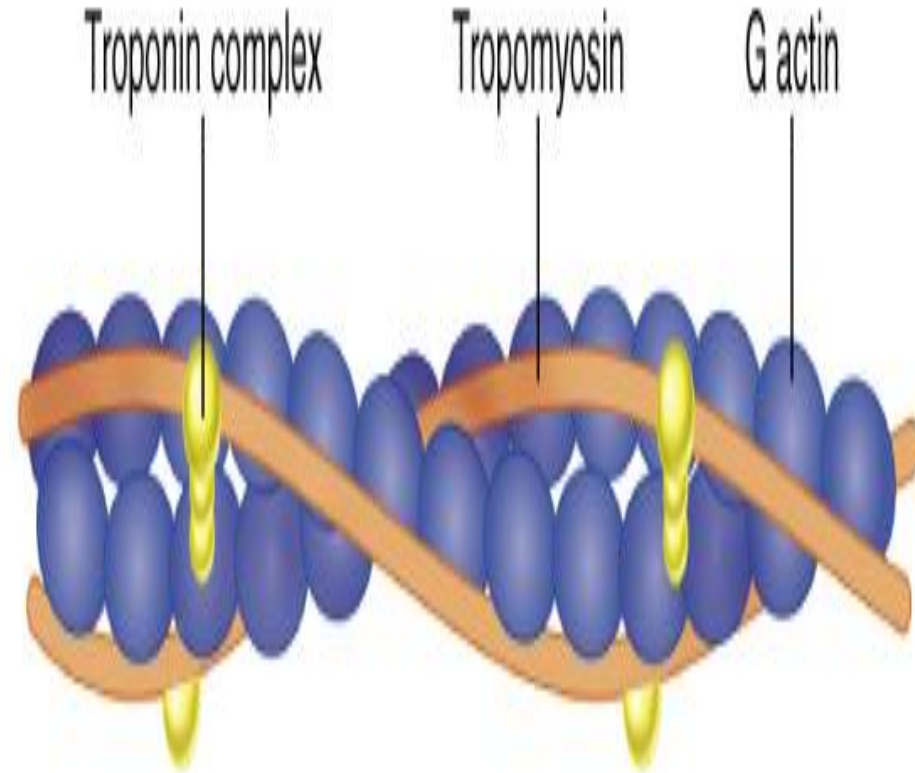


Fig. Many myosins form thick filament

Myofilaments cont...

Each thin filament is made up of 3 different types of proteins:

- **Actin**- bead like globular protein that has myosin binding site
- **Tropomyosin**- loosely wrapped around the actin helix and covering the myosin binding site
- **Troponin**- a trio of proteins bound to both actin and tropomyosin



Myofilaments cont...

Three types of troponins

- **Troponin T**: binds other troponin components to tropomyosin
- **Troponin I**: inhibits the interaction of myosin with actin
- **Troponin C**: has the binding site for Ca^{2+} that initiates contraction
- One tropomyosin molecule covers seven actin monomers

Myofilaments Cont...

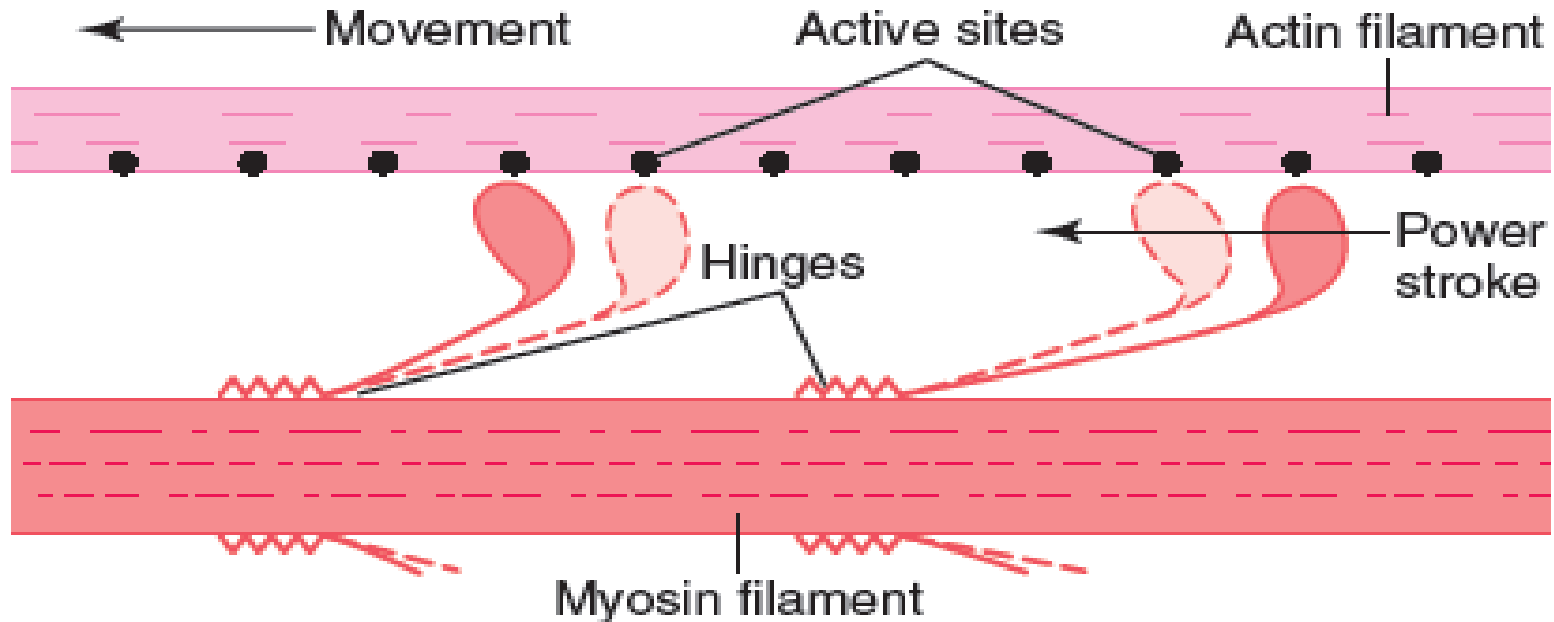
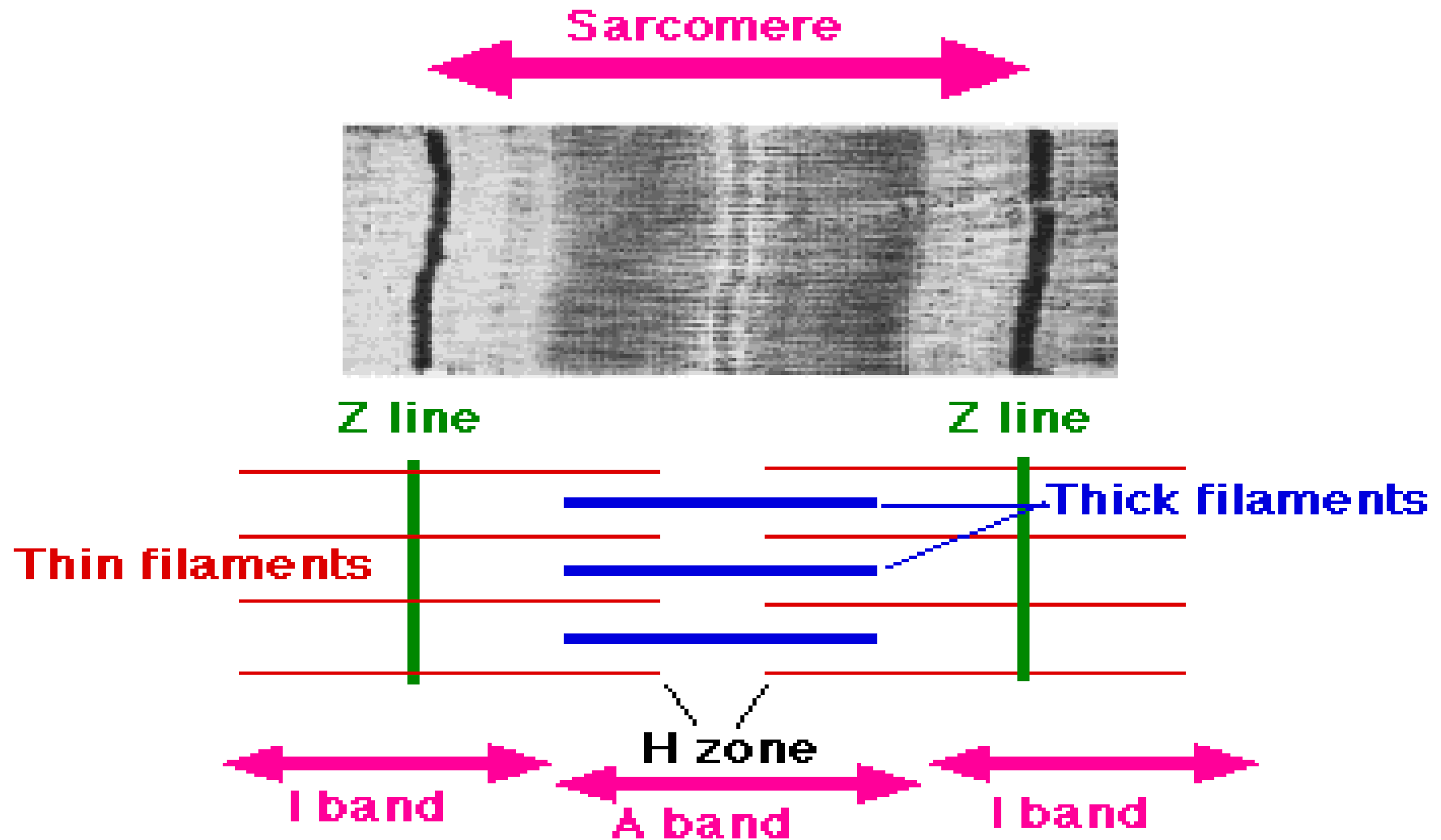


Fig. The “walk-along” mechanism for contraction of the muscle

Sarcomere

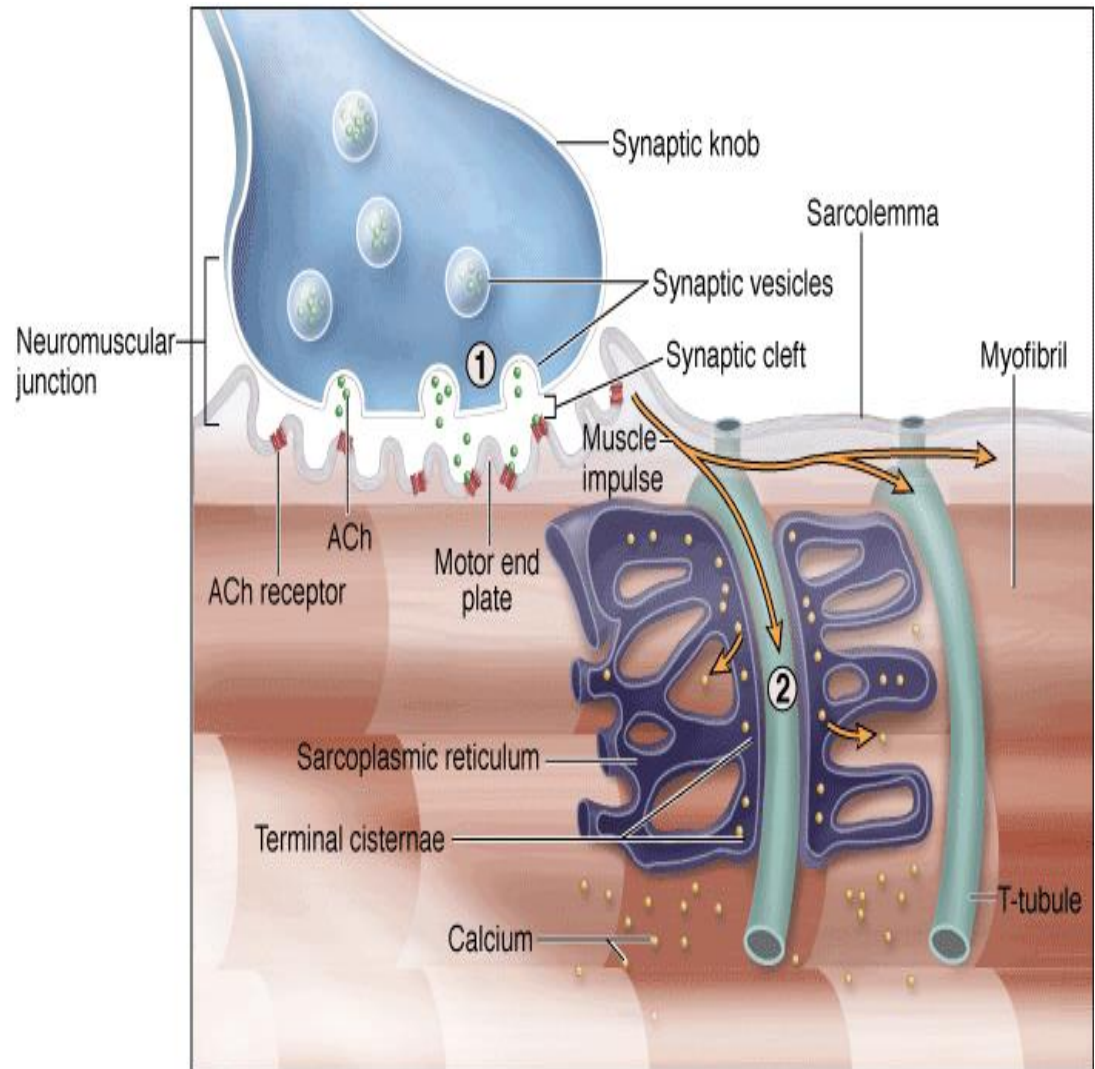
- Functional unit of striated muscles
- The distance between two z-lines
- Responsible for the striated appearance
- The resting length of a sarcomere is $2\mu\text{m}$ - $2.2\mu\text{m}$
- At this length it generates the greatest force of contraction

Sarcomere Cont....



Neuromuscular Junction (NMJ)

- The specialized **area** where a motor nerve terminates on a skeletal muscle fiber



NMJ Cont...

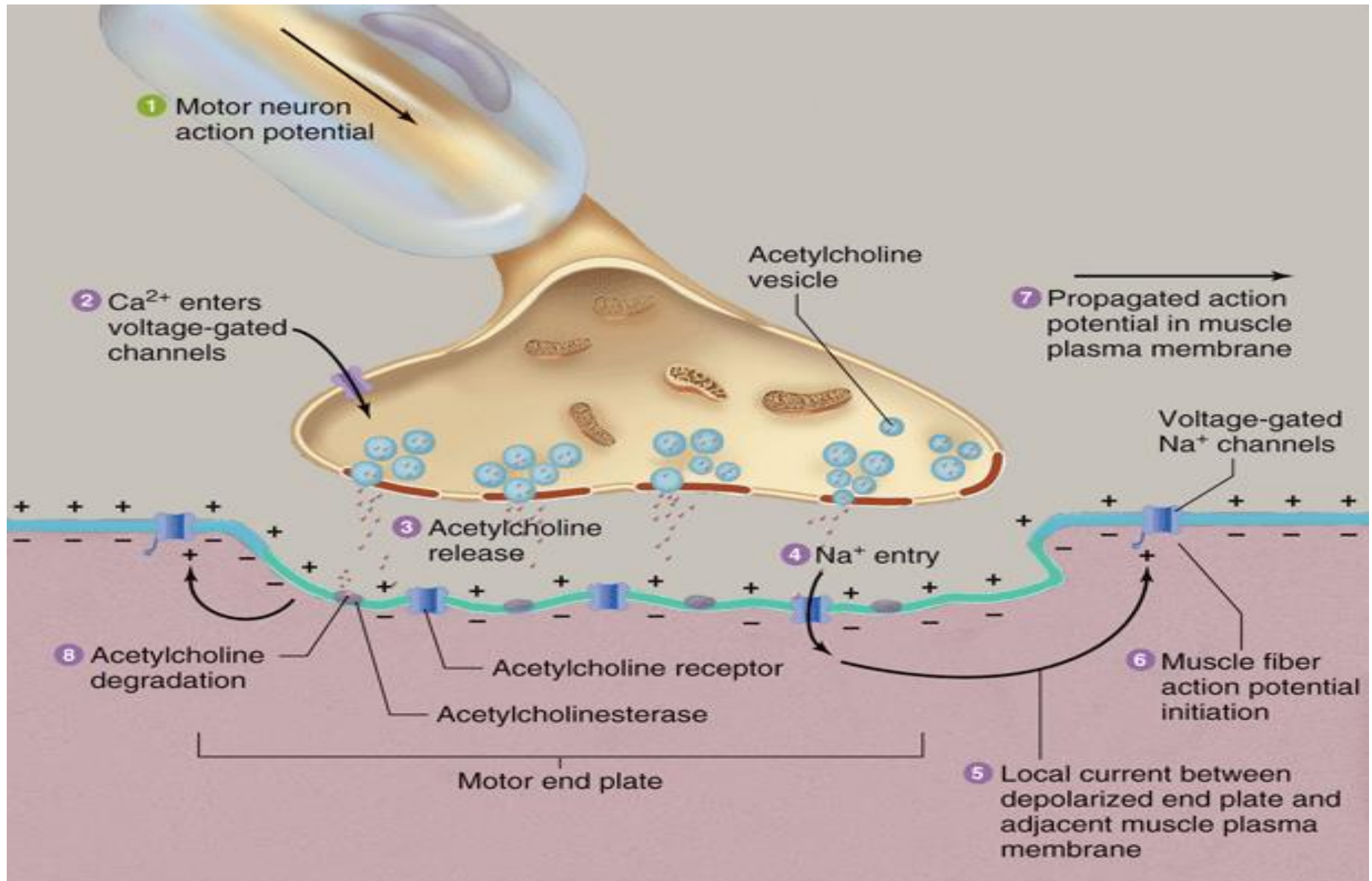


Fig. Events at the neuromuscular junction

Characteristics of NMJ

- Transmission is **unidirectional**
- There is a **single NMJ** per muscle fiber
- The neurotransmitter is always **acetylcholine (Ach)**
- The post junctional receptor is always **nicotinic receptor (NR)**
- The effect of Ach on NR is always **excitatory**
- There is a **synaptic delay** (0.2 – 0.3 ms)
- **Fatigable** due to depletion of ATP and NT storage

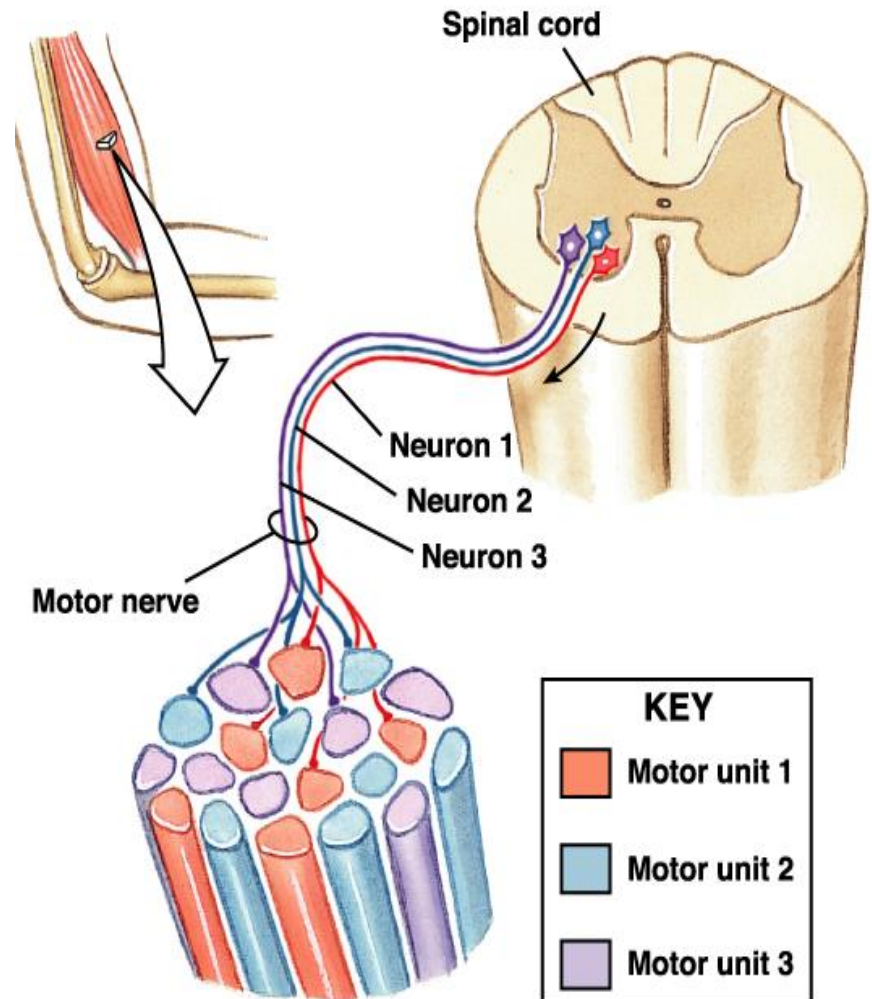
Factors Affecting NMJ

Can be affected by various factors

- Calcium level:
 - Hypercalcemia inhibits membrane excitability
 - Hypocalcemia increases membrane excitability
- Hypoxia: inhibits membrane excitability
- Drugs:
 - Nicotinic receptor (cholinergic) blockers: d-tubocurarine, α -cobratoxin
 - Cholinergic stimulants: nicotine, metacholine, carbacholine
 - Anti-cholinestrase drugs: physiostegmin, neostegmin

Motor Unit

- A **somatic motor neuron** and all the **skeletal muscle fibers** it innervates
- No. of muscle fibers per motor unit may be as high as **several hundred** or as few as **four**
- The smaller the motor unit, the **finer and more delicate** the movements



Muscle Contraction (The Sliding Filament Hypothesis)

- The thin filaments slide over the thick filaments
→ pulls the Z discs closer together
- When all the sarcomeres shorten, the entire fiber gets shorter which pulls the attached tendon and then the bone

Muscle Contraction Cont...

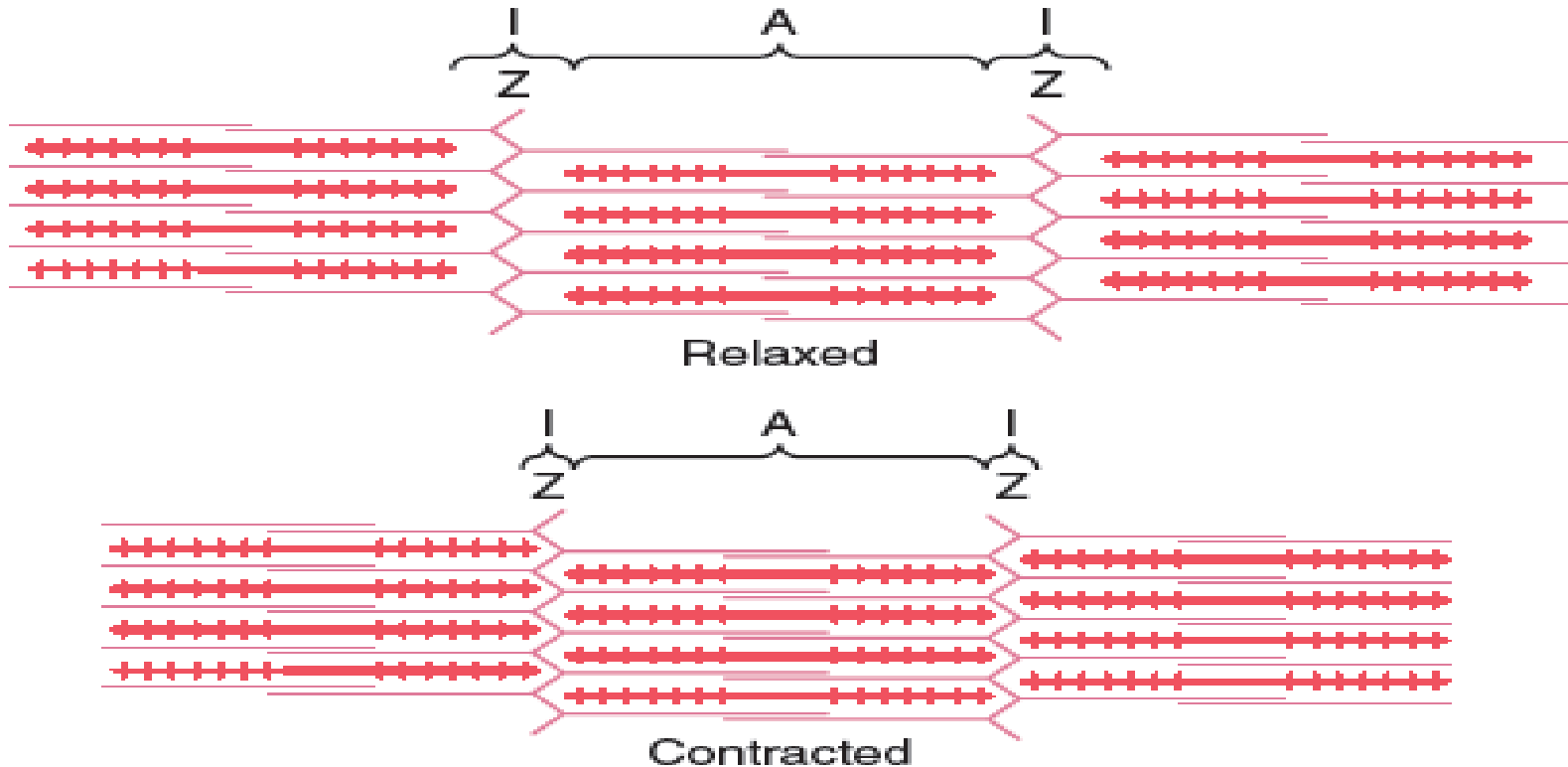
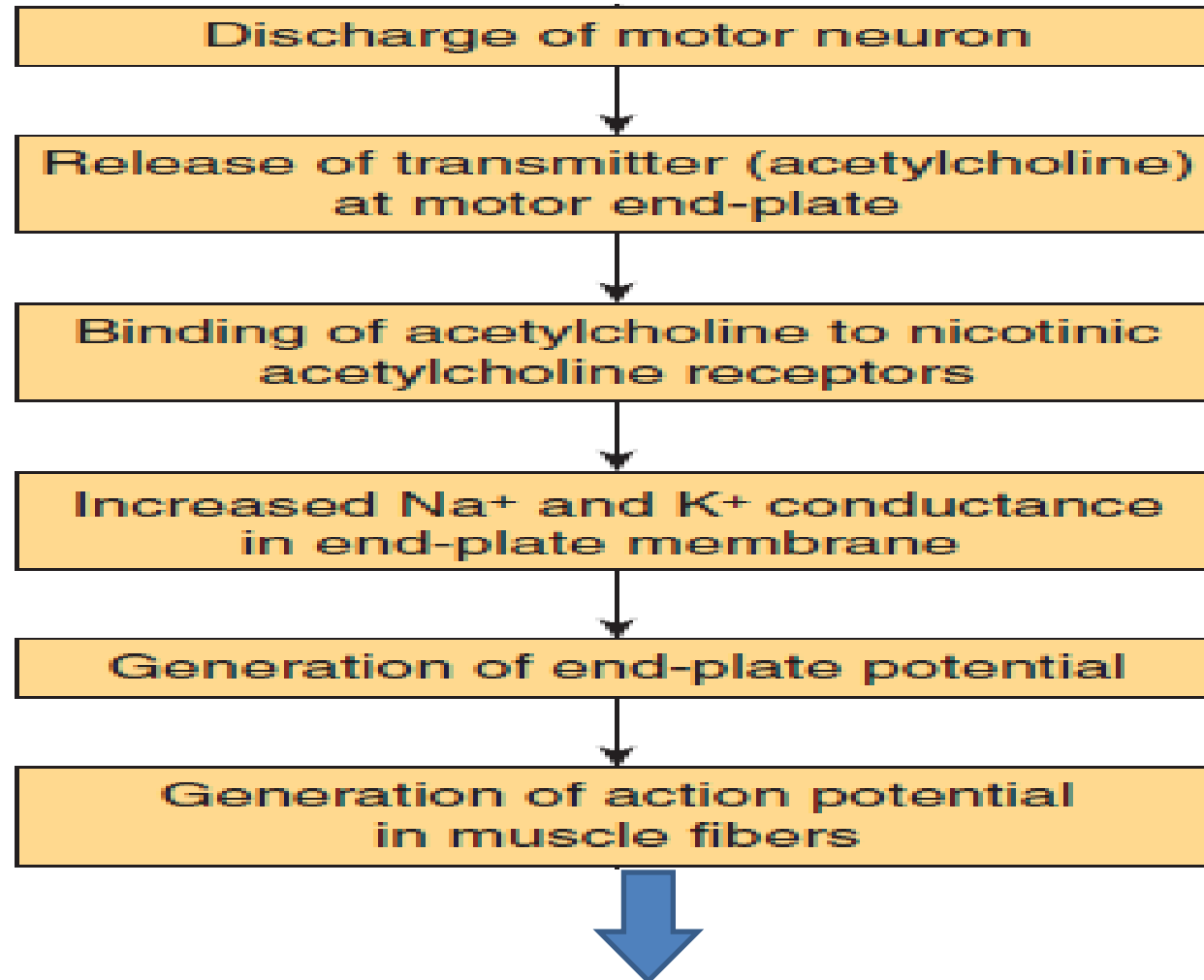


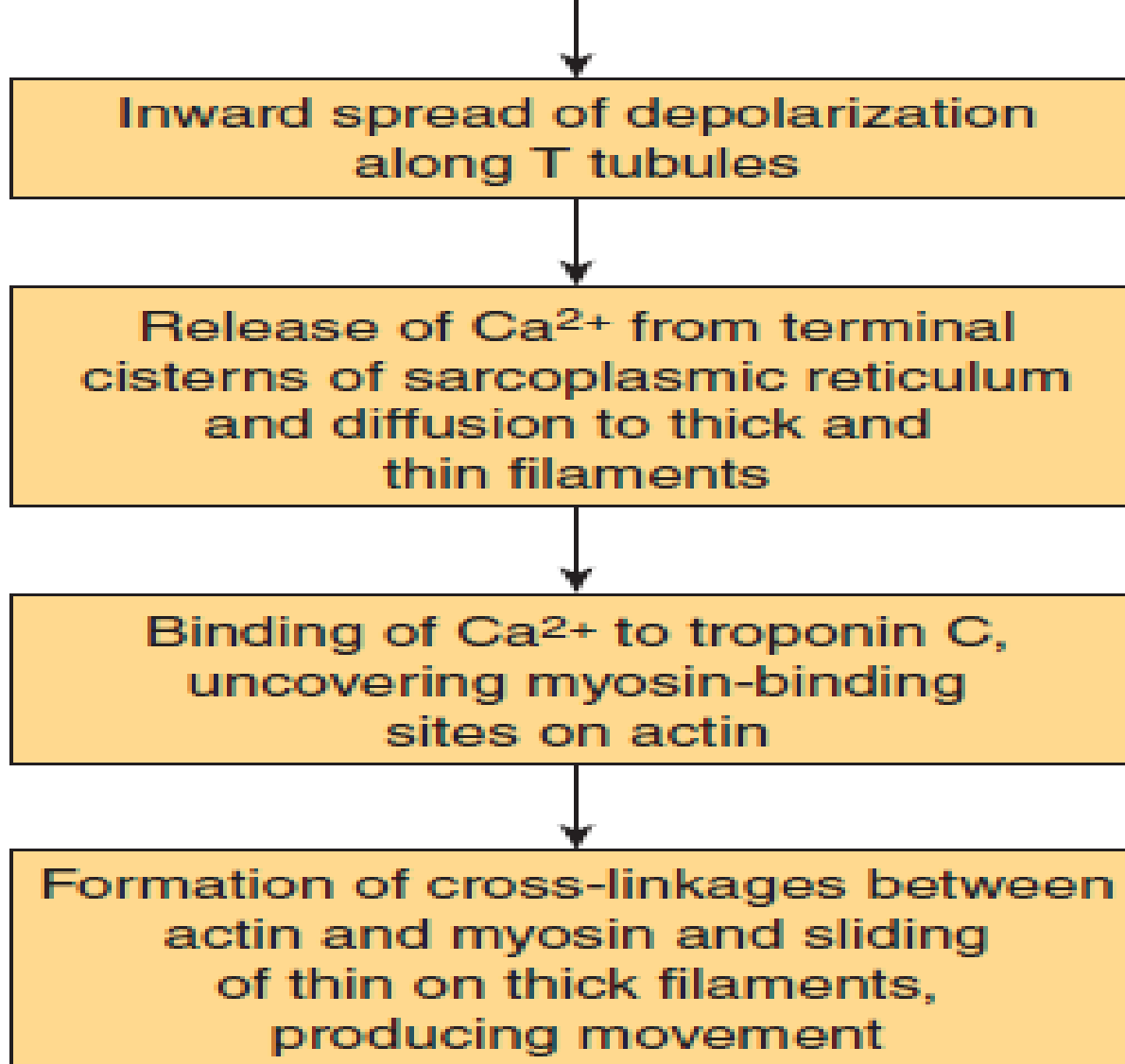
Fig. Relaxed and contracted states of a myofibril showing (top) sliding of the actin filaments (pink) into the spaces between the myosin filaments (red) and (bottom) pulling of the Z membranes toward each other.

Mechanism of Muscle Contraction (Excitation-contraction coupling)



Continue...

Mechanism Cont...



Mechanism Cont...

- During muscular contraction:
 - There is no change in length of either the thick or the thin filaments
 - H-zone disappears and Z-line gets considerably darker.
 - There is shortening of the sarcomere ($\downarrow$ I-band and H zone, and A-band remains constant)
- When a muscle increases its length, there is an increase in the N^o of sarcomeres (not the length of each sarcomere)
 - The length of thick & thin filaments of sarcomeres is identical in a neonate & in the adult muscle

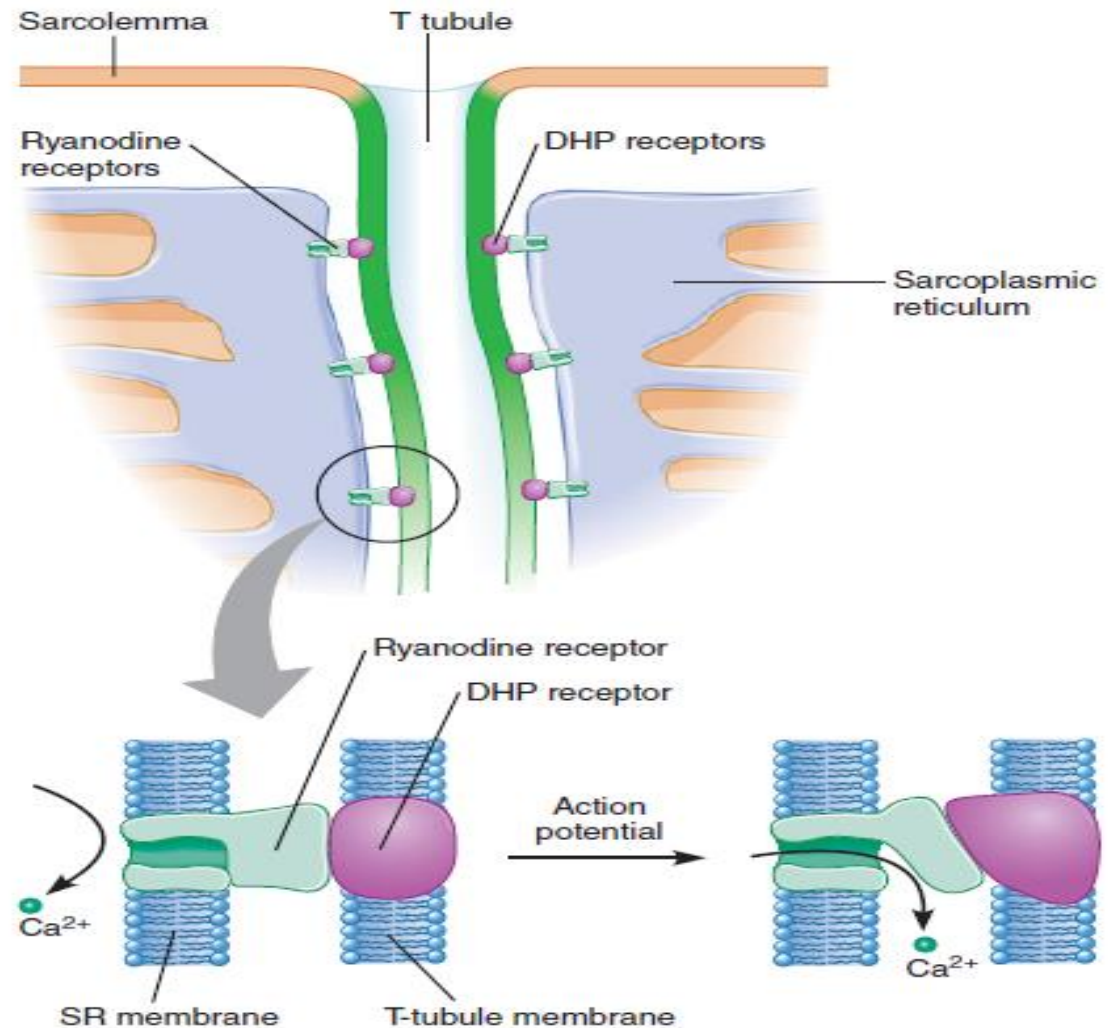
Release of Ca^{2+} from the Terminal Cisternae

- Voltage - gated Ca^{2+} channel (DHPR)
 - Found in the transverse tubule
 - Voltage sensor which is responsible for triggering Ca^{2+} release from the SR and for EC coupling
 - Sensitive to a drug called dihydropyridine (DHP) which can block this voltage-gated channels

Release of Ca^{2+} Cont...

Ca^{2+} -Release Channel (RyR)

- Found in sarcoplasmic reticulum membrane
- Sensitive for a drug called ryanodine (Ry)



Release of Ca^{2+} Cont...

Depolarization of the T-tubule



Opening of DHPR - RyR Ca^{2+} channels



Release of calcium

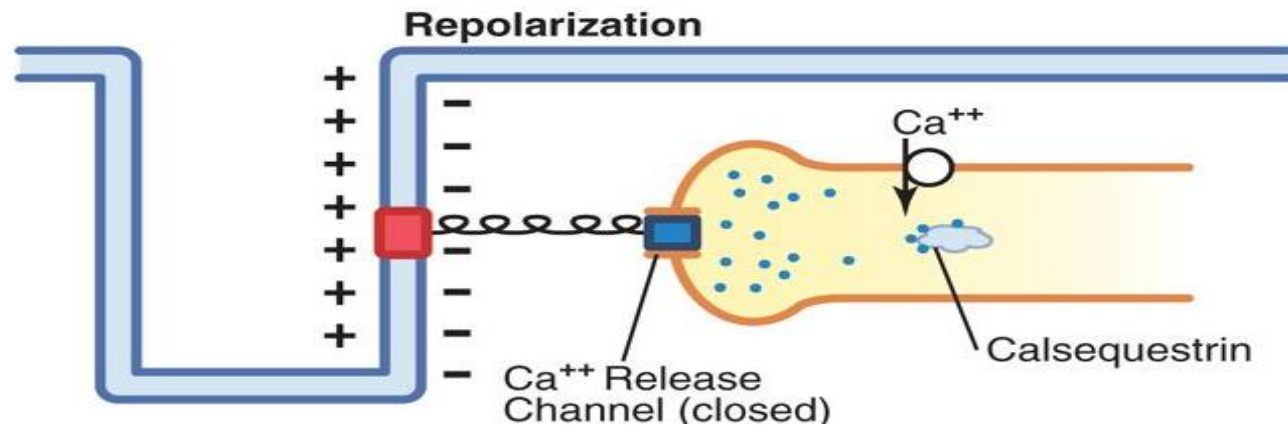
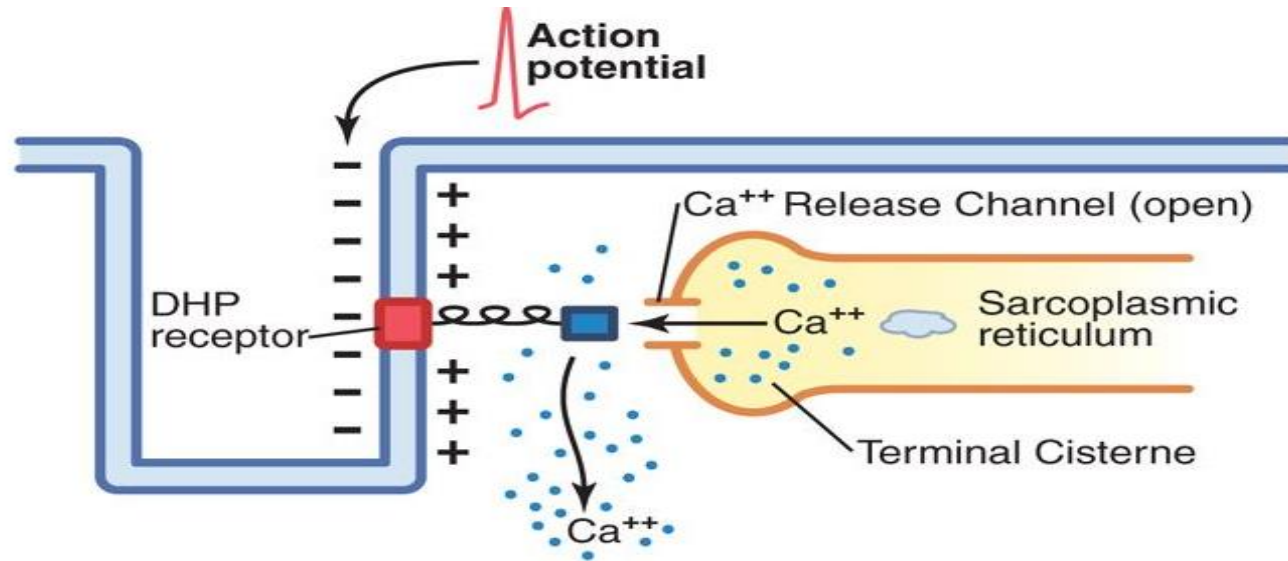


Calcium flows out of the terminal cisternae into the sarcoplasm



↑ $[\text{Ca}^{2+}]$

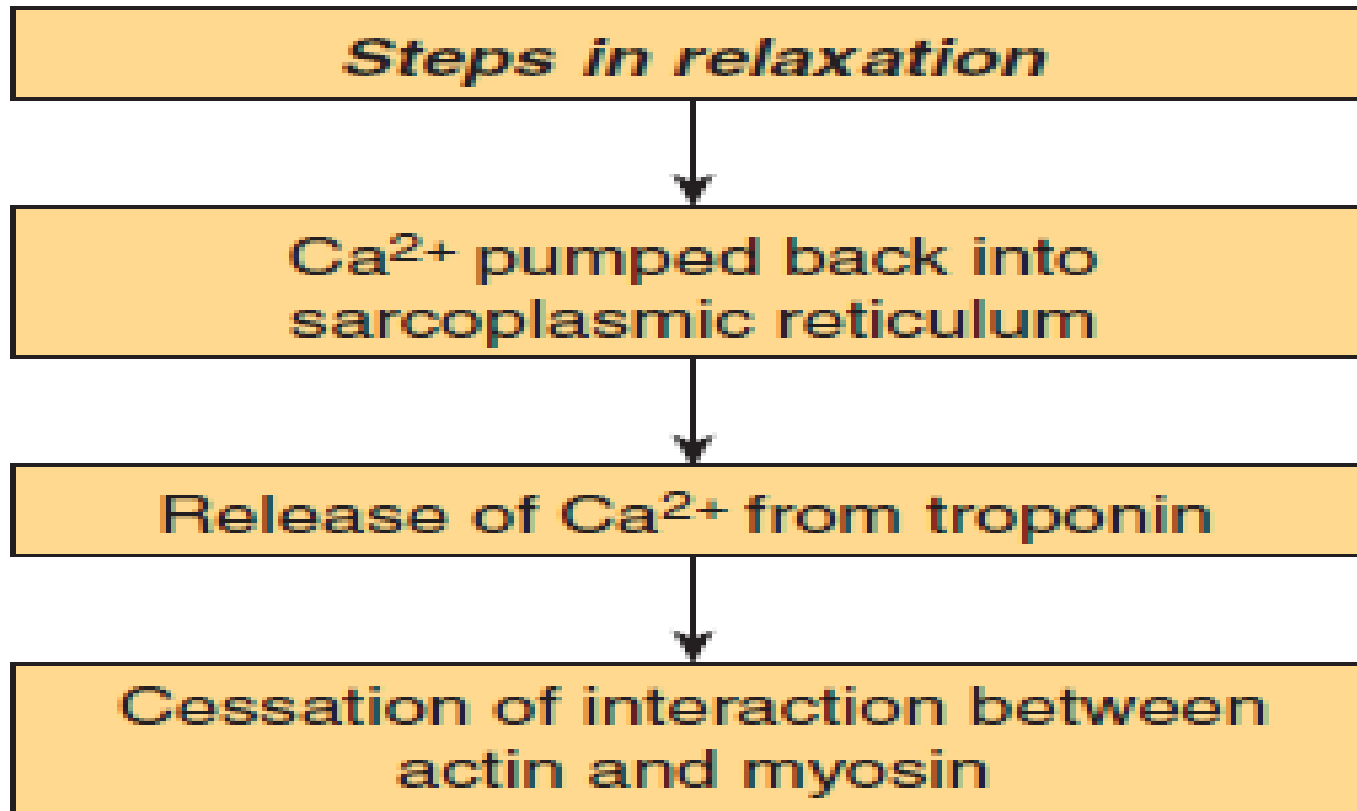
Release of Ca^{2+} Cont...



Release of Ca^{2+} Cont...

- Amount of Ca^{2+} released from the SR is proportional to change in membrane potential
- Caffeine → enhance calcium release → delay fatigue
- Agents or stimulants that decrease the threshold & prolong the duration of AP → $\uparrow \text{Ca}^{2+}$ release from SR → $\uparrow$ force of contraction (in heart muscle)

Mechanism of Muscle Relaxation



Muscle relaxation is an active process requiring energy

Energy Consumption During Muscle Contraction

Large amount of energy (ATP) is consumed during muscular performance for the following activities:

1. To move the head of myosin (power stroke)
2. For Na-K-pump in the membrane
3. Active Ca^{2+} pump from sarcoplasm to SR
4. For muscle relaxation

Whole Muscle Contraction

- A sub-threshold stimulus would not cause contraction because no AP would be produced!
- The response of a muscle to a single supra-threshold stimulus would be a twitch – the muscle quickly contracts and then relaxes
- The response of the whole muscle to multiple successive stimuli depends on the frequency of stimuli applied

Whole Muscle Cont...

- If high frequency stimuli are applied and fall on the contraction phase, the result is a continuous contraction without relaxation. This type of contraction is called **tetanic contraction or tetanus**
- If the stimuli are of moderate frequency just below the minimum tetanic frequency, and each stimulus falls in the relaxation phase, the result is a series of contraction with incomplete relaxation, called **clonic contraction**, clonus or incomplete tetanus

Types of Contractions

Isotonic Contraction

- No change in muscle tension
- There is shortening of the total length of the muscle
- Work is done in this type of contraction
- Occurs when contraction moves an object of moderate Weight

Isometric Contractions

- No change in muscle length
- No work is done
- Occurs when muscle contraction fails to move heavy objects

Rigor Mortis

- Upon death, muscle cells are unable to prevent calcium entry → allows myosin to bind to actin
- Since there is no ATP made postmortem, the myosin cannot unbind and the body remains in a state of muscular rigidity for almost the next couple days

Muscle Atrophy & Hypertrophy

Muscle atrophy:

- Decrease muscle size
- Disuse atrophy and denervation atrophy
- Denervation atrophy
 - Paresis
 - Paralysis

Muscle Cont...

Muscle hypertrophy:

- Increase in size of muscle
- Changes:
 - ↑No of actin and myosin filaments in each fiber
 - ↑No of sarcomers
 - ↑Enzyme system of glycolysis
 - ↑Amount of myoglobin, ↑Mitochondria
 - ↑No of capillaries
- As a result, there is an increase in the force and strength of contraction, decrease in fatigability

Smooth Muscles

- Located in the wall of hollow organs (GIT, blood vessels, uterus, u-bladder, iris)
- Not striated
- Mononucleated cells
- Involuntary muscle, controlled by ANS and hormones
- Have the property of **autorhythmicity** and **syncytium**
- **2 types**

Smooth Muscles Cont...

Single unit

- No direct innervation
- Have gap junctions → cells contract as a unit
- Have pacemaker cells
- Responsive to variety of stimuli including stretch and chemicals
- Found in the walls of the digestive tract, urinary bladder, and other organs

Multi-unit

- Innervated in motor units
- No gap junctions → each fiber is independent of all the others
- No pacemaker cells
- Responsive to neural & hormonal controls
- Found in large airways, large arteries, arrector pili, internal eye muscles

Contraction of Smooth Muscle

- Smooth muscle contains both **actin** and **myosin** filaments
- Does **not contain troponin** complex
- The contractile process is activated by Ca^{2+} and ATP is degraded to ADP to provide the energy for contraction
- Calcium ions combine with **calmodulin** to cause activation of myosin kinase and phosphorylation of the myosin head → binds to actin → contraction

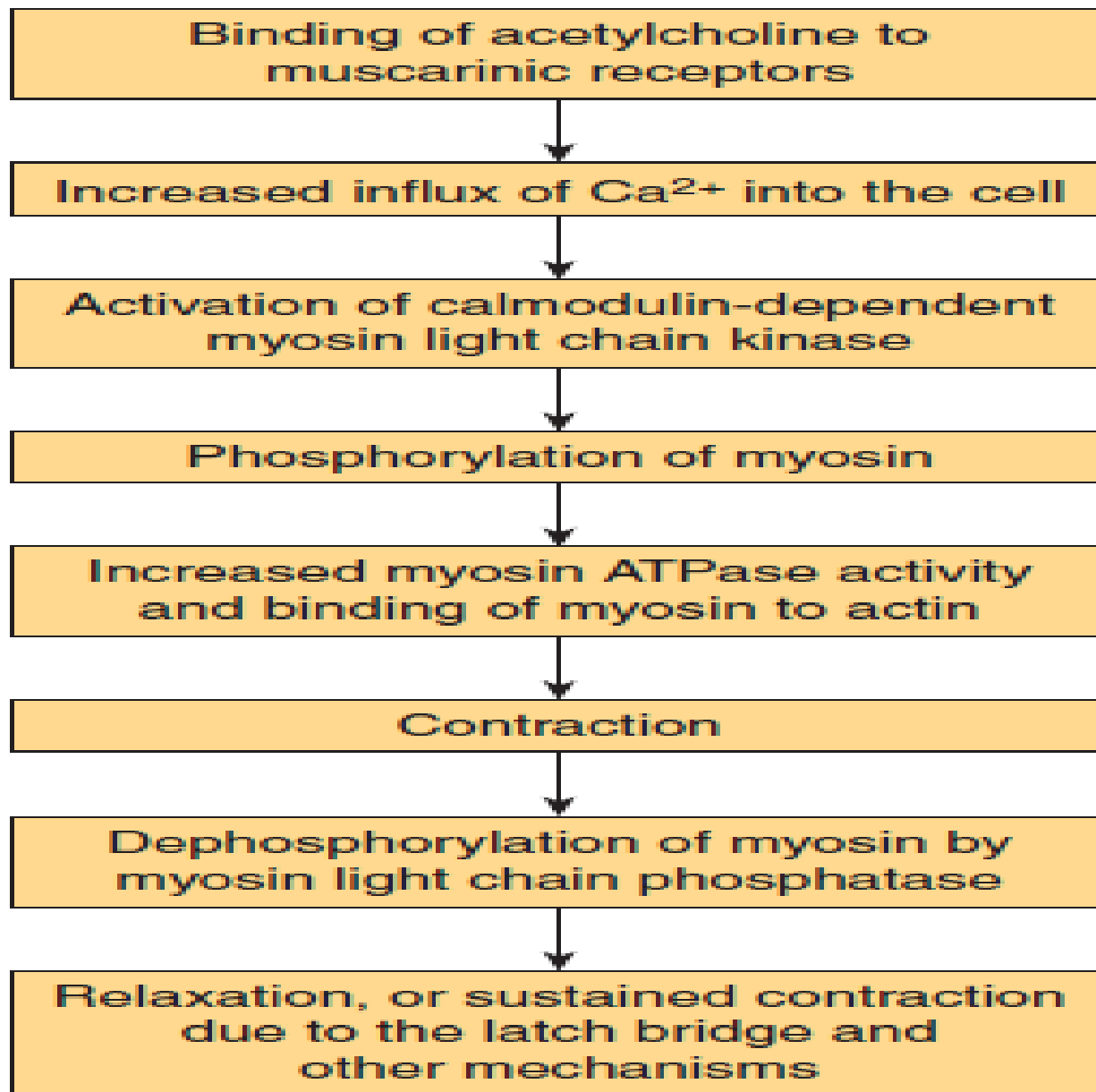


Fig. Sequence of events in contraction and relaxation of smooth muscle

Cardiac Muscle

- Muscle of the heart
- Striated, have sarcomeres & T-tubules
- Involuntary, controlled by **ANS** and **hormones**
- Have the property of **autorhythmicity** and **syncytium**
- Uni- or binucleate
- Cells are joined by structures called **intercalated discs** – which consist of desmosomes and gap junctions

Unit Three

Physiology of Autonomic Nerve System

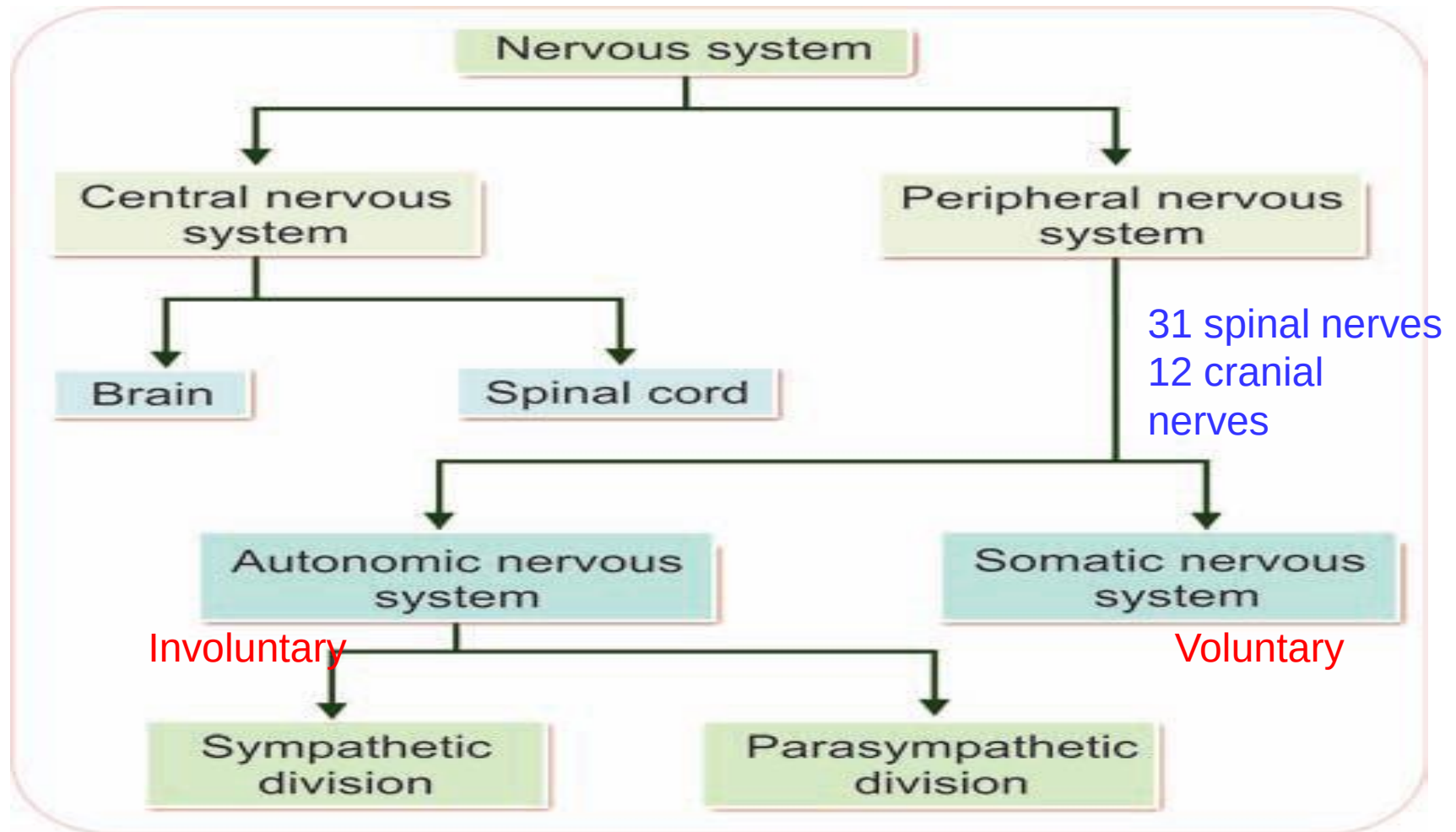
Objectives

- Explain the function of autonomic nerve system to maintain homeostasis.
- Discuss the effect of sympathetic and parasympathetic nerve system effects on the different organs of the body
- Analyze the neurotransmitters released by the preganglionic and post ganglionic neurons of sympathetic and parasympathetic nerve system
- Explain the receptors of autonomic nerve system

Introduction

- The human internal environments is regulated in large measure by the:
 - ANS
 - Endocrine glands and
 - Integrated activities of these two systems

Organization of the Nervous System



Introduction Cont...

PNS Can be divided further:

- **Somatic nervous system**
 - Voluntary
 - Somatic nerve fibers that conduct impulses from the CNS to skeletal muscles
- **Autonomic nervous system**
 - Involuntary
 - Conducts impulses from the CNS to smooth muscle, cardiac muscle, and glands

Comparison of Somatic & ANS

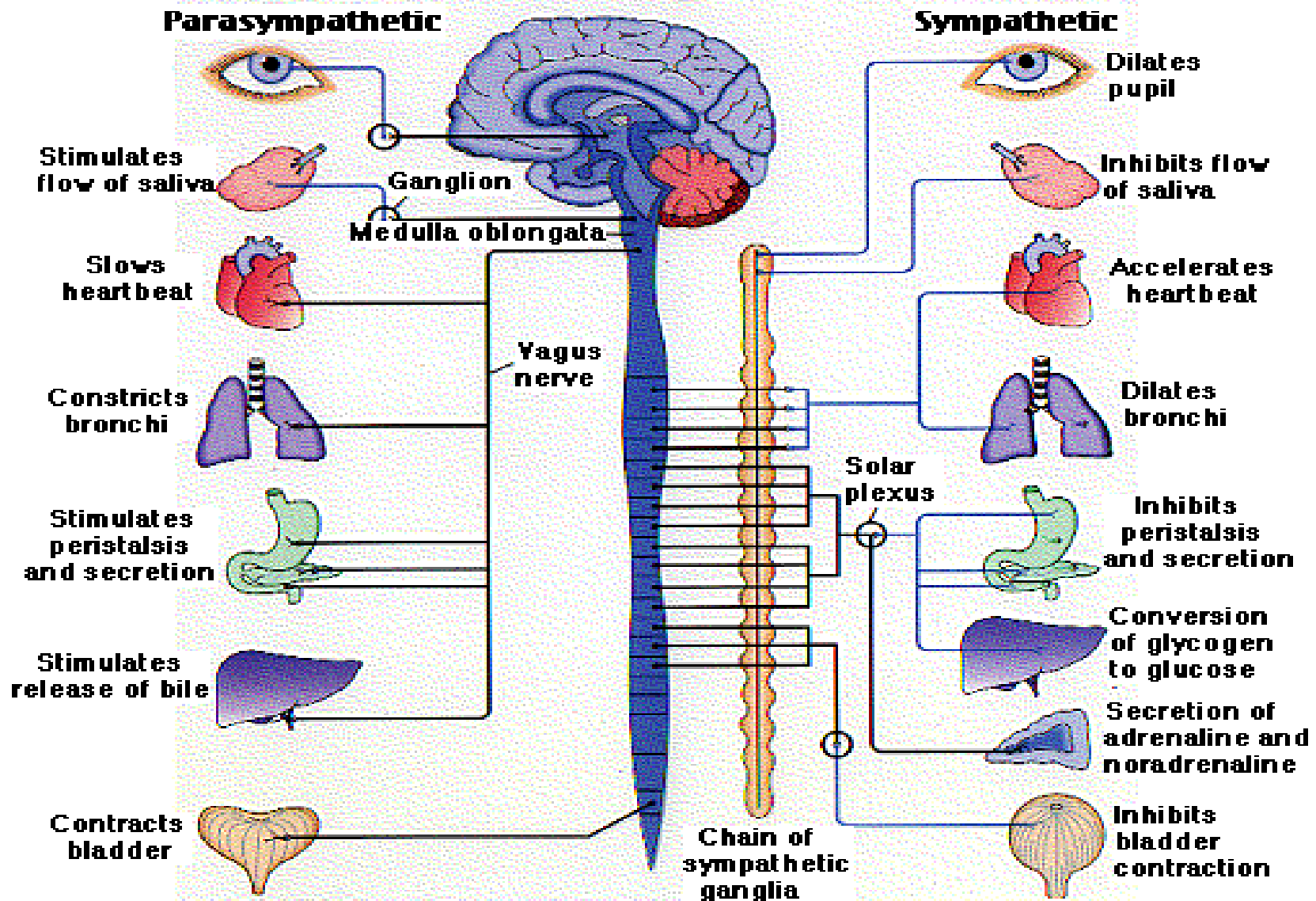
Feature	Somatic	Autonomic
Effectors	Skeletal muscle	Glands, smooth muscle, cardiac muscle
Control	Usually voluntary	Usually involuntary
Efferent pathways	One nerve fiber from CNS to effector; no ganglia	Two nerve fibers from CNS to effector; synapse at a ganglion
Neurotransmitters	Acetylcholine (ACh)	ACh and norepinephrine (NE)
Effect on target cells	Always excitatory	Excitatory or inhibitory
Effect of denervation	Flaccid paralysis	Denervation hypersensitivity

If the autonomic nerves to cardiac or smooth muscle are severed, the muscle exhibits exaggerated responses (denervation hypersensitivity)

Autonomic Nervous System (ANS)

- The portion of the NS that controls most visceral (involuntary) functions of the body. e.g.
 - Arterial pressure
 - Gastrointestinal motility
 - Gastrointestinal secretion
 - Urinary bladder emptying
 - Sweating
 - Body temperature, and many other activities

Autonomic Innervations



Characteristics of the ANS

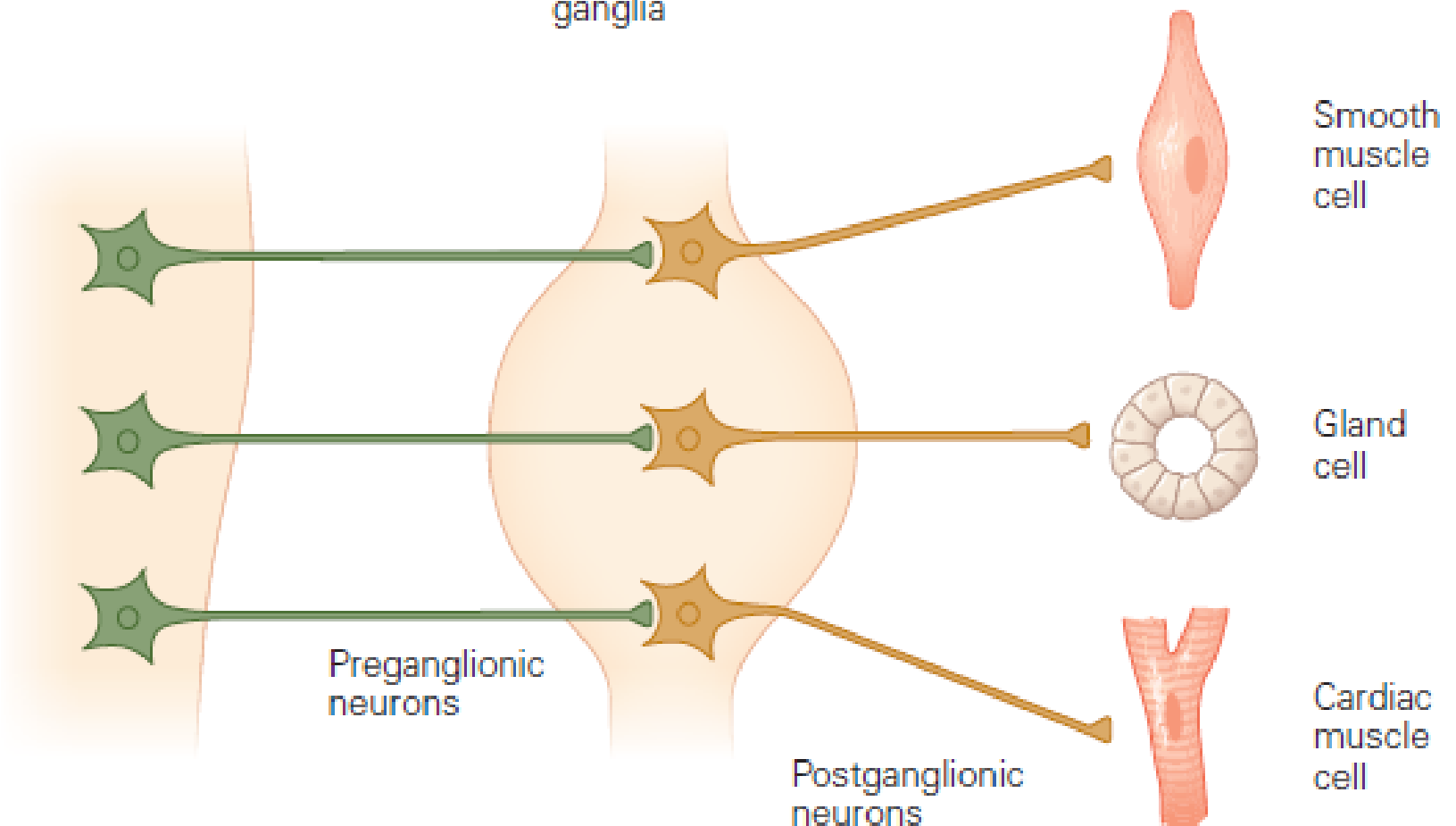
1. The rapidity and intensity with which it can change visceral functions
E.g. within 3 to 5 seconds it can increase the HR to twice normal
2. Innervates smooth muscle, cardiac muscle and glands of internal organs
3. Two neuron chain:
 - a. Preganglionic neurons – originate in the brain or spinal cord
 - b. Postganglionic neurons – originate in the ganglion located outside the CNS

Characteristics Cont...

Brain stem and
spinal cord

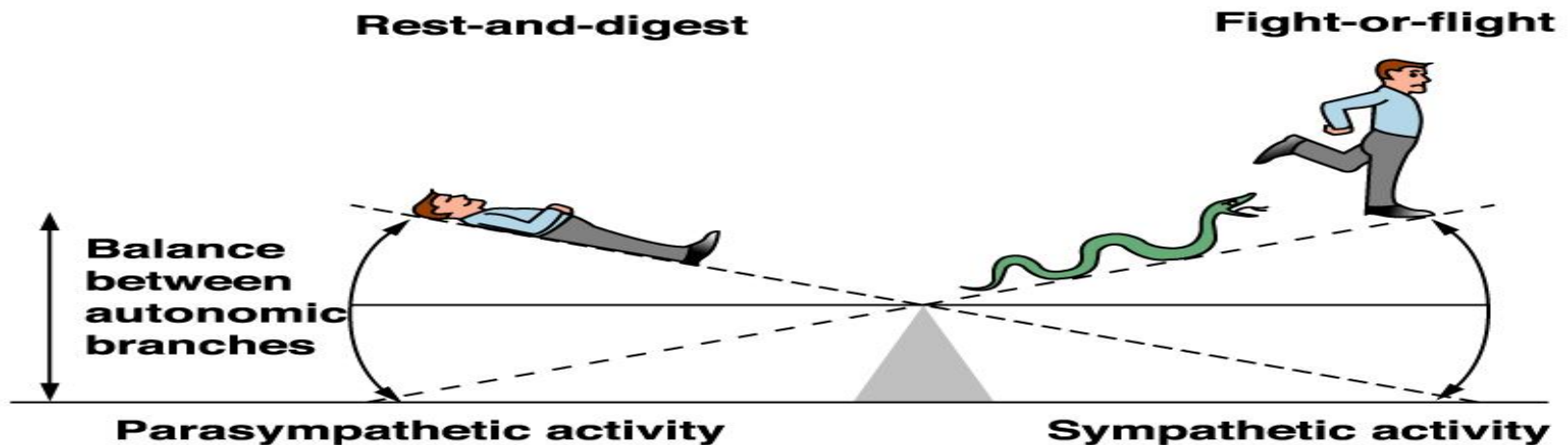
Sympathetic and
parasympathetic
ganglia

Effector cells



Division of Autonomic Nervous System

1. Sympathetic Nervous System:
 - For fight or flight response
2. Parasympathetic Nervous System:
 - Rest and digest



Function of Sympathetic Nerve System

- Sympathetic mass discharge during emergency situations (**fight or flight response**)
 - Simultaneous activation of various organs
 - Excitatory effects on most body tissues
 - Inhibitory on GIT
 - Catabolic, increases metabolic rate and energy output
- **Tonic discharge of impulse** to the heart and blood vessels

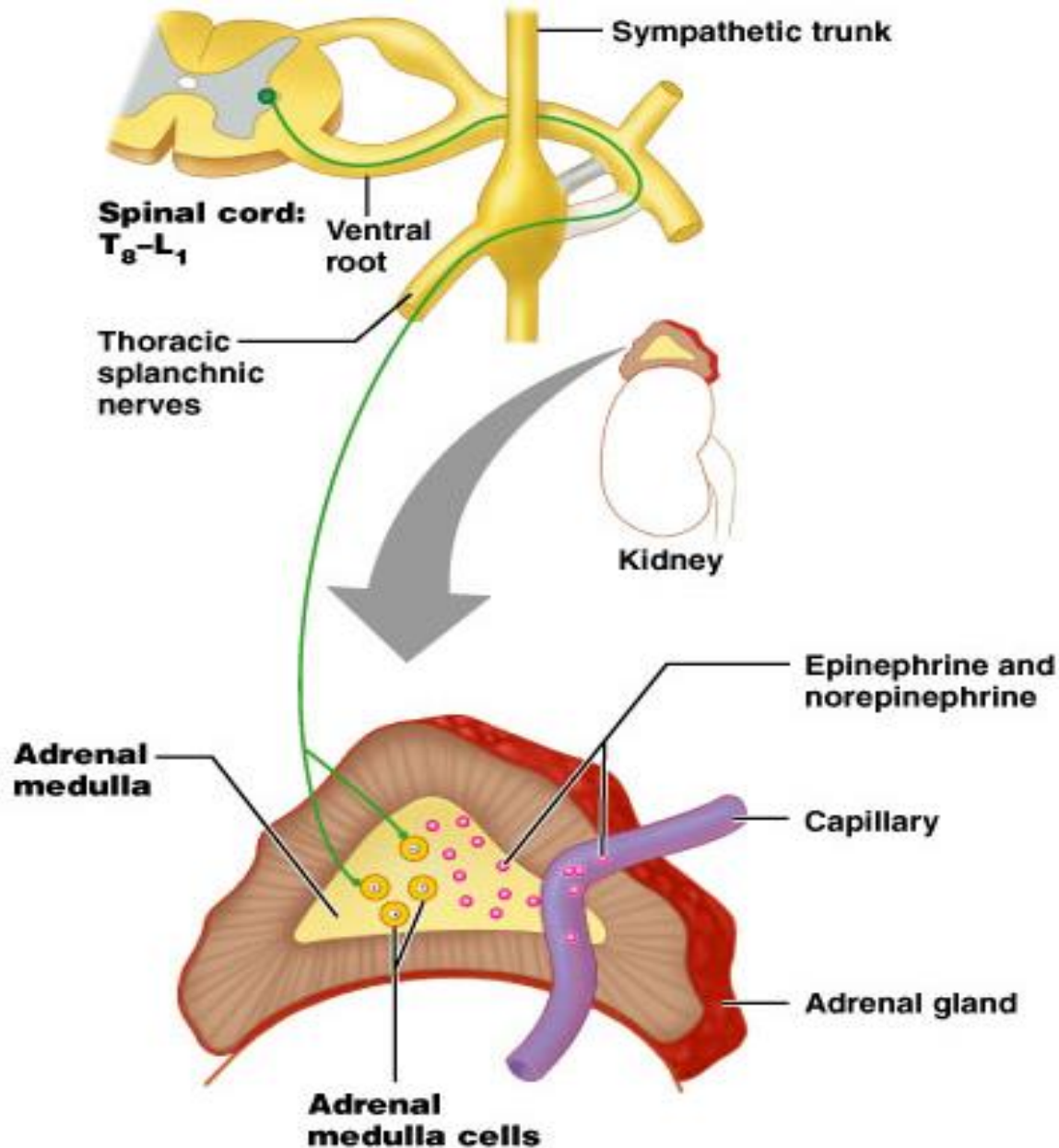
Sympathetic Nerve Endings in the Adrenal Medullae

- Preganglionic sympathetic nerve fibers pass, without synapsing, all the way from the intermediolateral horn cells of the spinal cord into the two adrenal medullae
- The adrenal medullae cells are:
 - Modified neuronal cells in adrenal medulla that secrete epinephrine and norepinephrine into the blood stream
 - Embryologically derived from nervous tissue and are actually postganglionic neurons

Adrenal Medulla Cont...

- The adrenal medullae cells even have rudimentary nerve fibers and it is the endings of these fibers that secrete the adrenal hormones epinephrine and norepinephrine
- Stimulation of the sympathetic nerves to the adrenal medullae causes large quantities of epinephrine and norepinephrine to be released into the circulating blood, and these two hormones in turn are carried in the blood to all tissues of the body.

Adrenal Medulla Cont...



Adrenal Medulla Cont...

- On average, about 80% of the secretion is epinephrine and 20% is norepinephrine
- The circulating epinephrine and norepinephrine have almost the same effects on the different organs as the effects caused by direct sympathetic stimulation, except that the effects last 5 to 10 times as long because both of these hormones are removed from the blood slowly over a period of 2 to 4 minutes

Adrenal Medulla Cont...

- The circulating norepinephrine causes constriction of most of the blood vessels of the body
- It also causes increased activity of the heart, inhibition of the gastrointestinal tract, dilation of the pupils of the eyes, and so forth.

Adrenal Medulla Cont...

- Epinephrine causes almost the same effects as those caused by norepinephrine, but the effects differ in the following respects:
 - Epinephrine, because of its greater effect in stimulating the beta receptors, has a greater effect on cardiac stimulation than does norepinephrine
 - Epinephrine causes only weak constriction of the blood vessels in the muscles, in comparison with much stronger constriction caused by norepinephrine

Adrenal Medulla Cont...

- Because the muscle vessels represent a major segment of the vessels of the body, this difference is of special importance because norepinephrine greatly increases the total peripheral resistance and elevates arterial pressure, whereas epinephrine raises the arterial pressure to a lesser extent but increases the cardiac output more.
- A third difference between the actions of epinephrine and norepinephrine relates to their effects on tissue metabolism

Adrenal Medulla Cont...

- Epinephrine has 5 to 10 times as great a metabolic effect as norepinephrine
- Indeed, the epinephrine secreted by the adrenal medullae can increase the metabolic rate of the whole body often to as much as 100 percent above normal, in this way increasing the activity and excitability of the body
- It also increases the rates of other metabolic activities, such as glycogenolysis in the liver and muscle and glucose release into the blood

Value of Adrenal Medullae to Function of SyNS

- The organs are stimulated in two ways:
 - Directly by the sympathetic nerves
 - Indirectly by the adrenal medullary hormones.
- The two means of stimulation support each other and either can, in most instances, substitute for the other
 - For instance, destruction of the direct sympathetic pathways to the different body organs does not abrogate sympathetic excitation of the organs because norepinephrine and epinephrine are still released into the circulating blood and indirectly cause stimulation.

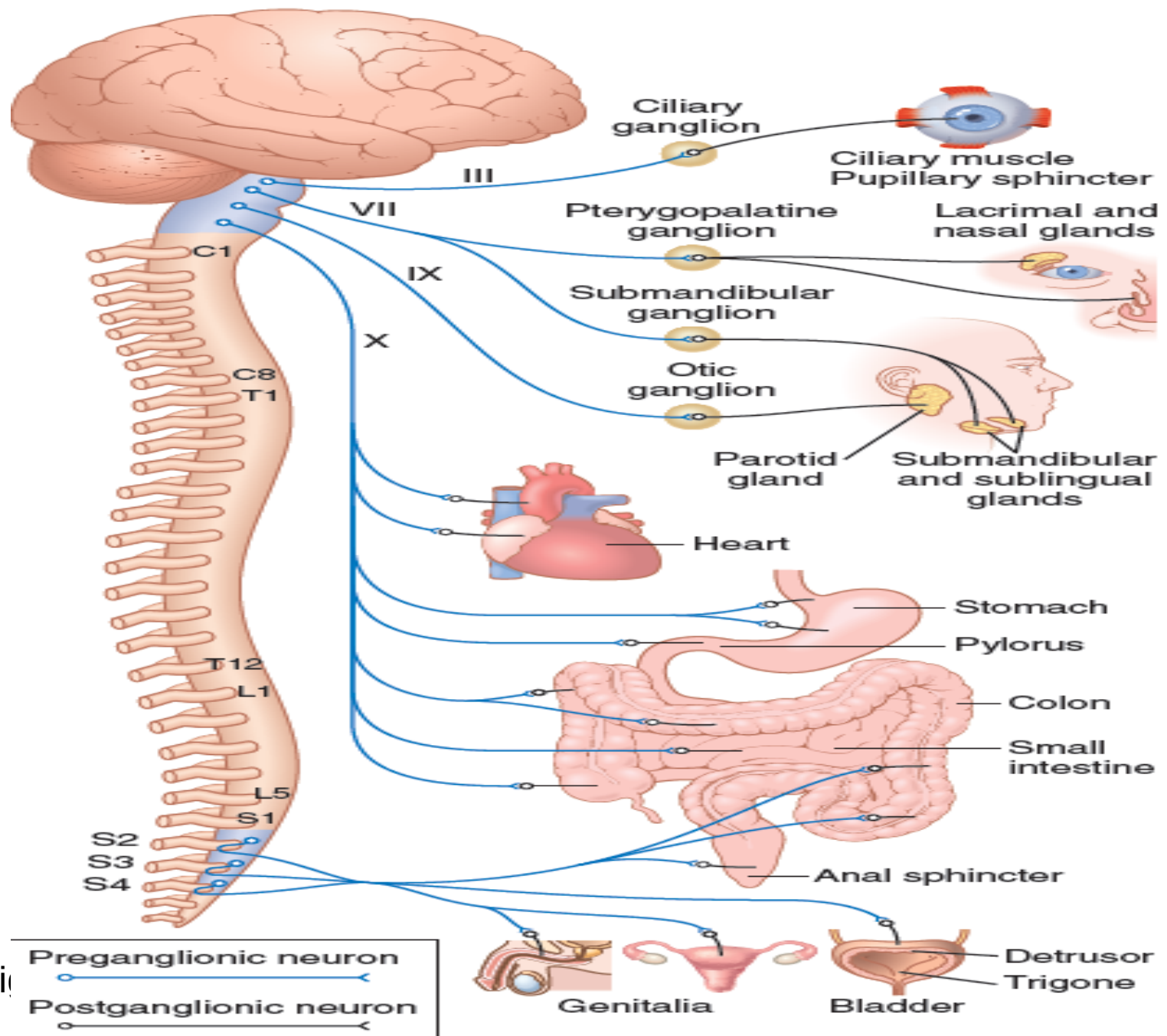
Value of Adrenal Medullae

Cont...

- Another important value of the adrenal medullae is the capability of epinephrine and norepinephrine to stimulate structures of the body that are not innervated by direct sympathetic fibers
- For instance, the metabolic rate of almost every cell of the body is increased by these hormones, especially by epinephrine, even though only a small proportion of all the cells in the body are innervated directly by sympathetic fibers.

Parasympathetic Nerve System

- Originates from cranial and sacral regions
(craniosacral)
- Cranial components are part of CN III, VII, IX, and X
- Sacral components are S2 - S4 segments of the spinal cord



Cranial Nerves with Parasympathetic outflow

1. Oculomotor nerve (III)

- Innervates the pupillary sphincter (constrict pupil) and ciliary muscle (focuses the lens) of the eye

2. Facial nerve (VII)

- Innervate lacrimal, nasal, and submandibular glands

3. Glossopharyngeal never (IX)

- Activates the parotid to secrete saliva

4. Vagus nerve (X)

- 2 vagus nerves account for 75% of all preganglionic parasympathetic fibers in the body
- Major portion of parasympathetic cranial outflow is via vagus nerve, mixed nerve containing both **sensory** and **motor fibers**
- **Sensory input** from **medulla** to cardiovascular, pulmonary, urinary, reproductive, and digestive system **travels in the afferent fibers** of the vagus nerve

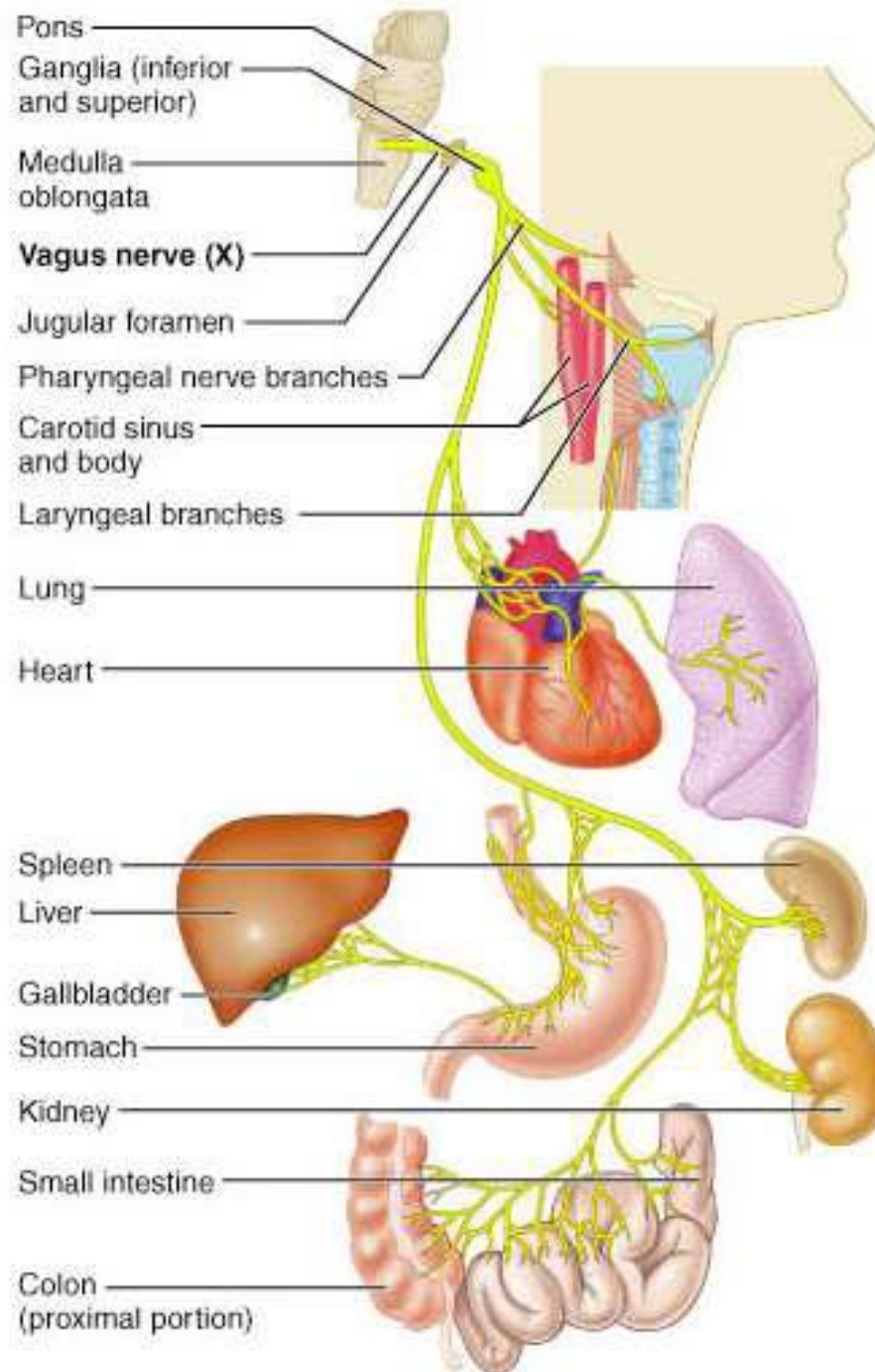


Fig. the distribution of vagus nerve

Cranial Nerves Cont...

- All parasympathetic nerve fibers in the vagus nerves (cranial nerve X) passes to the entire thoracic and abdominal regions of the body
- Therefore, the parasympathetic nervous system often thinks mainly of the two vagus nerves
- The vagus nerves supply parasympathetic nerves to the heart, lungs, esophagus, stomach, entire small intestine, proximal half of the colon, liver, gallbladder, pancreas, kidneys, and upper portions of the ureters

Cranial Nerves Cont...

- The **sacral parasympathetic fibers** distribute to:
 - Descending colon
 - Rectum
 - Urinary bladder
 - Lower portions of the ureters
 - External genitalia to cause erection

Function of Parasympathetic nerve system

- Maintains homeostasis
 - Have mostly inhibitory effect on body tissues
 - Have excitatory effects on the GIT
- Conservation of energy (anabolic)

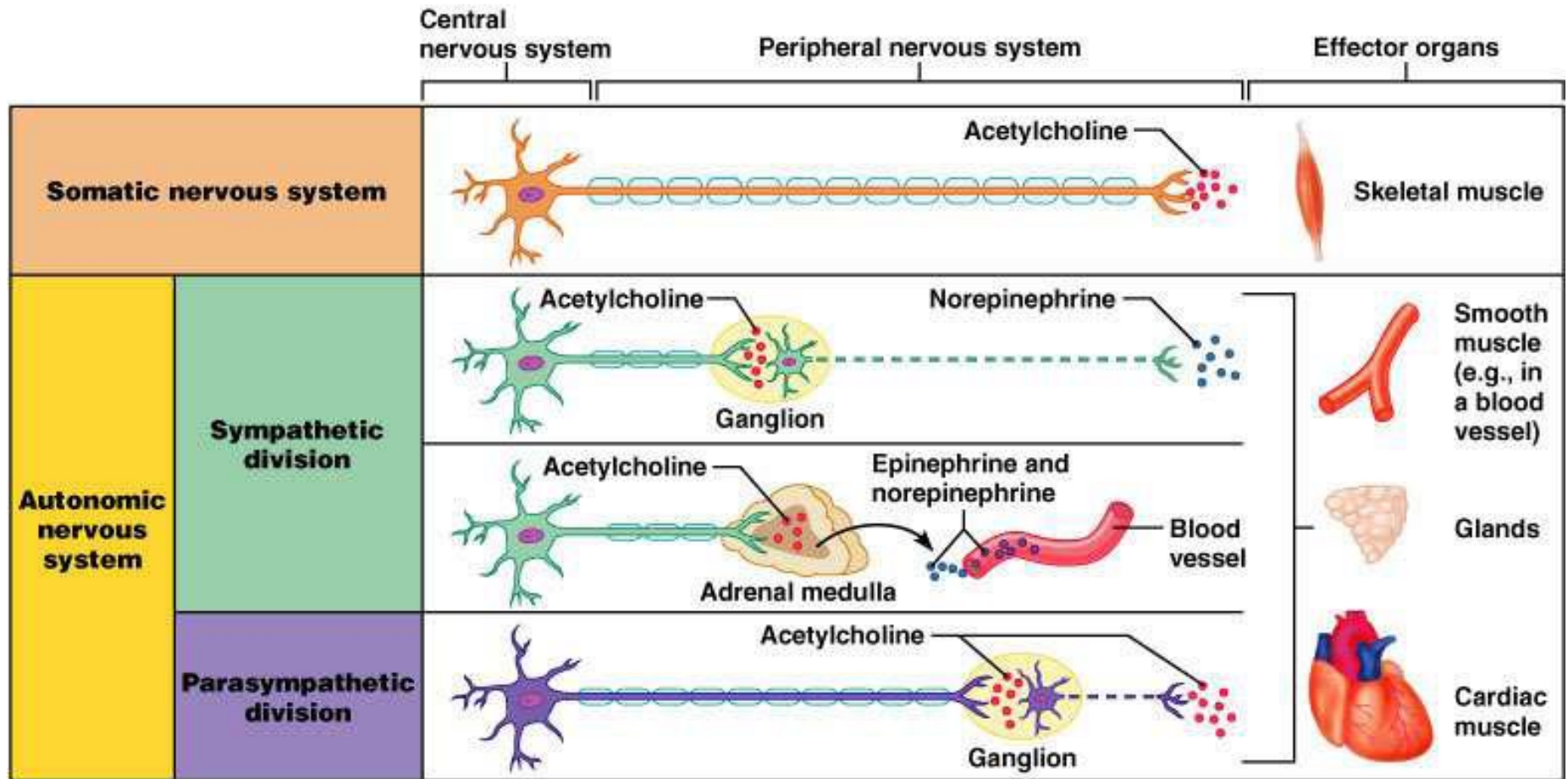
Properties of pre- and post ganglionic neurons

- All preganglionic neurons are cholinergic neurons
 - Secrete acetylcholine and are excitatory
- Sympathetic post ganglionic neurons are adrenergic with few exceptions
 - Secrete nor epinephrine and are either excitatory or inhibitory
- Postganglionic sympathetic nerve fibers to the sweat glands and a few blood vessels are cholinergic
- Parasympathetic post ganglionic neurons are cholinergic
 - Secrete acetylcholine and are either excitatory or inhibitory

Comparing SyNS & PaNS

Feature	Sympathetic	Parasympathetic
Origin in CNS	Thoracolumbar	Craniosacral
Location of ganglia	Paravertebral ganglia adjacent to spinal column and prevertebral ganglia anterior to it	Terminal ganglia near or within target organs
Fiber lengths	Short preganglionic	Long preganglionic
	Long postganglionic	Short postganglionic
Neural divergence	Extensive	Minimal
Effects of system	Often widespread and general	More specific and local

Comparing SyNS& PaNS Autonomic Systems



Key:

= Preganglionic axons (sympathetic)
 = Postganglionic axons (sympathetic)
 = Myelination
 = Preganglionic axons (parasympathetic)
 = Postganglionic axons (parasympathetic)

ANS Receptors

1. Adrenergic receptors

- Receptors for catecholamines (norepinephrine and epinephrine)

2. Cholinergic receptors

- Receptors for acetylcholine

Adrenergic Receptors

- Adrenergic receptors come in two varieties: α (alpha) and β (beta), with several subtypes of each
- There are two major types of alpha receptors, alpha1 and alpha2, which are linked to different G proteins
- The beta receptors are divided into *beta1*, *beta2*, and *beta3* receptors
- **Alpha receptors**—the most common sympathetic receptor—respond strongly to norepinephrine and only weakly to epinephrine

Adrenergic Cont...

- The three main subtypes of beta receptors differ in their affinity for catecholamines
 - β 1-receptors respond equally strongly to norepinephrine and epinephrine
 - β 2-receptors are more sensitive to epinephrine than to norepinephrine
 - β 3-receptors are more sensitive to norepinephrine than to epinephrine

Adrenergic Cont...

Properties of Adrenergic Receptors

Receptor	Found in	Sensitivity
α_1	Most sympathetic target tissues	NE > E*
α_2	Gastrointestinal tract and pancreas	NE > E
β_1	Heart muscle, kidney	NE = E
β_2	Certain blood vessels and smooth muscle of some organs	E > NE
β_3	Adipose tissue	NE > E

*NE = norepinephrine, E = epinephrine.

Source: Silverthorn, 2013

Adrenergic Cont...

- Certain alpha functions are excitatory, whereas others are inhibitory
- Likewise, certain beta functions are excitatory and others are inhibitory
- Therefore, alpha and beta receptors are not necessarily associated with excitation or inhibition but simply with the affinity of the hormone for the receptors in the given effector organ

Table: Adrenergic receptors and function

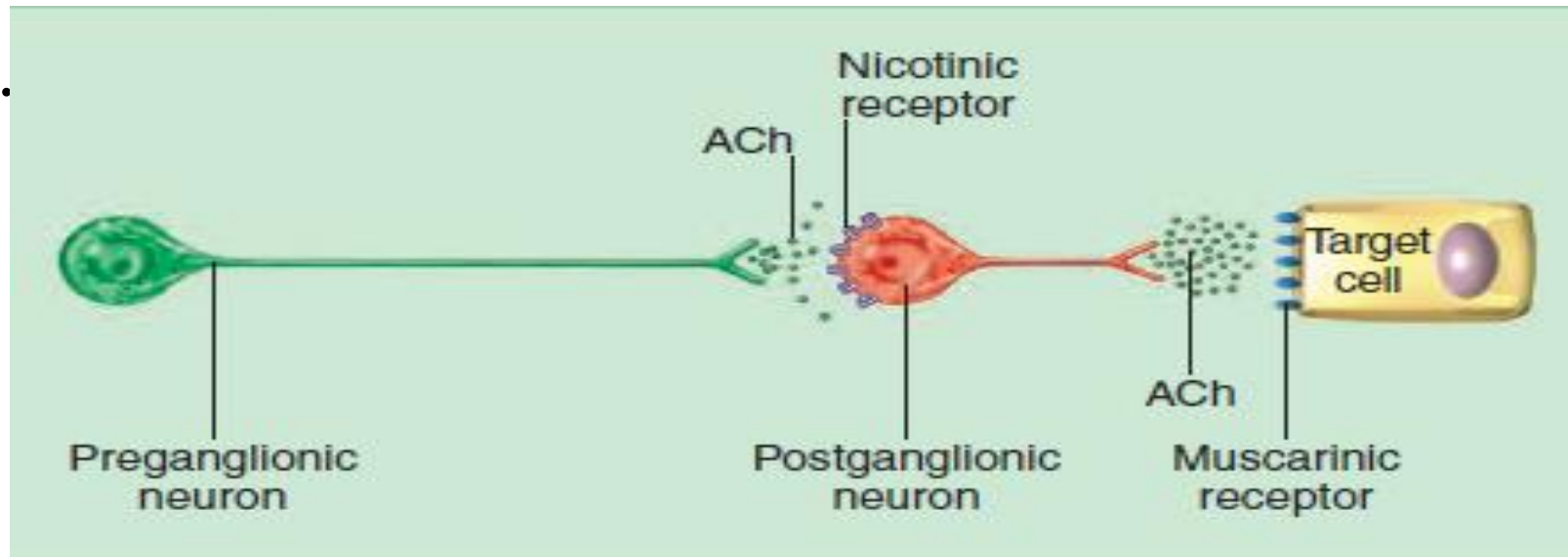
Alpha Receptor	Beta Receptor
Vasoconstriction	Vasodilation (β_2)
Iris dilation	Cardioacceleration (β_1)
Intestinal relaxation	Increased myocardial strength (β_1)
Intestinal sphincter contraction	Intestinal relaxation (β_2) Uterus relaxation (β_2)
Pilomotor contraction	Bronchodilation (β_2)
Bladder sphincter contraction	Calorigenesis (β_2)
Inhibits neurotransmitter release (α_2)	Glycogenolysis (β_2) Lipolysis (β_1) Bladder wall relaxation (β_2) Thermogenesis (β_3)

Cholinergic Receptors

Two principal receptors of acetylcholine

a. Nicotinic receptors

b. Muscarinic receptors



Nicotinic receptors:

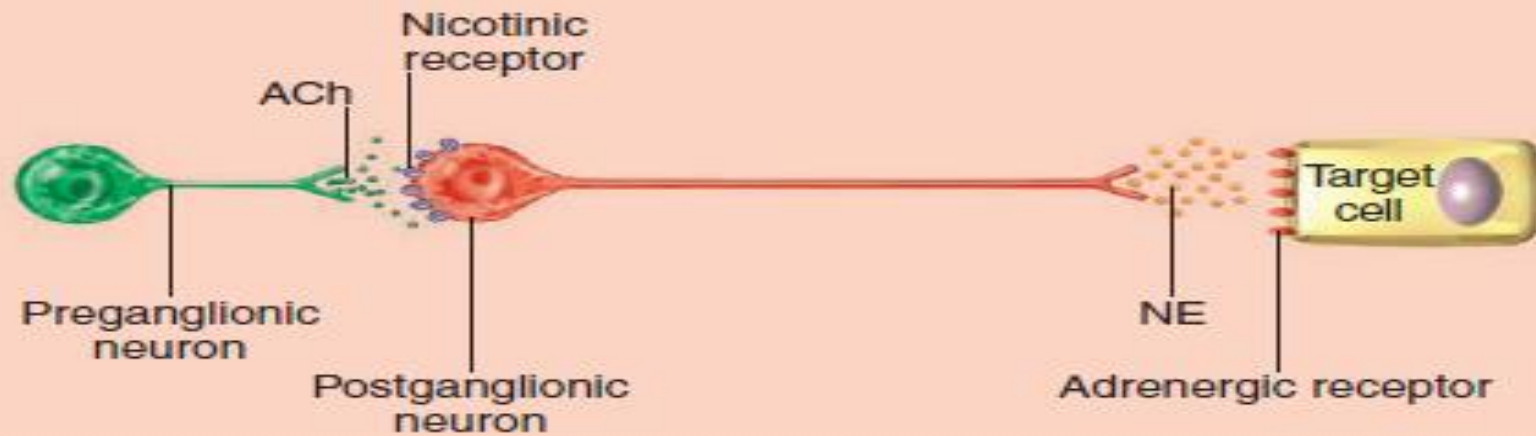
- Found between **pre-** and **post ganglionic neurons** (ganglia) of both PaNS and SyNS
- Ligand-gated ion channels
- Also found at many non- autonomic nerves e.g. NMJ
- Acetylcholine activates both receptors
- Are all excitatory
- Their response is rapid (milliseconds)

Cholinergic Cont...

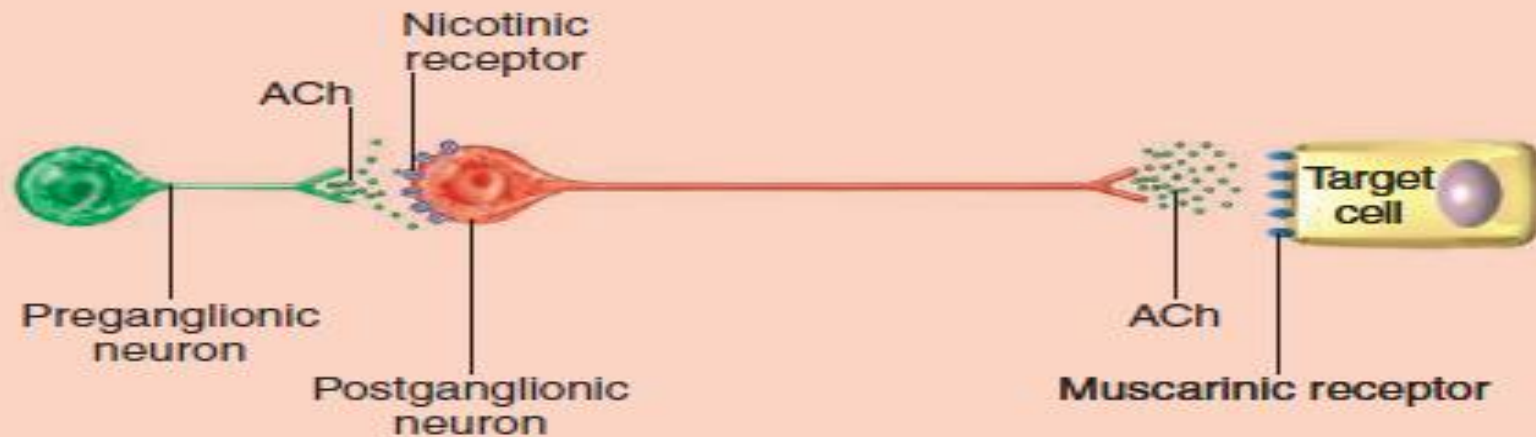
Muscarinic receptors:

- Found on **all effector cells** stimulated by postganglionic cholinergic neurons of both PaSN and SyNS
- Either **excitatory** or **inhibitory**, depending on the target organ
 - E.g.
 - Decrease heart activity
 - Increase motility in GIT
- Use G proteins as their signaling mechanism

(b) Sympathetic adrenergic fiber



(c) Sympathetic cholinergic fiber



Organs With Dual Innervations

- Most visceral organs receive dual innervations (innervations by both SyNS & PsNS)

Organs Without Dual Innervations

- Adrenal medulla
- Arrector pili muscle
- Sweat glands and
- Most blood vessels
receive only sympathetic innervations

- Regulation of blood pressure and routes of blood flow is without dual innervation
- The sympathetic fibers to a blood vessel have a baseline sympathetic tone, which keeps the vessels in a state of partial constriction called **vasomotor tone**

- An increase in firing rate constricts a vessel by increasing smooth muscle contraction
- A drop in firing frequency dilates a vessel by allowing the smooth muscle to relax
- The blood pressure in the vessel, pushing outward on its wall, then dilates the vessel
- The sympathetic division alone exerts opposite effects on the vessels

Pharmacology of ANS

Sympathomimetic Drugs

- Drugs that act on adrenergic effector organs
 - Exogenous norepinephrine, epinephrine
- Some drugs cause release of norepinephrine from nerve endings
 - **E.g** ephedrine, tyramine, and amphetamine
- Some drugs stimulate specific adrenergic receptors
 - Phenylephrine (alpha receptors), isoproterenol (beta receptors), and albuterol (only beta2 receptors)

Drugs that block adrenergic activity

- E.g. reserpine, atenolol, guanethidine

Parasympathomimetic Drugs (Cholinergic Drugs)

- E.g. pilocarpine and methacholine

Drugs that block cholinergic activity at effector organs (antimuscarinic drugs)

- Atropine, homatropine and scopolamine

Organ	Effect of Sympathetic Stimulation	Effect of Parasympathetic Stimulation
Eye		
Pupil	Dilated	Constricted
Ciliary muscle	Slight relaxation (far vision)	Constricted (near vision)
Glands	Vasoconstriction and slight secretion	Stimulation of copious secretion (containing many enzymes for enzyme-secreting glands)
Nasal		
Lacrimal		
Parotid		
Submandibular		
Gastric		
Pancreatic		
Sweat glands	Copious sweating (cholinergic)	Sweating on palms of hands
Apocrine glands	Thick, odoriferous secretion	None
Blood vessels	Most often constricted	Most often little or no effect

Organ	Effect of Sympathetic Stimulation	Effect of Parasympathetic Stimulation
Heart		
Muscle	Increased rate Increased force of contraction	Slowed rate Decreased force of contraction (especially of atria)
Coronaries	Dilated (β_2); constricted (α)	Dilated
Lungs		
Bronchi	Dilated	Constricted
Blood vessels	Mildly constricted	? Dilated
Gut		
Lumen	Decreased peristalsis and tone	Increased peristalsis and tone
Sphincter	Increased tone (most times)	Relaxed (most times)
Liver	Glucose released	Slight glycogen synthesis
Gallbladder and bile ducts	Relaxed	Contracted
Kidney	Decreased urine output and increased renin secretion	None
Bladder		
Detrusor	Relaxed (slight)	Contracted
Trigone	Contracted	Relaxed

Organ	Effect of Sympathetic Stimulation	Effect of Parasympathetic Stimulation
Penis	Ejaculation	Erection
Systemic arterioles		
Abdominal viscera	Constricted	None
Muscle	Constricted (adrenergic α) Dilated (adrenergic β_2) Dilated (cholinergic)	None
Skin	Constricted	None
Blood		
Coagulation	Increased	None
Glucose	Increased	None
Lipids	Increased	None
Basal metabolism	Increased up to 100%	None
Adrenal medullary secretion	Increased	None
Mental activity	Increased	None
Piloerector muscles	Contracted	None
Skeletal muscle	Increased glycogenolysis Increased strength	None
Fat cells	Lipolysis	None

Central Control of Autonomic Function

- The ANS is not an independent nervous system
- It is influenced by various levels of the central nervous system

Cerebral cortex

- Even if we usually cannot consciously control the ANS, the mind does influence it
- The limbic system provides a pathway connecting sensory and mental experiences with the autonomic nervous system
 - Involved in many emotional responses

Hypothalamus

- The major control center of the visceral motor system
- Output from the hypothalamus travels largely to nuclei in more caudal regions of the brainstem, and from there to the cranial nerves and the sympathetic neurons in the spinal cord

Midbrain, pons, and medulla oblongata

- House numerous autonomic nuclei
- Centers for cardiac and vasomotor control, salivation, swallowing, sweating, gastrointestinal secretion, bladder control, pupillary constriction and dilation, and other primitive functions
- Autonomic output from these nuclei travels by way of the spinal cord and the oculomotor, facial, glossopharyngeal, and vagus nerves

Spinal cord

- Integrates such autonomic reflexes as micturition, defecation, erection, and ejaculation
- Fortunately, the brain is able to inhibit defecation and urination consciously, but when injuries sever the spinal cord from the brain, the autonomic spinal reflexes alone control the elimination of urine and feces

Unit Four

Blood Physiology

Objectives

- Describe the components of blood.
- Explain the role of blood in maintaining homeostasis.
- Describe the physiological impacts of red blood disorder.
- Describe the mechanism of hemostasis.

Introduction

- Blood is a viscous fluid connective tissue provides important nourishment to all body organs and tissues and carries away waste materials
- An adult human has about 5 to 6 liters of blood, which is roughly 7 to 8 % of total body weight
- The volume of blood in an individual fluctuates
 - E.g Blood volume increases during pregnancy

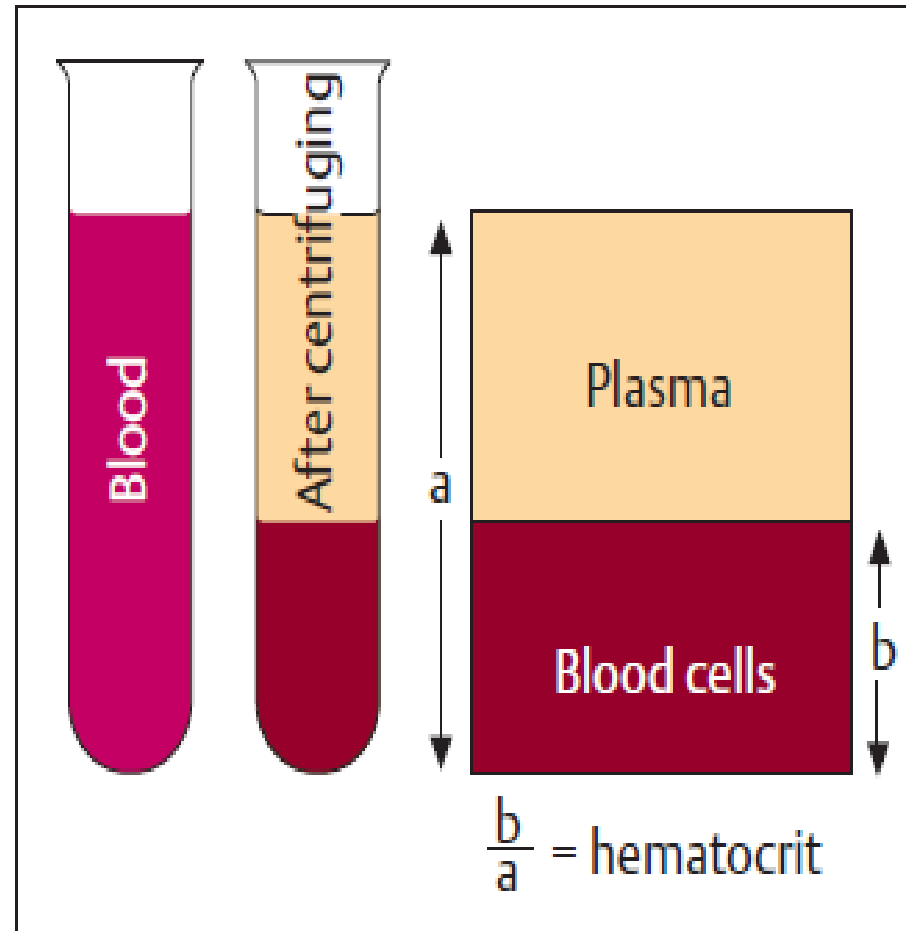
Components of Blood

Formed elements (45%)

- Red blood cells (erythrocytes)
- White blood Cells (leukocytes)
- Platelets (thrombocytes)

Plasma (55%)

- The fluid portion of blood



Functions of Blood

➤ Transport

- Gases; O_2 from lung to tissues and CO_2 from tissues to the lung
- Nutrients: organic (glucose, amino acids, lipids) and inorganic substances like Na^+ , Ca^{2+} are carried by blood
- Waste products: urea, uric acid, creatinine etc to the kidney etc

Functions Cont...

➤ Defense

- WBC defend the body from infectious attacks

➤ Regulation

a. Temperature regulation

- water has high specific heat (great heat storage than other liquids and solids)
- prevents sudden changes in T^0

b. Acid-base balance

- The Hb in RBC is an important chemical buffer

Properties of Blood

Color:

- bright red- oxygenated blood (arterial blood)
- dark red- deoxygenated (venous blood)

Viscosity:

- Refers to internal resistance of a liquid to flow
- Blood is 3X more viscous than pure water

pH :

- 7.4 (blood is slightly alkaline)

Volume

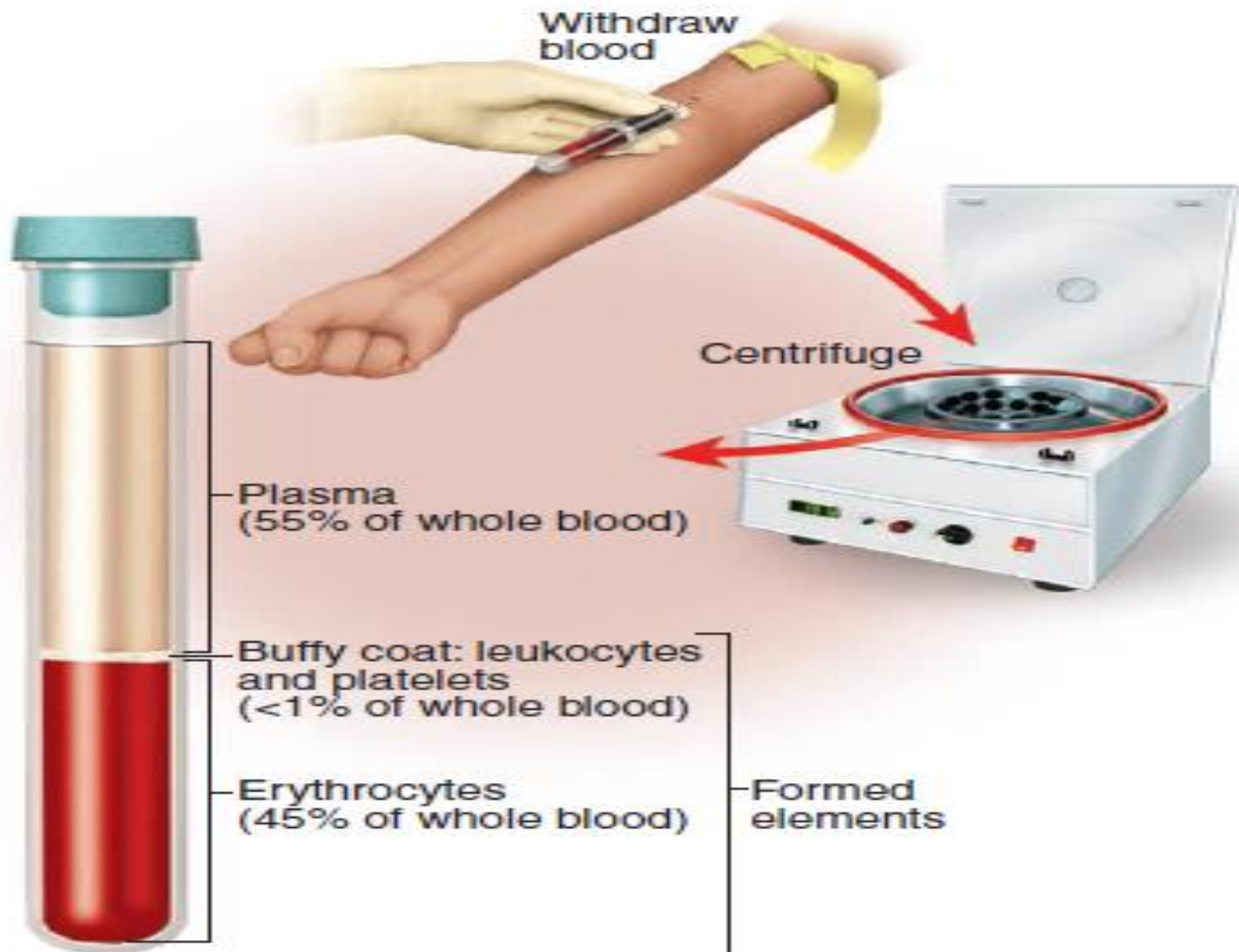
- Blood volume = 8% of total body weight
Male = 5-6 Lit &
Female= 4-5 Lit

Density (specific gravity)

- 1.050-1.060

Hematocrit (Packed cell volume)

- Hct is the volume percent (%) of RBC from whole blood
- Un-coagulated blood forms 3 layers when centrifuged for about 5 min
 - Upper suspension is the blood plasma (55%)
 - Middle layer is WBC and Platelets (< 1%)
 - Lower portion is RBC (45%)



Plasma

- The liquid portion of blood
- Composed of
 1. Water (90%)
 2. Organic constituents (9%)
 - Plasma proteins (7%)
 - Hormones and enzymes
 - Nutrients: CHO, vitamins, amino acids, fats
 - Metabolic waste products: urea, creatinine
 3. Inorganic constituents: electrolytes (1%)
 4. Respiratory gases – oxygen and carbon dioxide

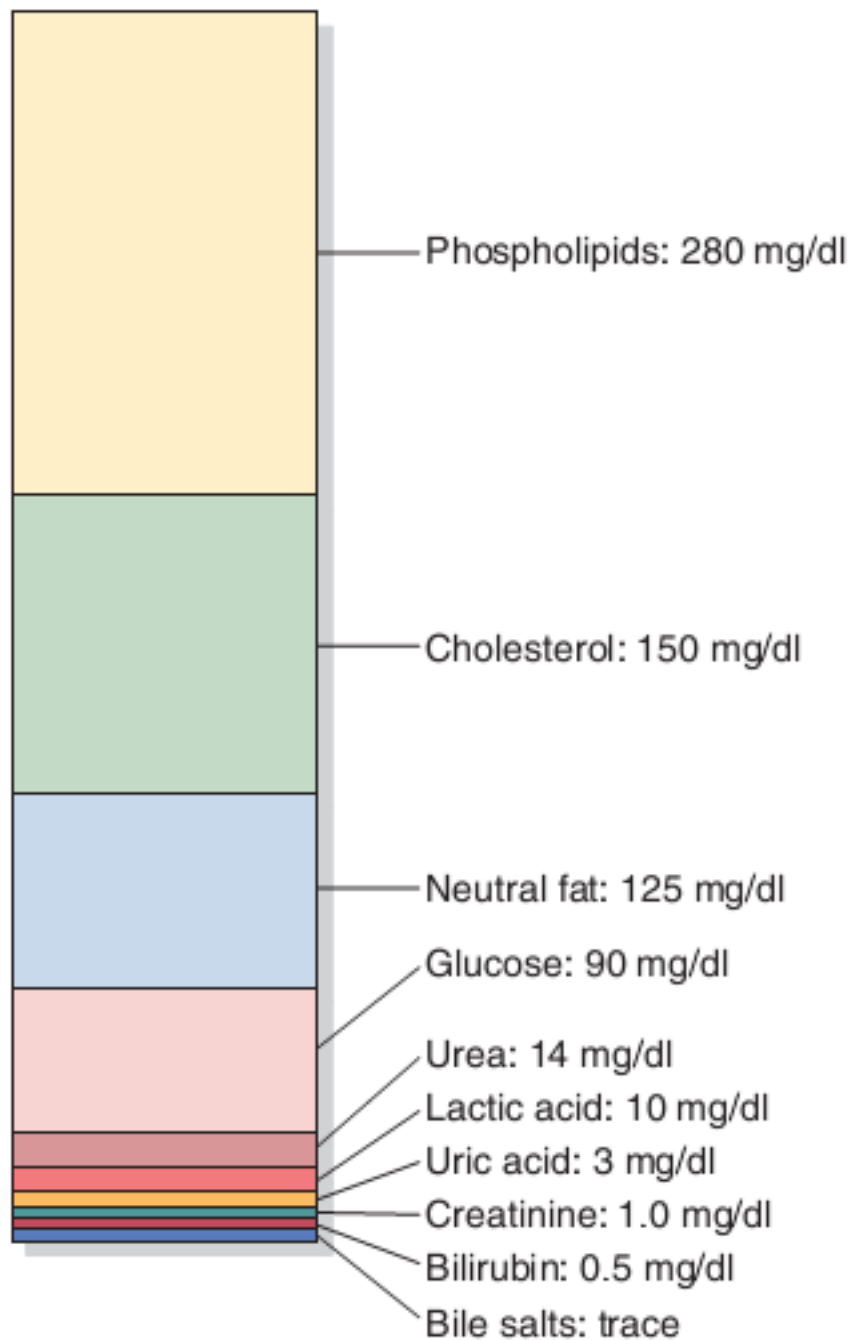


Figure: Nonelectrolytes of the plasma

Serum vs Blood Plasma

- Plasma contains all plasma proteins
- Serum is blood plasma without fibrinogen (a clotting factor).
- In other words, Serum has more or less similar composition to blood plasma except that its fibrinogen have been removed

Plasma Proteins

- Proteins found in blood plasma
- Many but most abundant are:

A. Albumin

- Produced in the liver
- ~ 60% or 4.5 gm/dl

B. Globulins

- ~ 36%, or 2.5 g/dl
- alpha, beta, gamma

C. Fibrinogen

- 4% or 0.25

Plasma Proteins Cont...

Albumin

- Responsible for Colloid osmotic pressure (oncotic pressure)
 - Helps to keep plasma fluid back to the circulation (i.e., it increases re-absorption pressure)
- Also transports nutrients (e.g., lipids, hormones, bilirubin etc.)



Fig. Children of with Kwashiorkor. They have thin limbs and fluid-distended abdomens 256

Plasma Proteins Cont...

Globulin

- 3-types: $\alpha_{1\&2}$, beta, and gamma globulins
- Alpha & gamma are made in the liver and transport lipoproteins, iron, hormones etc.
- Gamma globulins also act as antibodies

Fibrinogen

- Synthesized in the liver
- Involved in the process of blood clotting

Red Blood cells (RBC)

Mature RBC

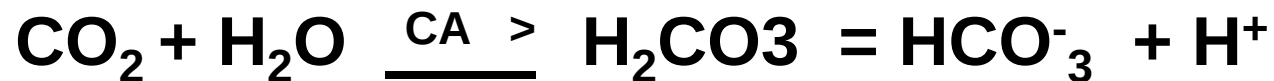
- Has a flexible biconcave shape
- Has no nucleus
- Has greater surface area/volume ratio.
 - Therefore, can bend and twist to pass through the narrow capillaries very easily

RBCs Cont...

- The shapes of RBCs can change remarkably as the cells squeeze through capillaries
- Actually, the RBC is a “bag” that can be deformed into almost any shape
- Normal RBC has a great excess of cell membrane for the quantity of material inside, deformation does not stretch the membrane greatly and, consequently, does not rupture the cell, as would be the case with many other cells

RBC Function

1. Carries hemoglobin that in turn **transports respiratory gases** and **buffers H⁺**
2. Contain a large quantity of **carbonic anhydrase (CA)**



CA increases the rate of this reaction 5000 fold.

Good to transport CO₂ from the tissues to the lung very fast

RBC number & its indices with sex

TABLE 13-1

Standard Laboratory Values for Red Blood Cells

Test	Normal Values	Significance
Red blood cell count (RBC)		
Men	$4.2\text{--}5.4 \times 10^6/\mu\text{L}$	Number of red cells in the blood
Women	$3.6\text{--}5.0 \times 10^6/\mu\text{L}$	
Reticulocytes	1.0%–1.5% of total RBC	Rate of red cell production
Hemoglobin		
Men	14–16.5 g/dL	Hemoglobin content of the blood
Women	12–15 g/dL	
Hematocrit		
Men	40%–50%	Volume of cells in 100 mL of blood
Women	37%–47%	

RBC Number Cont...

- The values of RBC, hematocrit and Hb tend to be lower in women than in men due to the following reasons:
 1. Androgens stimulate RBC production, and men have higher androgen levels than women
 2. Women of reproductive age have periodic menstrual losses
 3. Hematocrit is inversely proportional to percentage body fat, which is higher in women than in men

Areas of the Body That Produce RBCs

- First trimester of gestation
 - Yolk sac produces RBC
- Second trimester of gestation
 - Liver, Lymph and Spleen produce RBC
- Third trimester gestation up to 20 years:
 - Red bone marrow of all cells but after 5 years the active regions of marrow decrease

Areas Cont...

- Adults (after age 20 years):
 - Membranous bones like ribs, sternum, vertebrae, and pelvic bones
 - Not in long bones like femur or tibia (become fatty)

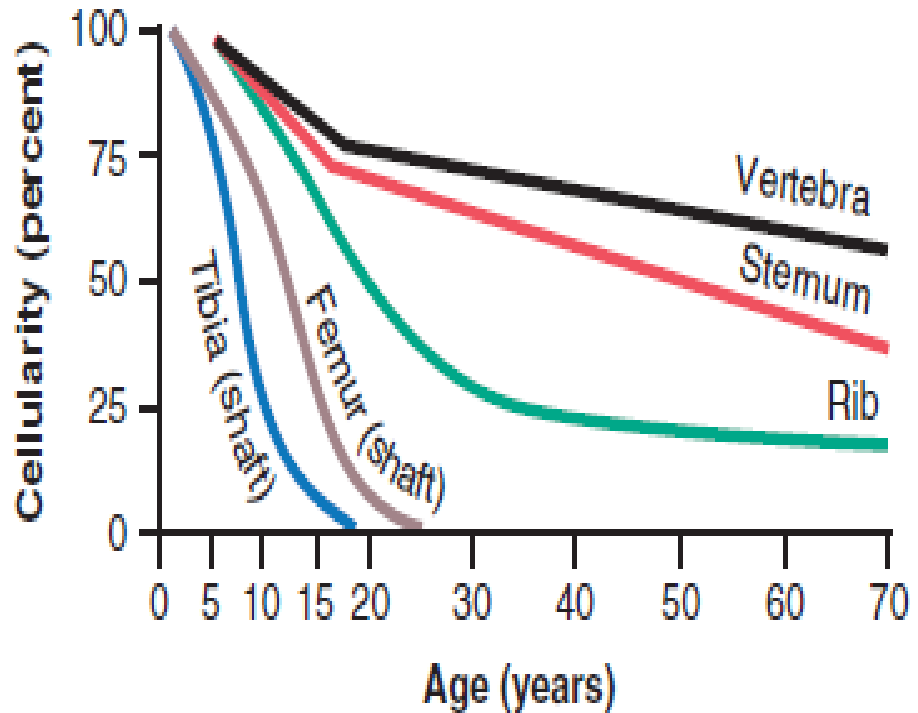


Fig. Relative rates of red blood cell production in the bone marrow of different bones at different ages

Production of RBCs in the Body

- The blood cells begin their lives in the bone marrow from a single type of cell called the pluripotential hematopoietic stem cell, from which all the cells of the circulating blood are eventually derived
- Cells that produce RBC's are called colony-forming unit–erythrocytes (CFU-E)
- Further, colony forming granulocytes, monocytes and megakaryocytes (for platelets) develop to produce other types of WBC's
- Growth inducers and differentiation inducers outside the bone help growth and differentiation of blood cells

Production of RBCs Cont...

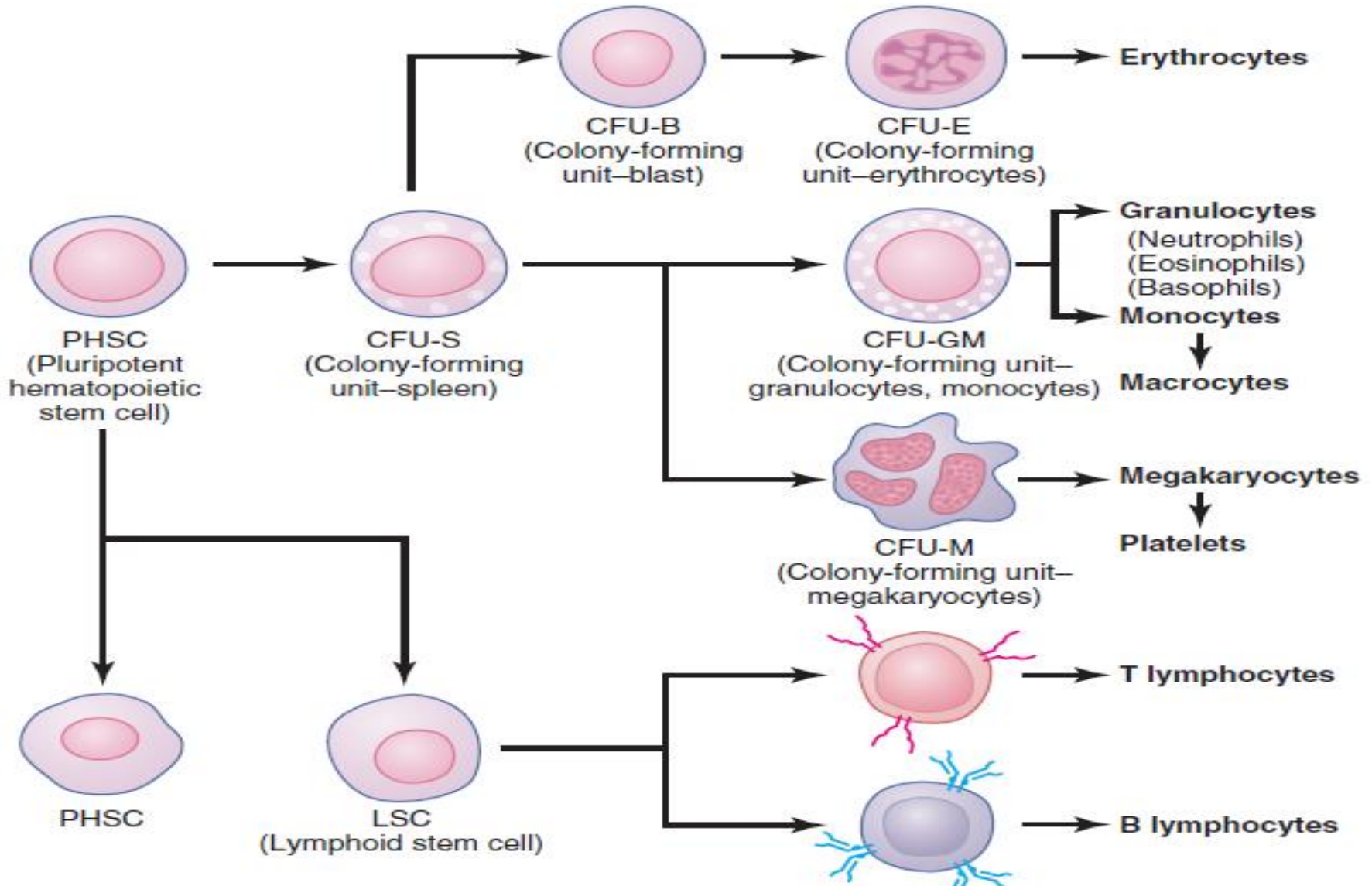
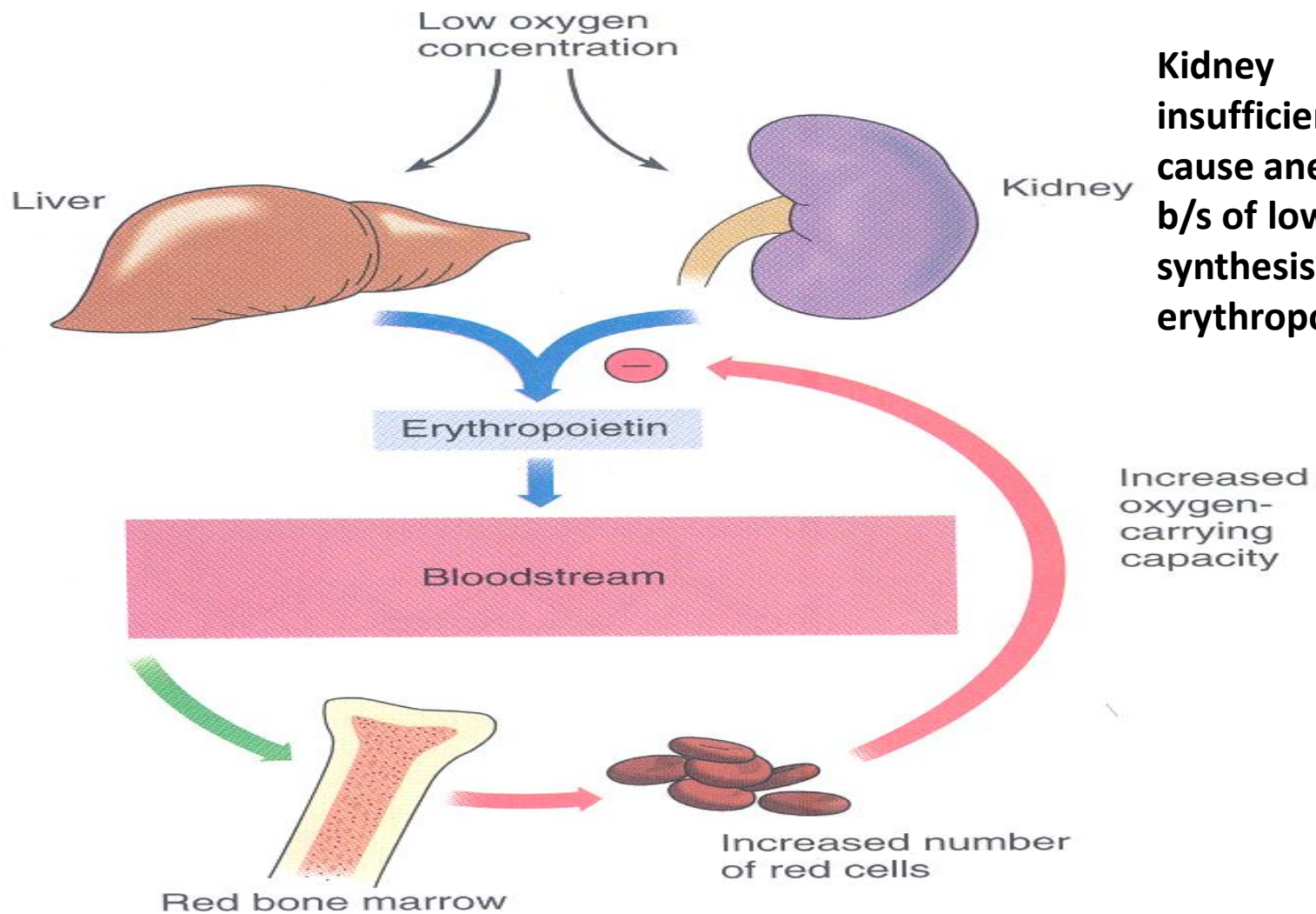


Fig. Formation of the multiple different blood cells from the original pluripotent hematopoietic stem cell in the bone marrow

Regulation of RBCs Production by Erythropoietin

- Regulation of RBC production (erythropoiesis) occurs by negative feed back mechanism
- Hypoxia stimulates kidney cells to release the hormone erythropoietin
- Erythropoietin reaches bone marrow through blood and induce stem cells to produce more RBC's into the blood



**Kidney
insufficiency can
cause anemia,
b/s of lower
synthesis of
erythropoietin**

FIGURE 14.6

Low oxygen concentration causes the kidneys and liver to release erythropoietin, which stimulates production of red blood cells that carry oxygen to tissues.

Regulation of RBCs Cont...

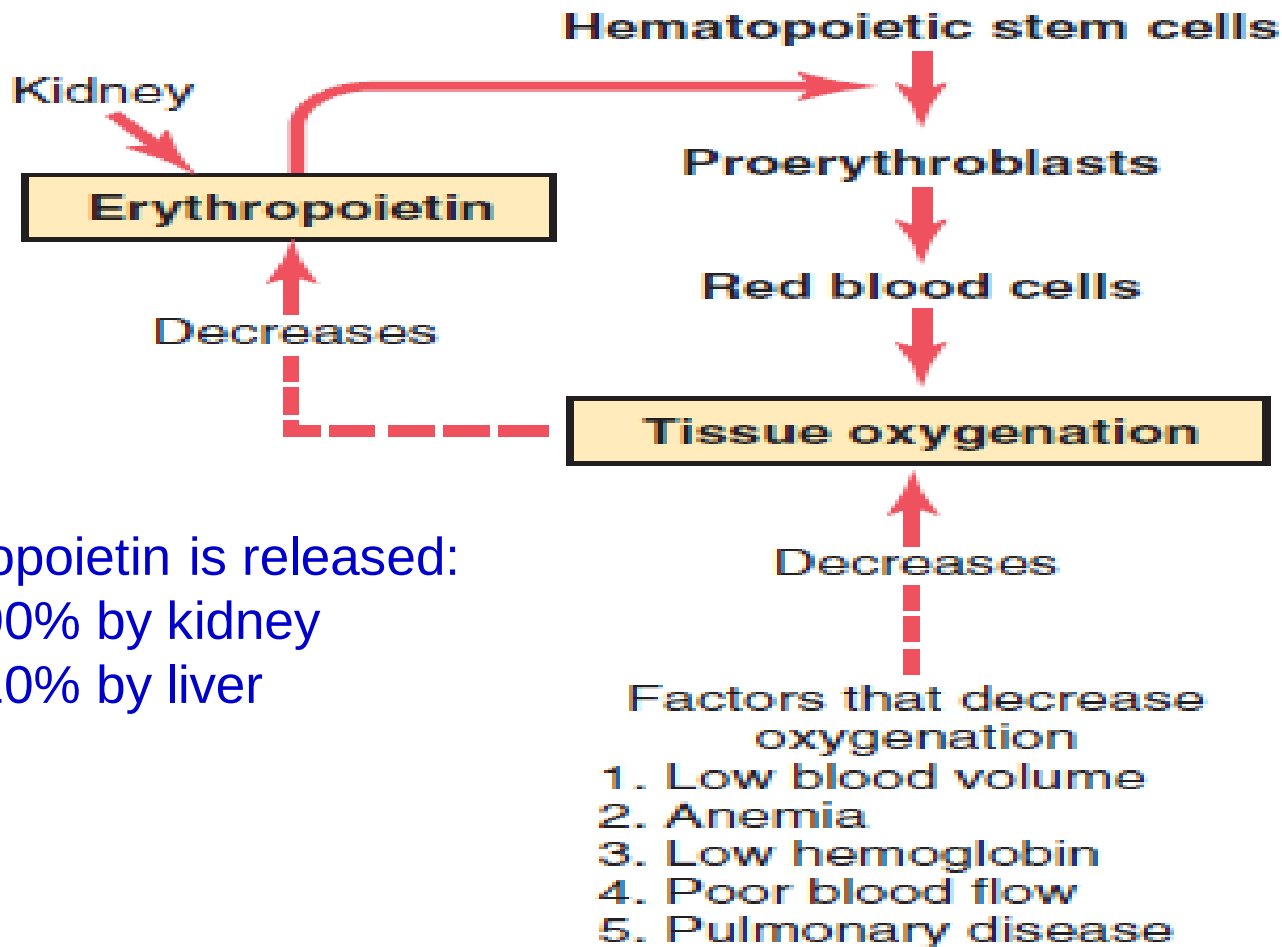


Fig. Function of the erythropoietin mechanism to increase production of red blood cells when tissue oxygenation decreases

Substances Necessary for RBC Maturation

a. Vitamin B₁₂ (cyanocobalamin):

- Important for DNA synthesis and thus for cell division
- Requires intrinsic factor for absorption

b. Folic acid: important in DNA synthesis

c. Iron:- necessary for Hb-synthesis

d. Also others like Cu²⁺ and Vitamin C

- Cofactors for some of the enzymes that synthesize hemoglobin

Erythrocyte Sedimentation Rate (ESR)

- ESR is the rate at which un-coagulated blood (RBC) settles down when allowed to stand in a tube
- RBC & protein concentration affect ESR
 - Polycythemia : Hct value is large, so ESR is low
 - Anemia: increases ESR
- ESR vales:
 - Male= 3-7 mm/hr
 - Female = 3-12 mm/hr

Hb Structure and Function

- Hemoglobin is large molecule inside RBC & it has:
 - a. Globin part: protein with 4-polypeptides
 - b. Heme group: Fe^{2+} containing central part to which oxygen binds
- Each polypeptide has one heme group
- Each heme with Fe^{2+} carries one O_2 molecule, total = 4- O_2 molecules are carried with in Hb molecule

Functions of Hb

- Carrying O_2 and CO_2 gases
- It is a buffer to maintains acid-base balances

Hb Cont...

- The whole blood of men & women contains an average of 15 & 14 grams of Hb per 100 ml respectively
- Each gram of Hb can combine with 1.34 ml of oxygen if the Hb is 100% saturated
- In a normal man a maximum of about 20 ml of oxygen can be carried in combination with Hb in each 100 ml of blood
- In a normal woman 19 milliliters of oxygen can be carried with Hb in each 100 ml of blood

Iron Metabolism

- Iron is important for the formation of:
 - Hemoglobin
 - Myoglobin
 - Cytochromes, etc
- The total quantity of iron in the body averages 4 to 5 grams:
 - 65% in hemoglobin
 - 4% in myoglobin
 - 15 to 30% stored for later use principally in the form of ferritin

Iron Metabolism Cont...

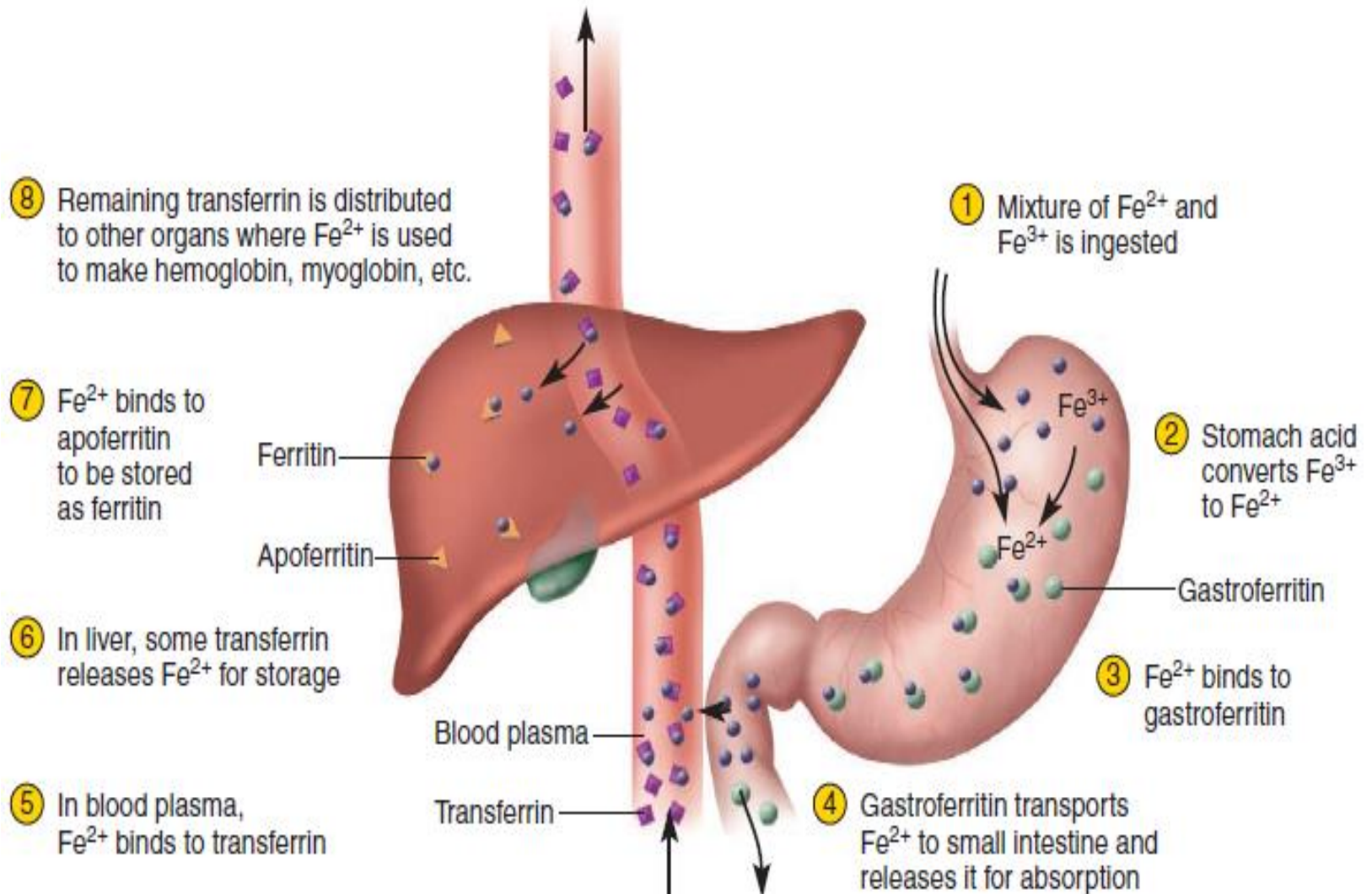


Fig. Iron Metabolism

Combination of Hb with Other Molecules

A. Met-hemoglobin:

- Occurs when blood is exposed to some **oxidizing chemicals**
- These chemicals will convert Fe^{2+} Hb into Fe^{3+} Hb form, that is toxic and has decreased ability to carry O_2

B. Carboxy-Hb:

- Occurs when Hb combines with carbon-monoxide.
- Hb has greater affinity to CO than O_2
- CO is also toxic and reduces the ability of Hb to carry O_2 (Smokers)
- CO can also be lethal, b/s CO can easily displace the O_2 molecule from Hb

RBC Destruction Cont..

- After RBCs are delivered from the bone marrow into the circulatory system, they normally circulate an average of 120 days before being destroyed
- Many of the RBCs self-destruct in the spleen, where they squeeze through the red pulp of the spleen
- When RBCs burst and release their hemoglobin
- Macrophages of reticuloendothelial system phagocytize the hemoglobin and destroy them

RBC Destruction Cont...

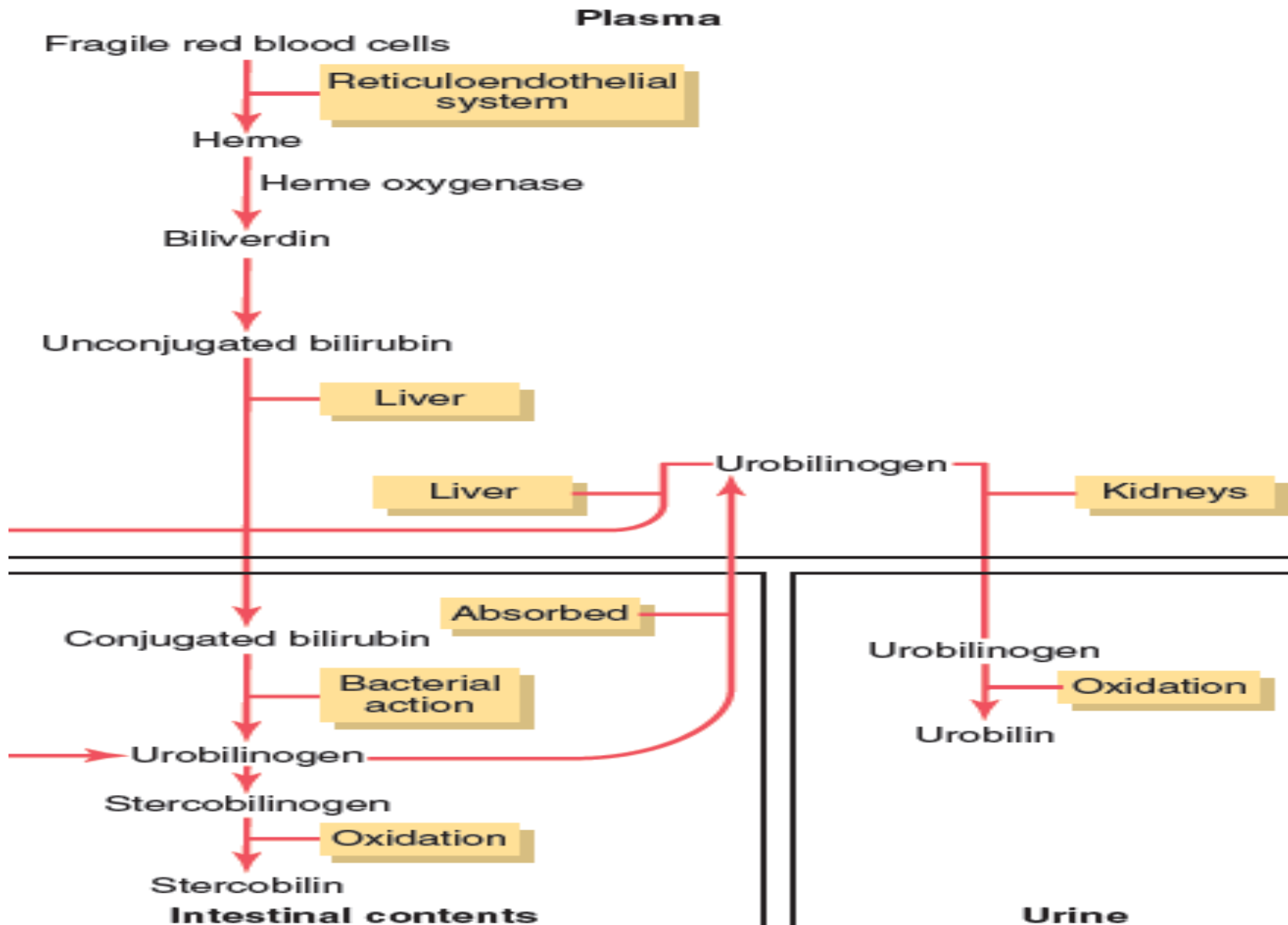
- Steps in the destruction of RBC
 - RBC $\rightarrow$ Globin + Heme
 - Globin $\rightarrow$ broken to AA's $\rightarrow$ used for protein synthesis
 - Heme $\rightarrow$ Fe^{2+} + porphyrine rings

Fe^{2+} is used to synthesize new Hb or stored in the liver for other time

RBC Destruction Cont...

- Porphyrine rings → oxidatize to biliverdin which inturn is reduced to green pigment called **bilirubin**
 - Bilirubin is carried by serum albumin & reaches liver
 - Bilirubin conjugates with glucuronic acid in liver
 - Liver releases bilirubin as **bile** to small intestine
 - Conjugated bilirubin is converted to urobilinogen by bacterial action
 - Some of the urobilinogen is reabsorbed through the intestinal mucosa back into the blood
 - Others will remove out through **feces** (brown color) and **urine** (yellow)

RBC Destruction Cont...



Jaundice

- Yellowish tint to the body tissues
- Caused by large quantities of bilirubin in the ECF, either unconjugated or conjugated bilirubin
- The normal plasma concentration of bilirubin, which is almost entirely the unconjugated form, averages 0.5 mg/dl of plasma
 - Can rise to as high as 40 mg/dl
- The skin usually begins to appear jaundiced when the concentration rises to about three times normal (above 1.5 mg/dl)

Jaundice Cont...

- The common causes of jaundice are:
 - ↑destruction of RBCs, with rapid release of bilirubin into the blood (**hemolytic jaundice**)
 - Obstruction of the bile ducts or damage to the liver cells so that even the usual amounts of bilirubin cannot be excreted into the GIT (**obstructive jaundice**)

Erythrocyte Disorders

- Any imbalance between the rates of erythropoiesis and RBC destruction may produce an excess or deficiency of RBC
- RBC excess is called polycythemia, and a deficiency of either RBCs or hemoglobin is called anemia

Anemia

- Deficiency of hemoglobin in the blood which can be caused by either too few RBCs or too little hemoglobin in the cells
- The causes of anemia fall into three categories:
 - (1) Inadequate erythropoiesis or hemoglobin synthesis
 - (2) Hemorrhagic anemia from bleeding and
 - (3) Hemolytic anemia from RBC destruction

Physiological Effects of Anemia

a. Anemia decreases viscosity:

- The decrease in viscosity causes decreased resistance that in turn causes increased blood flow or (venous return) to the heart
- The increased venous return increases cardiac output
- Tachycardia and palpitation may occur as the body tries to compensate with an increase in cardiac output (CO)

Physiological Effects Cont...

b. Anemia causes vasodilatation:

- Diminished O_2 dilates blood vessels b/s of hypoxia
- Dilation increase return of blood to the heart that again increases cardiac output (CO).

Increased CO increases the work load of the heart which leads to **hear failure**

Polycythemia

- Excessive production of red blood cells
- Two types

1. Primary polycythemia (polycythemia vera)

- Due to cancer of the erythropoietic line of the red bone marrow
- Can result in RBC count as high as 11 million RBCs/ μ L blood and a hematocrit as high as 80%

Polycythemia Cont...

2. Secondary polycythemia:

- Characterized by RBC counts as high as 6 to 8 million / μ L blood
- Can result from dehydration, smoking, air pollution, high altitude, strenuous physical conditioning, or other factors that create a state of hypoxemia and stimulate erythropoietin secretion

Polycythemia Cont...

- The principal dangers of polycythemia are increased blood volume, pressure and viscosity
- Blood volume can double in primary polycythemia and cause the circulatory system to become tremendously engorged
- Blood viscosity may rise to three times normal
- Chronic (long-term) polycythemia can lead to embolism, stroke, or heart failure

Leukocytes (White Blood Cells)

- Mobile units of the body's protective system
- They are formed:
 - Partially in the bone marrow:
Granulocytes, monocytes & a few lymphocytes
 - Partially in the lymph tissue:
Lymphocytes

Leukocytes Cont...

- Have nucleus all the time, but lack Hb, so they are colorless
- Normal number: 4000-10,000 / mm³ of blood
- Fight infection by direct destruction (e.g., phagocytosis) & by producing antibodies and sensitized lymphocytes
- When infection occurs, WBC increase in number
- Life span: many (not all) live only a few days, may be b/s of their engagement with pathogens

Leukocytes Cont...

- After formation, they are transported in the blood to different parts of the body where they are needed
- Most of them are specifically transported to areas of:
 - serious infection and inflammation, thereby providing a rapid and potent defense against infectious agents

Leukocytes Cont...

- According to the type of **cytoplasmic granules** (small particles) and the **shape of nuclei** leukocytes are classified into two:-

1. Granulocytes and their life span

- Polymorphonuclear WBC's (i.e. their nuclei have 3-5 lobes)
- 3 types
 - a. Neutrophils- ~ 62%, life span 4-5 days
 - b. Eosinophils- ~ 2-3%, “
 - c. Basophiles- ~ 0.1-0.4%, “

Leukocytes Cont...

- 2. Agranulocytes and their life span
 - d. Lymphocytes- ~ 30%, weeks or months
 - e. Monocytes- ~ 5 %, 20 hrs
- Monocytes circulate in blood and change into macrophages that attach to tissues e.g.
 - alveolar macrophages in the lung
 - kuffer cells in the liver etc.
- Macrophages live longer times (months)

Leukocytes Cont...

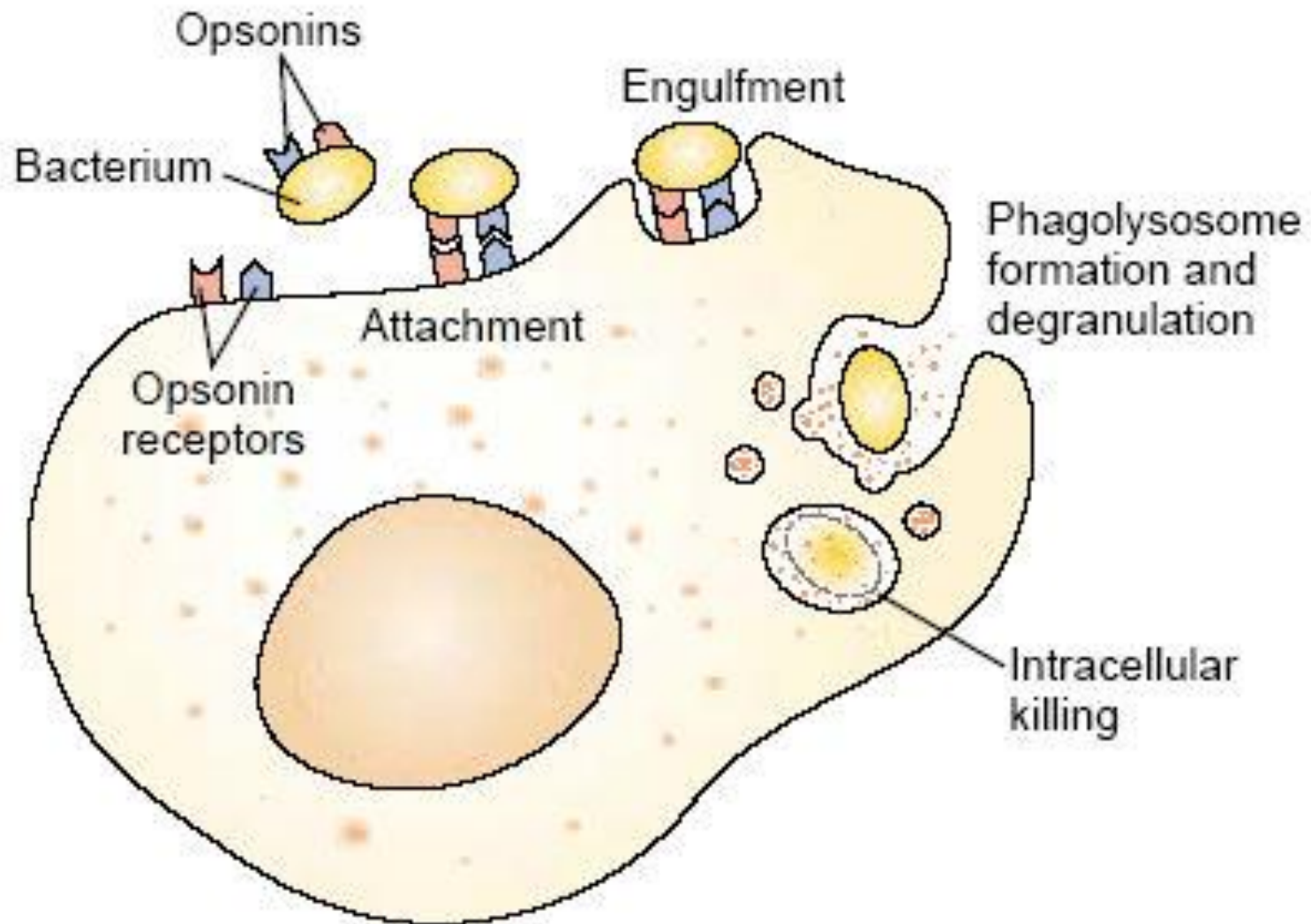
- Granulocytes (neutrophils, eosinophils, basophiles) and monocytes destroy invading organisms by phagocytosis
- Lymphocytes, to the contrary, attack infections through the immune system by producing sensitized lymphocytic cells and plasma cells that produce antibodies that are produced in the bone marrow and lymphogenous(spleen, thymus, tonsils, Peyer's patches etc) organs

Leukocytes Cont...

- Neutrophils can engulf 3-20 bacteria's at once
- Macrophages can phagocytize >100 bacteria at once and even engulf bigger ones like RBC's, malaria parasites etc
- Presence of rough space facilitates phagocytosis
- Dead tissues are easily phagotized
- Antibodies by Opsonization promote phagocytosis
- Lysosomes, and oxidizing agents like lipases, peroxisomes, H_2O_2 , etc. produced from macrophages are lethal for bacterial membranes

Mechanism of Phagocytosis

1. Opsonization
2. Attachment
3. Engulfment
4. Intracellular killing by producing:
 - Lysosomes, and oxidizing agents like lipases, peroxisomes, H_2O_2 , OH^- ions are produced from macrophages that are lethal for bacterial cell membranes



■ **FIGURE 9-4** ■ Phagocytosis of a particle (*e.g.*, bacterium): opsonization, attachment, engulfment, and intracellular killing.

Eosinophils

- Have granules in the cytoplasm that have enzymes
- Phagocytize antigen-antibody complexes and destroy them
- Their number increases during asthma and other allergic attacks

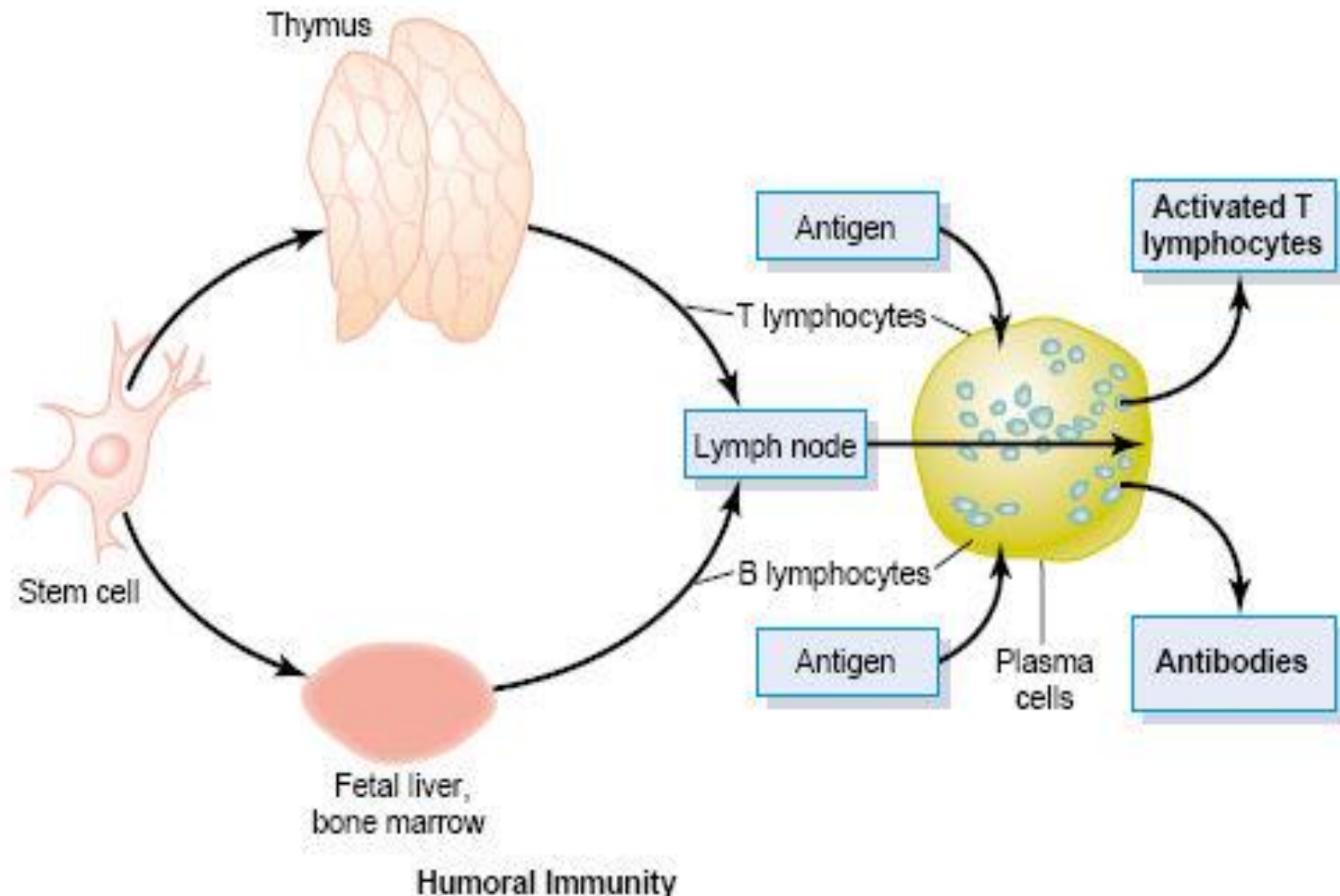
Basophils

- Have granules
- Produce heparin, so act as natural inhibitors of blood clotting
- They also release histamine, serotonin, etc

Lymphocytes

- Are responsible for specific immunity that consists of:
 - a. Cell mediated immunity (T-cell immunity)
 - Achieved through formation of large numbers of activated T lymphocytes that are specifically crafted in the lymph nodes to destroy the foreign agent
 - b. Humoral immunity (B-cell immunity)
 - The body develops circulating antibodies, which are capable of attacking the invading agent

Cell-Mediated Immunity



WBC Abnormalities

Leukocytosis

- WBC count above 10,000 / μ l blood
- Usually indicates infection, allergy, or other diseases
- Can also occur in response to dehydration or emotional disturbances
- A high neutrophil count is a sign of bacterial infection
- A high eosinophil count usually indicates an allergy or a parasitic infection such as hookworms or tapeworms

WBC Abnormalities Cont...

Leukopenia

- Abnormally low level of WBCs
- Leaves the body unprotected against many bacteria and other agents that might invade the tissues

WBC Abnormalities Cont...

Leukemia

- A cancer of the hemopoietic tissues that usually produces an extraordinarily high number of circulating leukocytes and their precursors
- Classified as:
 1. **Myeloid leukemia-** marked by uncontrolled granulocyte production
 2. **Lymphoid leukemia-** involves uncontrolled lymphocyte or monocyte production

Platelets

- Are not cells but small fragments of marrow cells, called mega-karyocytes
- Second most abundant formed elements, after erythrocytes
 - from 130,000 to 400,000/ μ l blood (average 250,000)
- Have a complex internal structure that includes lysosomes, mitochondria, microtubules and microfilaments, granules filled with platelet secretions

Platelets Cont...

- They have no nucleus
- When activated, they form pseudopods and are capable of ameboid movement
- Has a half-life in the blood of 8 to 12 days, then eliminated from the circulation mainly by the tissue macrophage system

Platelets Cont..

- Platelets are responsible for clotting because their cytoplasm synthesizes the following chemicals which enhance clotting:
 - Thromboxane A_2
 - Serotonin
 - Histamine
 - Von Willbrand's factor (important for adherence of platelets) and
 - Minerals like Cu^{2+} and Fe^{2+} that are involved in clotting processes

Properties of platelets

1. Adhesiveness :

- Platelets stick when they come in contact with wet and rough surfaces
- Normally, their glycoprotein (structure in their cell membranes) prevent adhesiveness to the normal endothelium)

2. Aggregation:

- When platelets are activated, they usually **group together**
- Their aggregation and **stickiness** is mainly due to **ADP and Thromboxane A2** found in their cytoplasm

3. Agglutination: Platelets clump together and form clots

Functions of plateletes

- Secrete vasoconstrictors, chemicals that stimulate spasmodic constriction of broken vessels and thereby help to reduce blood loss
- They stick together to form temporary platelet plugs that seal small breaks in injured blood vessels
- They secrete procoagulants, or clotting factors, which promote blood clotting

Functions Cont...

- They initiate the formation of a clot-dissolving enzyme that dissolves blood clots that have outlasted their usefulness
- They secrete chemicals that attract neutrophils and monocytes to sites of inflammation
- They internalize and destroy bacteria
- They secrete growth factors that stimulate mitosis in fibroblasts and smooth muscle and thereby help to maintain and repair blood vessels

Functions of Platelets

- For blood clotting- secrete clotting factors, vasoconstrictor chemicals & form temporary platelet plugs to stop bleeding
- Dissolve blood clots that have outlasted their usefulness
- Engulf and destroy bacteria
- Activate inflammation

The ABO Group

- Blood types A, B, AB, and O form the ABO blood group
- The ABO blood type is determined by the hereditary presence or absence of **antigens A** and **B** on the RBCs
- The antibodies **of the ABO group** begin to appear in the plasma 2 to 8 months after birth
- They are produced mainly in response to the bacteria that live in our intestines

ABO Group Cont...

- The antigens of RBC surfaces are also called **agglutinogens** because they are partially responsible for RBC agglutination in mismatched transfusions
- The **plasma antibodies** that react **against** antigens of RBC are also called **agglutinins**

ABO Group Cont...

- The antibody that reacts against antigen A is called **alpha agglutinin** or **anti-A**
- Anti-A antibody is present in the plasma of people with type O or type B blood—that is, anyone who does not possess antigen A.
- The antibody that reacts against antigen B is **beta-agglutinin**, or **anti-B**, and is present in type O and type A individuals—those who do not possess antigen B

ABO Group Cont...

- A person's ABO blood type can be determined by placing one drop of blood in a pool of **anti-A serum** and another drop in a pool of **anti-B serum**
- Blood **type AB** exhibits noticeable **agglutination (adhesion)** in both antisera
- Type A or B agglutinates only in the corresponding antiserum
- Type O does not agglutinate in either one

Effects of a Mismatched Transfusion

- A mismatched transfusion causes a transfusion reaction
- The agglutinated RBCs block small blood vessels, hemolyze or burst, and release their hemoglobin over the next few hours to days
- Free hemoglobin can block the kidney tubules and cause death from acute renal failure within a week

Mismatched Transfusion Cont...

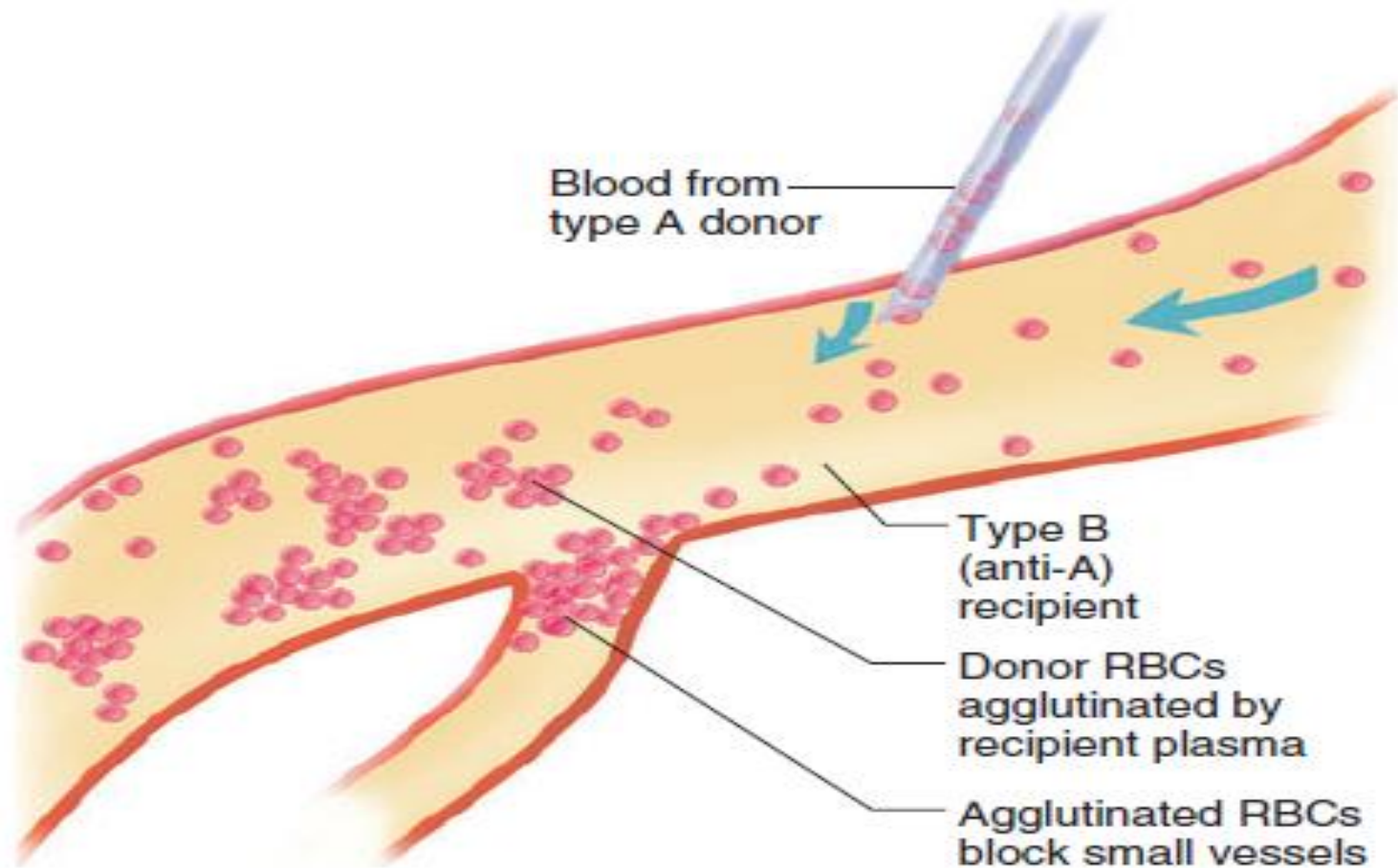


Fig. Mismatched Transfusion on small vessels

The ABO Blood Group Summary

	ABO Blood Type			
	Type O	Type A	Type B	Type AB
<i>Possible Genotypes</i>	<i>ii</i>	<i>I^A I^A, I^A i</i>	<i>I^B I^B, I^B i</i>	<i>I^A I^B</i>
<i>RBC Antigen</i>	None	A	B	A,B
<i>Plasma Antibody</i>	Anti-A, anti-B	Anti-B	Anti-A	None
<i>Compatible Donor RBCs</i>	O	O, A	O, B	O, A, B, AB
<i>Incompatible Donor RBCs</i>	A, B, AB	B, AB	A, AB	None

Rh Group

- The Rh blood group is named for the rhesus monkey, in which the Rh antigens were discovered in 1940
- This group is determined by three antigens called C, D, and E, each of which has two alleles: C, c, D, d, E, e.
- Whatever other alleles a person may have, anyone with genotype DD or Dd has **D antigens** on his or her RBCs and is classified as **Rh-positive (Rh +)**
- In Rh-negative (Rh -) people, the **D antigen** is lacking
- The Rh blood type is tested by using an **anti-D reagent**
- ABO blood type has no influence on Rh type, or vice versa

Rh Group Cont...

- In contrast to the ABO group, anti-D antibodies are not normally present in the blood
- They form only in Rh -ve individuals who are exposed to Rh +ve blood
- If an Rh -ve person receives an Rh+ transfusion, the recipient produces **anti-D antibody**
- Since anti-D does not appear instantaneously, this presents little danger in the first mismatched transfusion
- But if that person should later receive another Rh+ transfusion, his or her anti-D could **agglutinate** the donor's RBCs

Rh Group Cont...

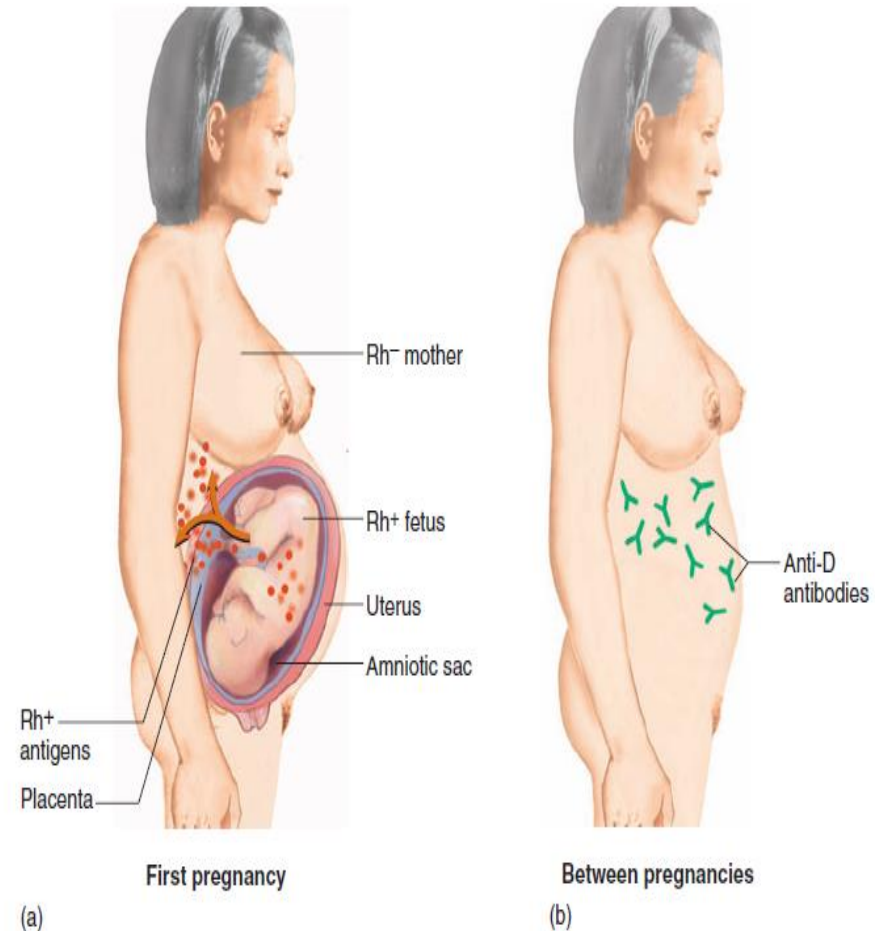
- A related condition sometimes occurs when an Rh -ve woman carries an Rh +ve fetus
- The first pregnancy
 - is likely to be uneventful because the placenta normally prevents maternal and fetal blood from mixing
 - However, at the time of birth, or if a miscarriage occurs, placental tearing exposes the mother to Rh+ fetal blood
 - She then begins to produce anti-D antibodies

Rh Group Cont...

- If she becomes pregnant again with an Rh+ fetus,
 - her anti-D antibodies may pass through the placenta and agglutinate the fetal erythrocytes
 - Agglutinated RBCs hemolyze or burst, and the baby is born with a severe anemia called **hemolytic disease of the newborn (HDN), or erythroblastosis fetalis**

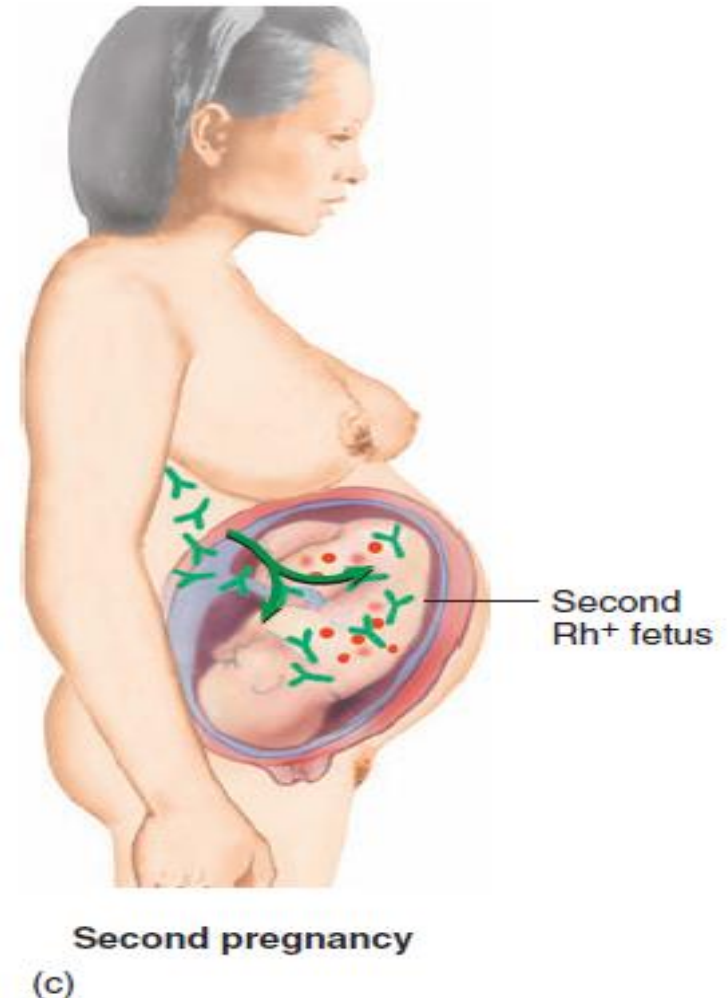
Hemolytic Disease of the Newborn (HDN)

- A. When an Rh –ve woman is pregnant with an Rh +ve fetus, she is exposed to D (Rh) antigens, especially during childbirth
- B. Following that pregnancy, her immune system produces anti-D antibodies



HDN Cont...

C. If she later becomes pregnant with another Rh +ve fetus, her **anti-D antibodies** can cross the placenta and agglutinate the blood of that fetus, causing that child to be born with **Hemolytic Disease of the Newborn** .



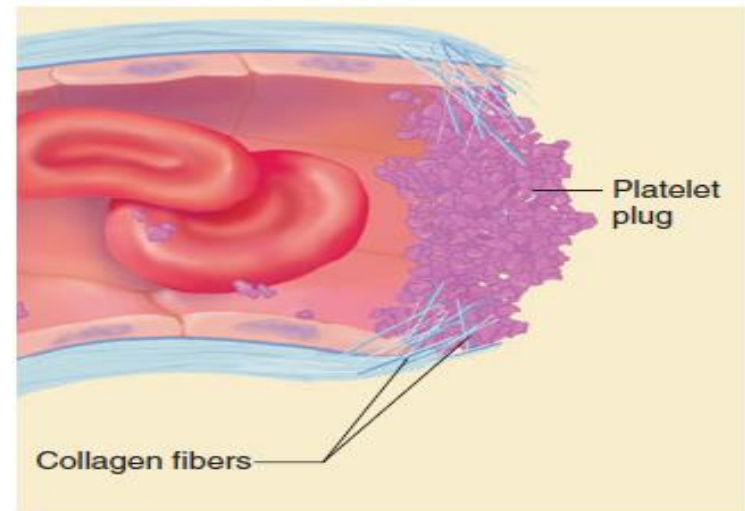
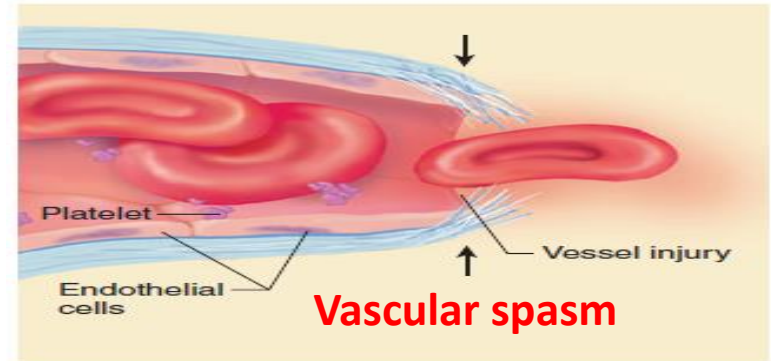
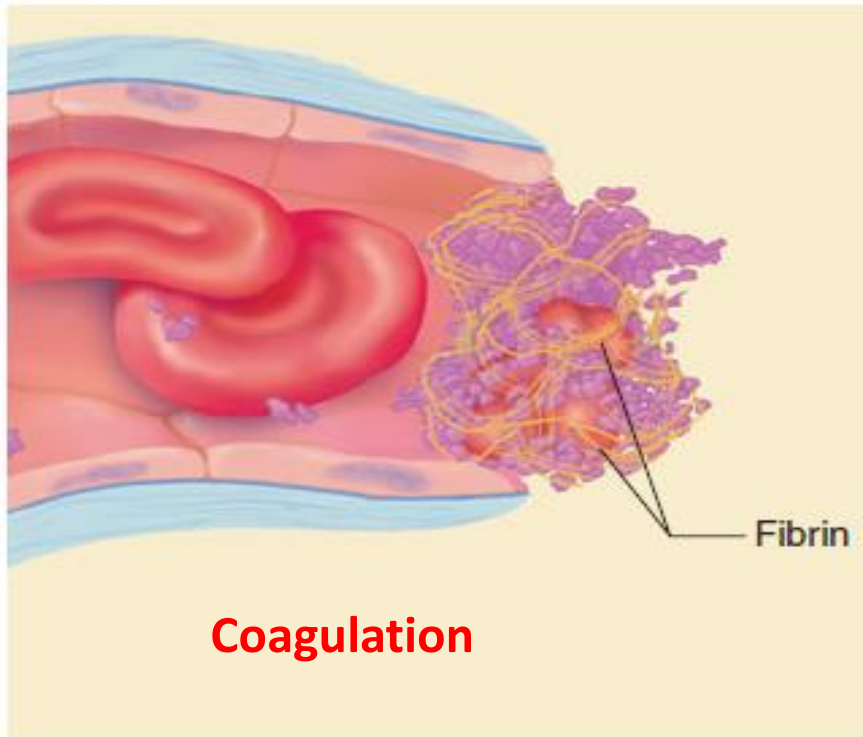
Note

- Since ABO antibodies belong to the IgM class, they usually do not cross the placenta
- Anti-D antibodies belong to the IgG class of immunoglobulins, which are capable of crossing the placenta

Hemostasis

- Hemostasis means arrest or prevention of bleeding
- Whenever a vessel is severed or ruptured, hemostasis is achieved by several mechanisms:
 1. Vasoconstriction (vascular spasm)
 2. Platelet plug
 3. Blood clot formation (coagulation)
 4. Growth of fibrous tissue into the blood clot to close the hole in the vessel permanently

Hemostasis Cont...



Vascular spasm (vasoconstriction)

- Small blood vessels and arterioles constrict at local injured regions and decrease blood flow to injured areas
- The general mechanism of vasoconstriction involves:
 1. Local myogenic spasm:
 - Contraction of vascular smooth muscle itself, initiated by direct damage to the vascular wall

Vascular Spasm Cont...

2. Local metabolites:

- Released from platelets and traumatized tissues and cause spasm of small blood vessels
- Include serotonin, histamine, Thromboxane A_2 etc...

3. Nervous reflexes:

- initiated by pain nerve impulses or other sensory impulses that originate from the traumatized vessel or nearby tissues

Platelet Plug

- If the cut in the blood vessel is very small, the cut is often sealed by a platelet plug rather than by a blood clot
- 3- chemicals are released from platelets to plug the cut space
 1. Von Willbrands factor:
 - Sticking is facilitated by protein called von Willebrand's factor released from plasma & leaks into the traumatized tissues
 2. Adenosine diphosphate (ADP)
 3. Thromboxane A₂ are also released from their cytoplasm that attract more and more platelets to the injured area and plug or seal the cut space.

Platelet Plug Cont...

- Apart from producing ADP and Thromboxane A₂, platelets at their cell membranes contain phospholipids, glycoproteins and other important substances
- Glycoproteins repel platelets not to adhere to the endothelium in normal conditions
- Platelets, when die, are phagocytized by the macrophage system mainly in the spleen

Formation of Blood Clot (Coagulation)

- This is a phase where blood loses its fluidity and becomes a jelly-solid mass
- Generally activator substances from **injured vascular walls**, **platelets**, and **blood plasma** near the injured site initiate cascade of reactions to clot the wound
- This cascade of reactions occur by intrinsic & extrinsic mechanisms

Coagulation Cont...

- Coagulation sets into play by:
 1. Trauma to the vascular wall and adjacent tissues
 2. Trauma to the blood
 3. Contact of the blood with damaged endothelial cells or with collagen and other tissue elements outside the blood vessel
- In each instance, this leads to the formation of *prothrombin activator*, which then causes prothrombin conversion to thrombin and all the subsequent clotting steps.

Coagulation Cont....

- Prothrombin activator is generally considered to be formed in two ways, although, in reality, the two ways interact constantly with each other:

1. Extrinsic pathway

- Begins with trauma to the vascular wall and surrounding tissues

2. Intrinsic pathway

- Begins in the blood

Coagulation Cont....

- In both the extrinsic and the intrinsic pathways, a series of different plasma proteins called blood-clotting factors plays a major role
- Most of these proteins are inactive forms of proteolytic enzymes
- When converted to the active forms, their enzymatic actions cause the successive, cascading reactions of the clotting process
- To indicate the activated form of the factor, a small letter “a” is added after the Roman numeral

Factor ^a	Names
I	Fibrinogen
II	Prothrombin
III	Thromboplastin
IV	Calcium
V	Proaccelerin, labile factor, accelerator globulin
VII	Proconvertin, SPCA, stable factor
VIII	Antihemophilic factor (AHF), antihemophilic factor A, antihemophilic globulin (AHG)
IX	Plasma thromboplastic component (PTC), Christmas factor, antihemophilic factor B
X	Stuart–Prower factor
XI	Plasma thromboplastin antecedent (PTA), antihemophilic factor C
XII	Hageman factor, glass factor
XIII	Fibrin-stabilizing factor, Laki–Lorand factor
HMW-K	High-molecular-weight kininogen, Fitzgerald factor
Pre-Ka	Prekallikrein, Fletcher factor
Ka	Kallikrein
PL	Platelet phospholipid

Fig. System for naming blood-clotting factors

Extrinsic pathway

- The formation of prothrombin activator is initiated by the tissue thromboplastin(factor III), which is formed from injured tissues
- **Tissue thromboplastin**, together with **factor VII** & Ca^{2+} activates **factor X** to its active form **Xa**
- Activated factor Xa with Ca^{2+} and **factor V** forms a prothrombin activator that in turn activates and converts prothrombin to thrombin
- Thrombin together with Ca^{2+} converts fibrinogen to fibrin (loose solid clot)

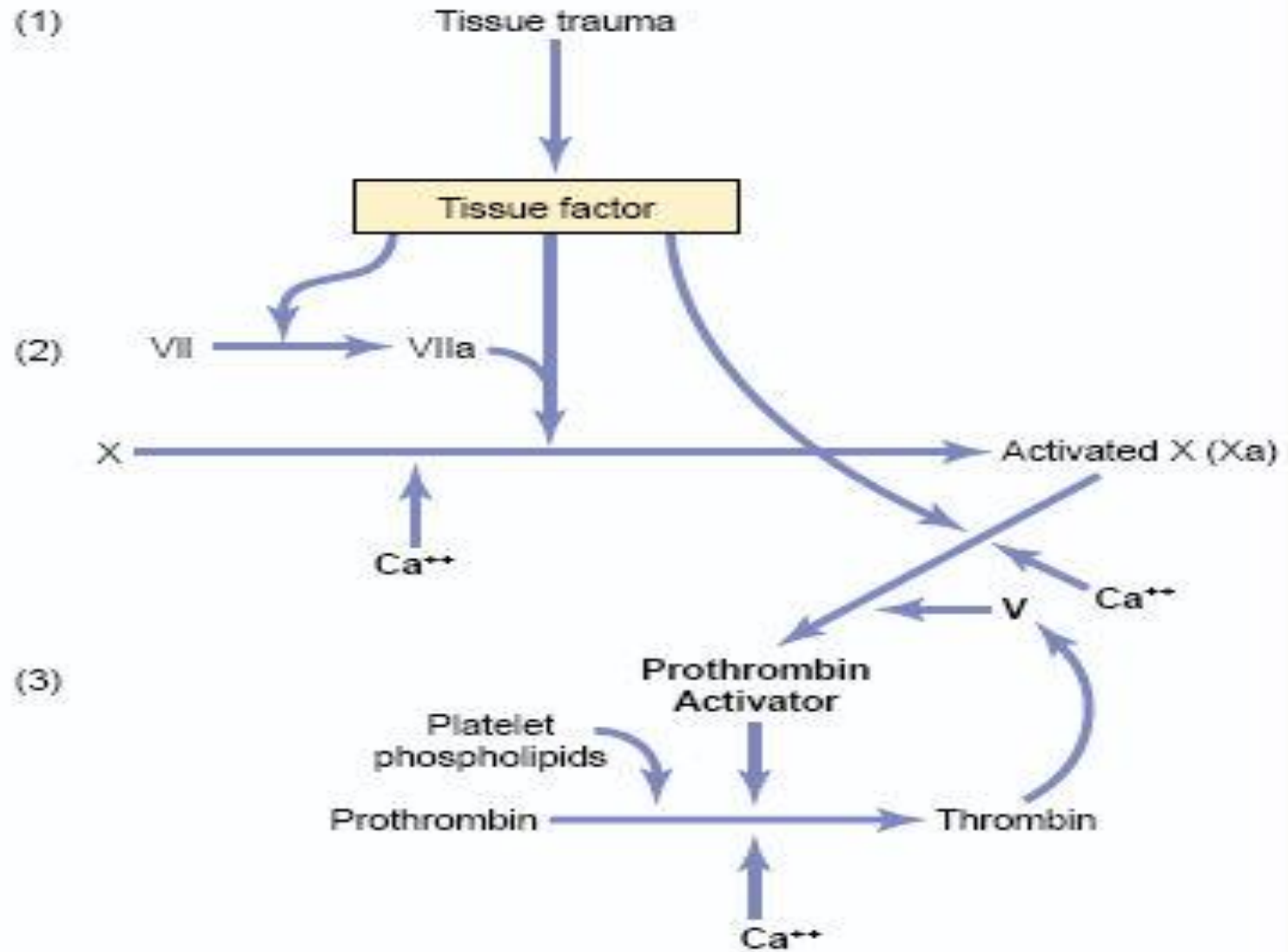


Fig. Extrinsic pathway for initiating blood clotting

Intrinsic Pathway

- Begins with trauma to the blood or exposure of the blood to collagen from a traumatized blood vessel wall
- Blood trauma causes (1) activation of Factor XII (**XII** to **XIIa**) & release of platelet phospholipids
- Then a cascade of reactions continues until the formation of activated **factor Xa**
- Factor **VIII** + **IX** + platelet phospholipids (tissue thromboplastin) are involved in the activation

Intrinsic pathway Cont...

- The absence of **factor VIII** causes **classic hemophilia** and **deficiency in platelet number** causes the bleeding disease **thrombocytopenia**
- The activated Xa combines with Ca^{2+} and thrombin to produce the **prothrombin activator**
- The rest is the same like extrinsic pathway until the formation of fibrin thread

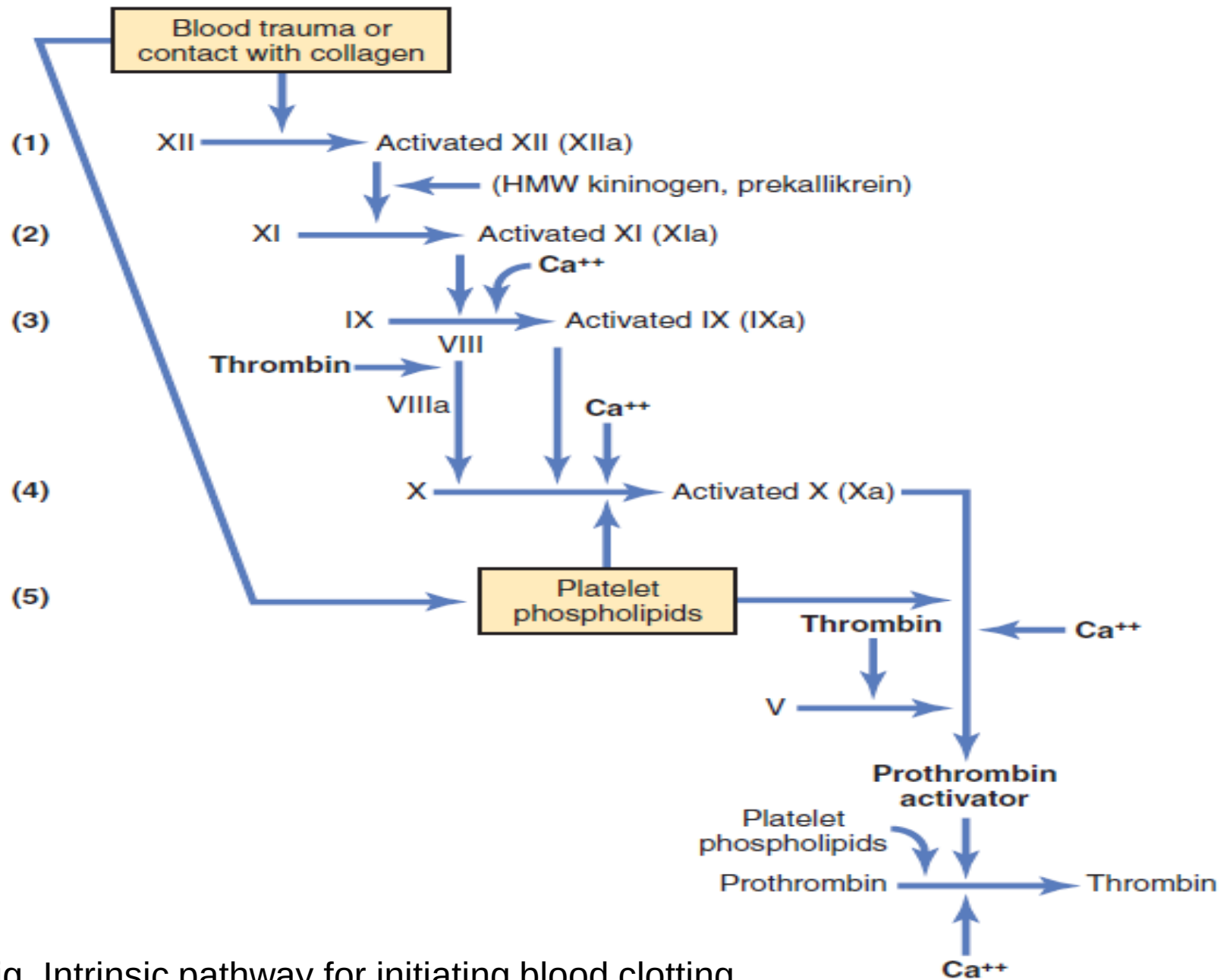


Fig. Intrinsic pathway for initiating blood clotting

Prevention of Clotting in Normal Vascular System

- 1. Smoothness of the endothelial cell surface**
 - The smoothness prevents **contact** activation of the intrinsic clotting system
- 2. A glycocalyx (a polysaccharide on endothelial cell surfaces)**
 - **Repels clotting factors and platelets** thereby preventing activation of clotting factors
- 3. A protein called thrombomodulin**
 - **binds thrombin and prevents clotting**

Prevention of Clotting Cont...

- When the endothelia wall is traumatized, the smoothness and the glycocalyx layer are lost or injured
- This effect activates factor XII that begins contact activation and start the cascade reaction for blood clotting

Bleeding Disorders

- Excessive bleeding can be caused due to 3 major factors:

Hemophilia:

- Due to insufficiency of **factor VIII** and **IX**
- Bleeding occurs at big blood vessels
- An “X” linked inherited recessive bleeding disorder (i.e., the person does not have enough clotting factors)
- Passes as a **recessive trait** on the **X-chromosome**

Bleeding Disorders Cont...

- **Hemophilia A (classic hemophilia):** is due to inadequate production of **Factor-VIII**
- **Hemophilia-B (charismas disease):** is due to inadequate production of **Factor-IX**
- When one or both of the above are absent, **factor-X** can **not** be activated
- **Factor-X** - is the main enzyme that converts **fibrinogen to Fibrin**
- When **Factor X** is not activated, a good clot can not be formed and excessive bleeding occurs

Bleeding Disorders Cont...

Thrombocytopenia (platelet deficiency)

- Bleeding at small vessels, capillaries and venules
- Platelets usually plug small blood vessels, so their absence causes thrombocytopenic purpura (small purplish blotches)

Bleeding Disorders Cont...

- **Thrombus** : is an abnormal clot that develops in a blood vessels.
- **Emboli**: is a thrombus that is freely flowing through the circulation, the thrombi detaches, forced by flowing blood and cause the clot to flow through the circulation
- Causes:
 1. Rough endothelial surfaces of a vessel
 2. Slow stagnant flowing blood in blood vessels can initiate clotting and emboli formation

Bleeding Disorders Cont...

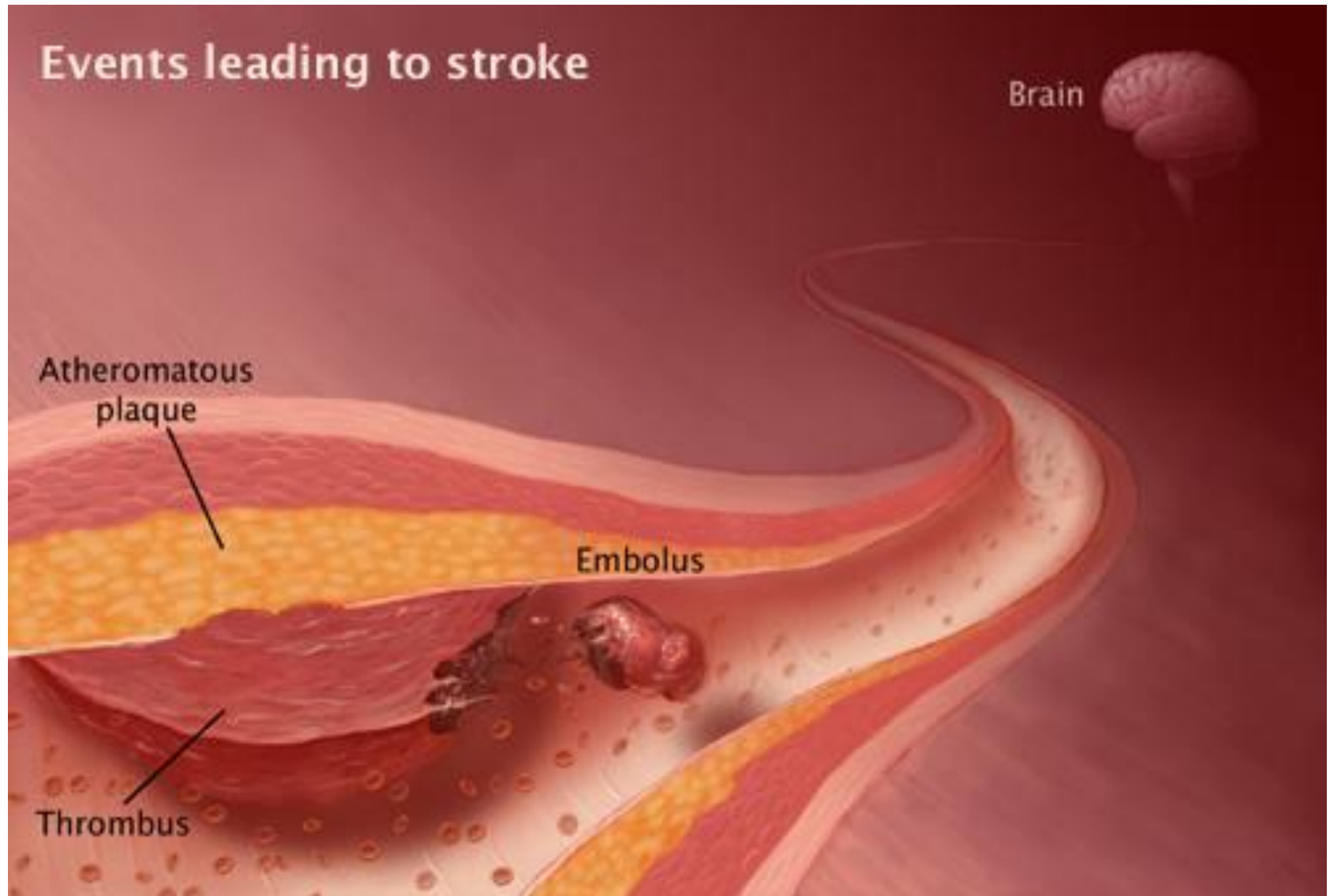


Fig. Thrombus and embolus

Fibrinolysis

- Lysis of blood clot inside the blood vessel
- Helps to remove the clot from lumen of the blood vessel
- Done by **plasmin (fibrinolysin)**, which breaks down fibrin and fibrinogen
- Plasmin is formed from inactivated glycoprotein called **plasminogen**

Fibrinolysis Cont...

- Plasminogen is synthesized in liver and it is incorporated with other proteins in the blood clot
- The activation of plasminogen is catalyzed by two factors, which are released from capillary endothelial cells: **tissue plasminogen activator** and **urokinase-type plasminogen activator**

Fibrinolysis Cont...

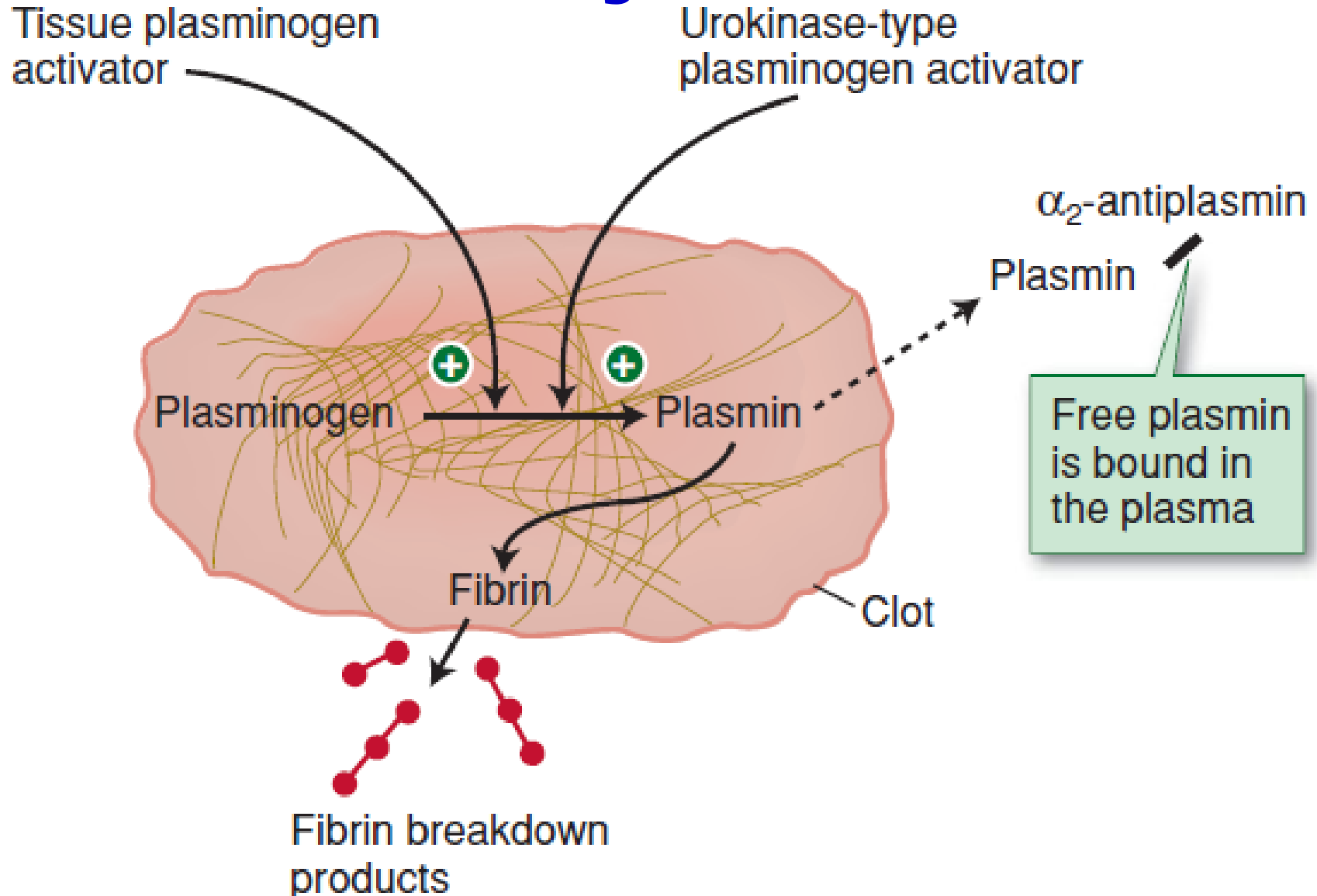


Fig. Fibrinolysis. The cleavage of plasminogen produces the protease plasmin, which breaks down fibrin

Fibrinolysis Cont...

- It is important that plasmin is not active in the circulation because it can also break down fibrinogen
- If plasmin escapes from the clot, it is rapidly bound and inactivated by the circulating plasma protein **α 2-antiplasmin**

Anticoagulants

1. Heparin:

- Has anti-thrombin activity and also inactivates factor IX, X, XII

2. Warfarin:

- Inhibit Vitamin K that is necessary to produce factor X, IX and VII

3. EDTA (Ethylene diamine tetra acetic acid):

- Removes Ca^{2+} from blood

Anticoagulants Cont...

4. Oxalate :

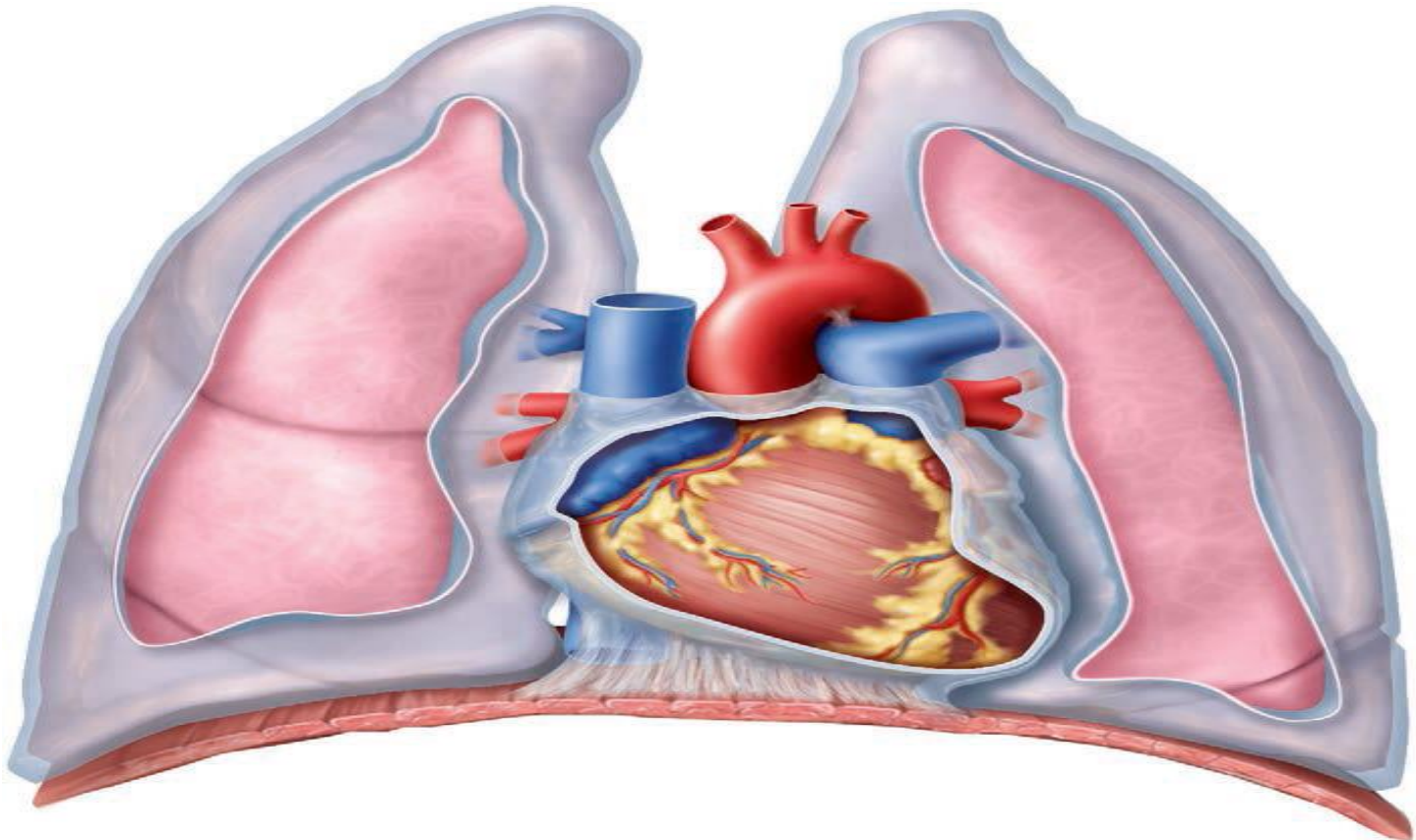
- Combines with Ca^{2+} and forms Ca^{2+} oxalate
- Ca^{2+} is made to precipitate

5. Citrates:

- Form a complex with Ca^{2+} and decreases its level in plasma (in vitro for a blood bank) etc.

Unit Five

Physiology of the Cardiovascular System



Objectives

At the end of this unit, you will be able to explain:

- General organization & function of CVS
- Mechanism of cardiac muscle excitation
- Factors that affect cardiac output, blood pressure & venous return
- Blood flow and its regulation
- Overview of lymphatic system

Introduction

- The cardiovascular system comprises heart and blood vessels
- Pressure generated in the heart propels blood through the system continuously
- The blood picks up oxygen at the lungs and nutrients in the intestine and then delivers these substances to the body's cells while simultaneously removing cellular wastes and heat for excretion

Introduction Cont...

Functions:

- Transport of materials to and from all parts of body

Transport in the Cardiovascular System		
Substance Moved	From	To
Materials entering the body		
Oxygen	Lungs	All cells
Nutrients and water	Intestinal tract	All cells

Substance Moved	From	To
-----------------	------	----

Materials moved from cell to cell

Wastes	Some cells	Liver for processing
Immune cells, antibodies, clotting proteins	Present in blood continuously	Available to any cell that needs them
Hormones	Endocrine cells	Target cells
Stored nutrients	Liver and adipose tissue	All cells

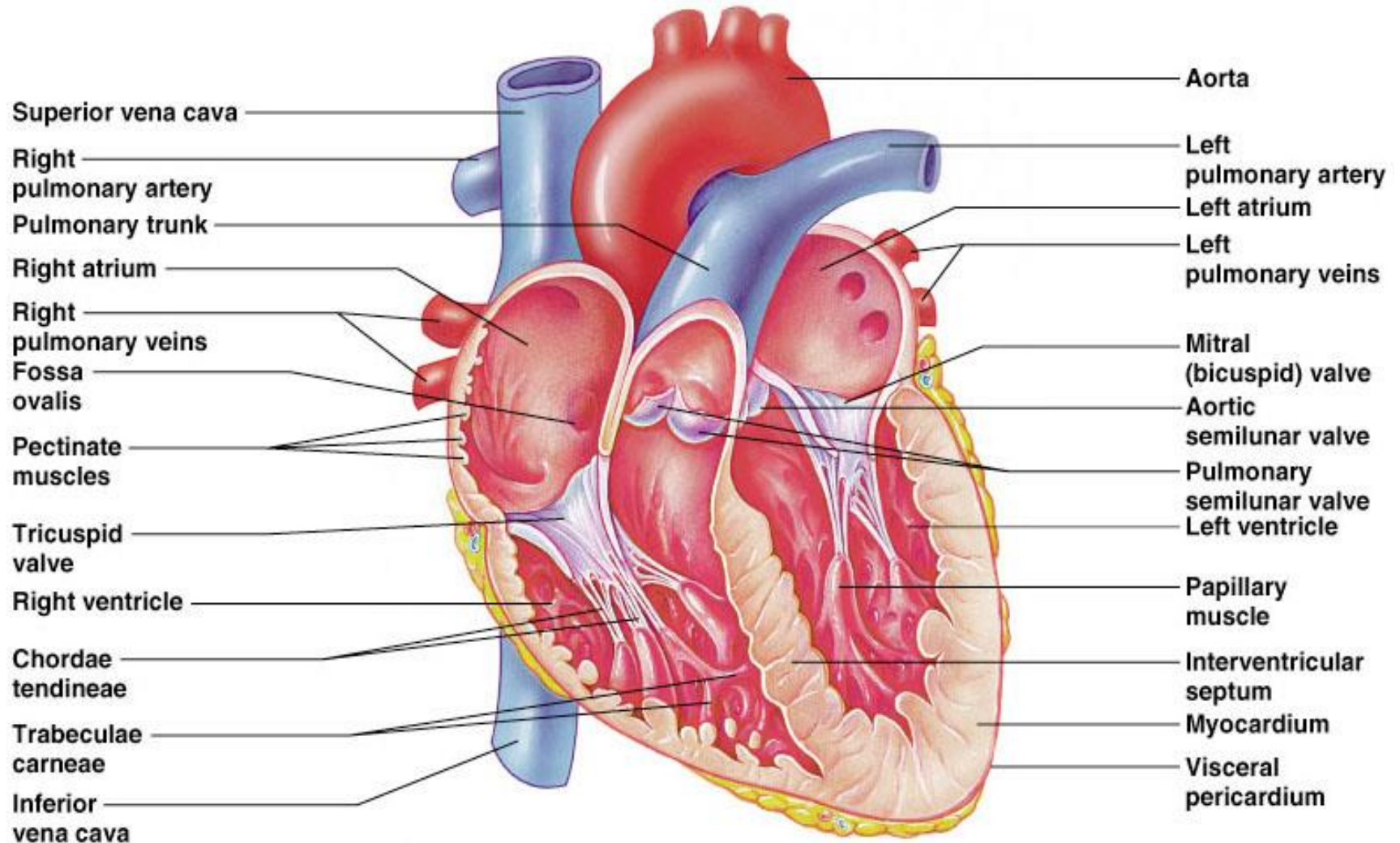
Materials leaving the body

Metabolic wastes	All cells	Kidneys
Heat	All cells	Skin
Carbon dioxide	All cells	Lungs

Heart

- The muscular pump that forces blood through vessels
- A **dual pump** that drives blood into two consecutive circuits:
 - **systemic** and
 - **pulmonary circulations**
- Receives blood from the rest of the body through the vena cava
- Equivalent to the size of a **clenched fist**, about 320gm in males and 250 gm in the female

Gross Anatomy of Heart



Chambers of Heart

Two atria (Right and left atria):

- Thin-walled muscular sheaths
- Blood enters right atria from venae cavae and coronary sinus
- Blood enters left atria from pulmonary veins

Two Ventricles (Rt & Lt ventricle):

- Thicker-walled
- The right and left ventricles are the pumps that eject blood into the arteries

Pathway of Blood Through the Heart and Lungs

- Right atrium → tricuspid valve → right ventricle
→ pulmonary semilunar valve → pulmonary
arteries → lungs → pulmonary veins → left
atrium → bicuspid valve → left ventricle → aortic
semilunar valve → aorta → systemic circulation

Cardiac Valves

- Valves are thin and flexible fibrous tissue firmly attached to fibrous rings at the base of the heart
- Valves are highly responsible for the **unidirectional flow of blood** through the heart

Types of Valves

1. Atrio-Ventricular (AV) Valves

- ✓ Thin-walled and located b/n the atria and the ventricles
- ✓ Contains 2 valves:

a. Mitral (bicuspid) valve

- ✓ Lies b/n left atrium and left ventricle
- ✓ Responsible for preventing the back flow of blood from the LV to the LA

b. Tricuspid (three cusps) valve

- ✓ Lies b/n Rt atrium and Rt ventricle.
- ✓ They are responsible for preventing the back flow of blood from the RV to RA

Valves Cont...

2. The semilunar valves

- Constitute the aortic and pulmonary valves located at the exits of the right and left ventricles

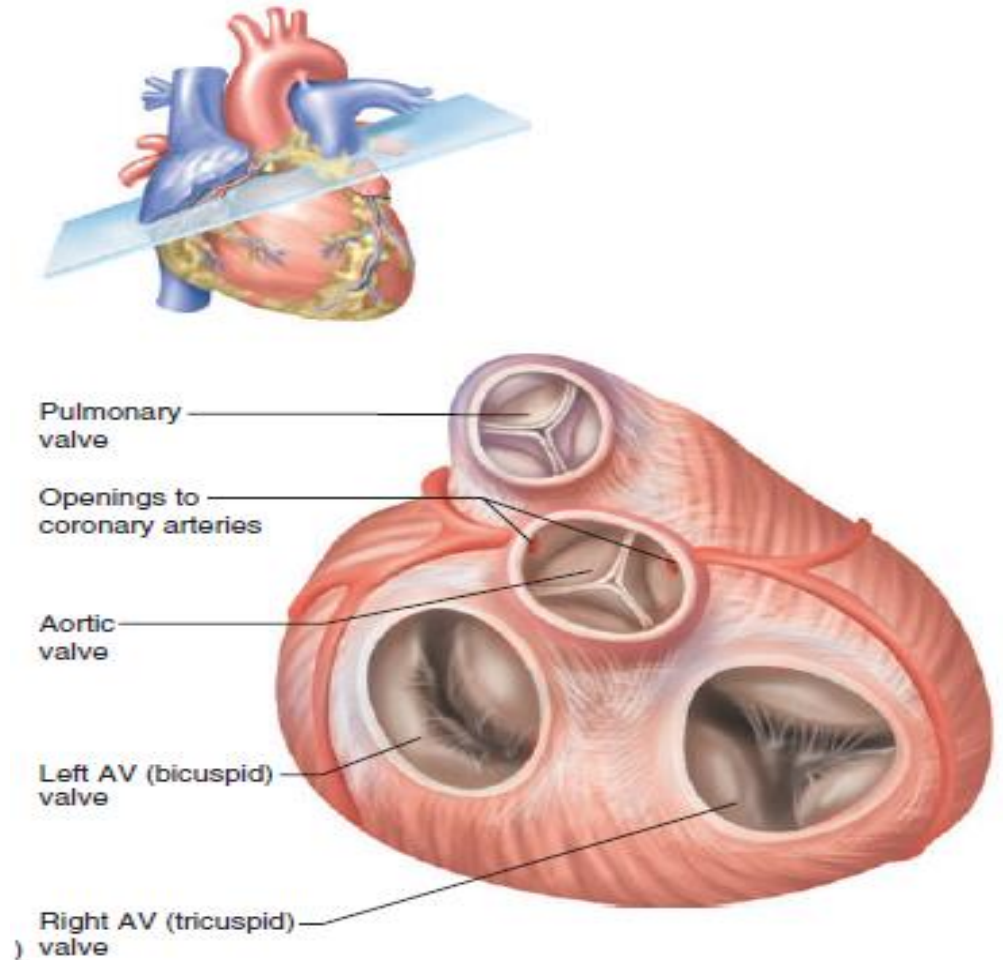
a. Aortic valve

- Lies between left ventricle & aorta
- Open during ventricular systole and close during ventricular diastole
- Prevent back flow of blood from the aorta to the left ventricle

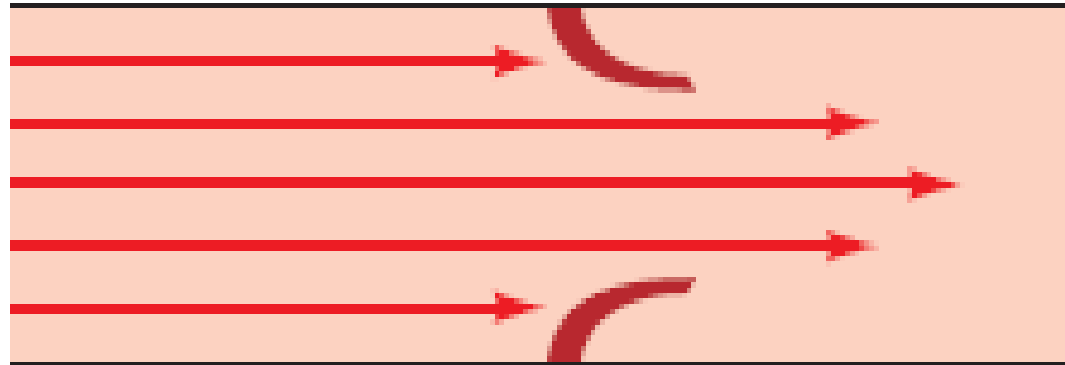
Valves Cont...

b. Pulmonary valve

- ✓ Lies between right ventricle & pulmonary artery
- ✓ Prevent the back flow of blood from pulmonary artery to the right ventricle

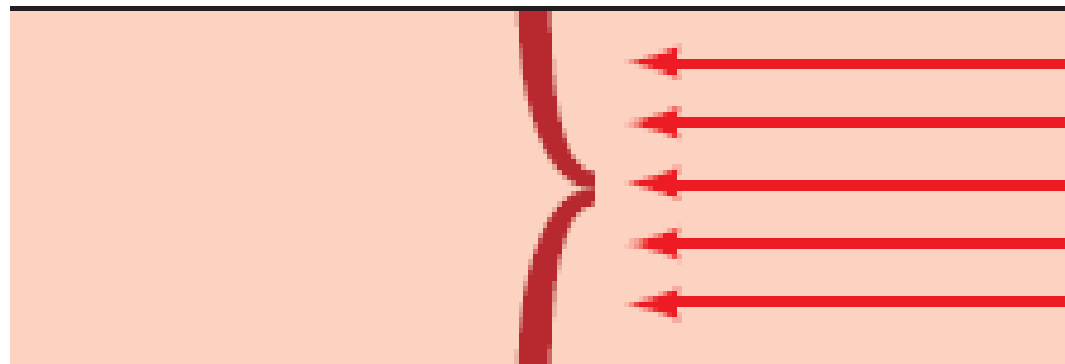


Mechanism of valve action



When pressure is greater behind the valve, it opens.

Valve opened

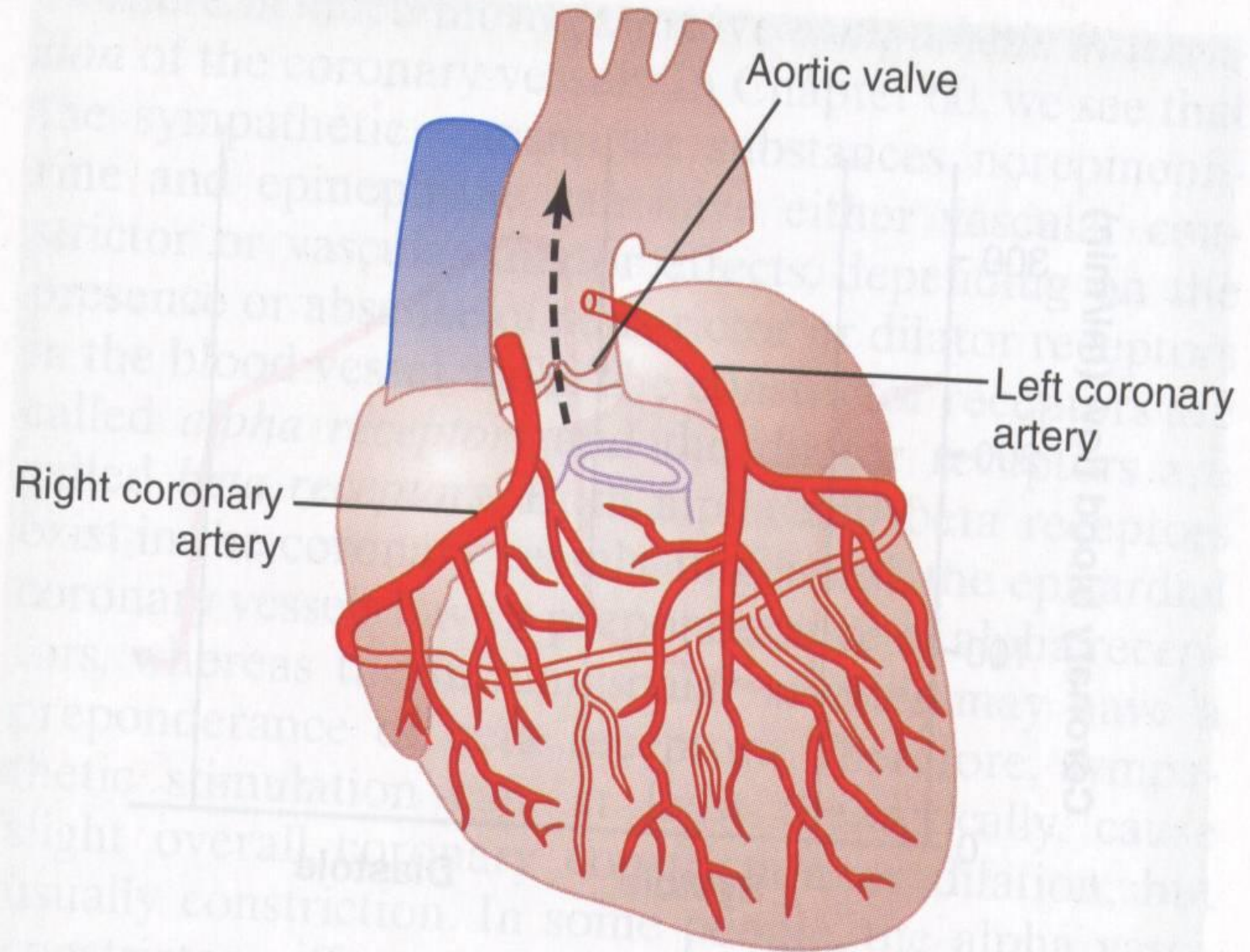


When pressure is greater in front of the valve, it closes. Note that when pressure is greater in front of the valve, it does not open in the opposite direction; that is, it is a one-way valve.

Valve closed; does not open in opposite direction

Blood Supply to Heart

- Carry blood to myocardium
- Heart depends strongly on aerobic metabolism
- Brief period of low oxygen damages the myocardium
- Coronary arteries (2) open out of aorta just above aortic valve
 - Left coronary artery supply posterior part
 - Right coronary artery supply anterior part



Blood Supply Cont...

- Coronary veins: return blood to coronary sinus located near right atrium
- The coronary circulation has many **anastomoses**, where two arteries come together and combine their blood flow to points farther downstream
- Thus, if one artery becomes obstructed, some blood continues to reach myocardial tissue through the alternative route

Coronary Flow in Relation to the Cardiac Cycle

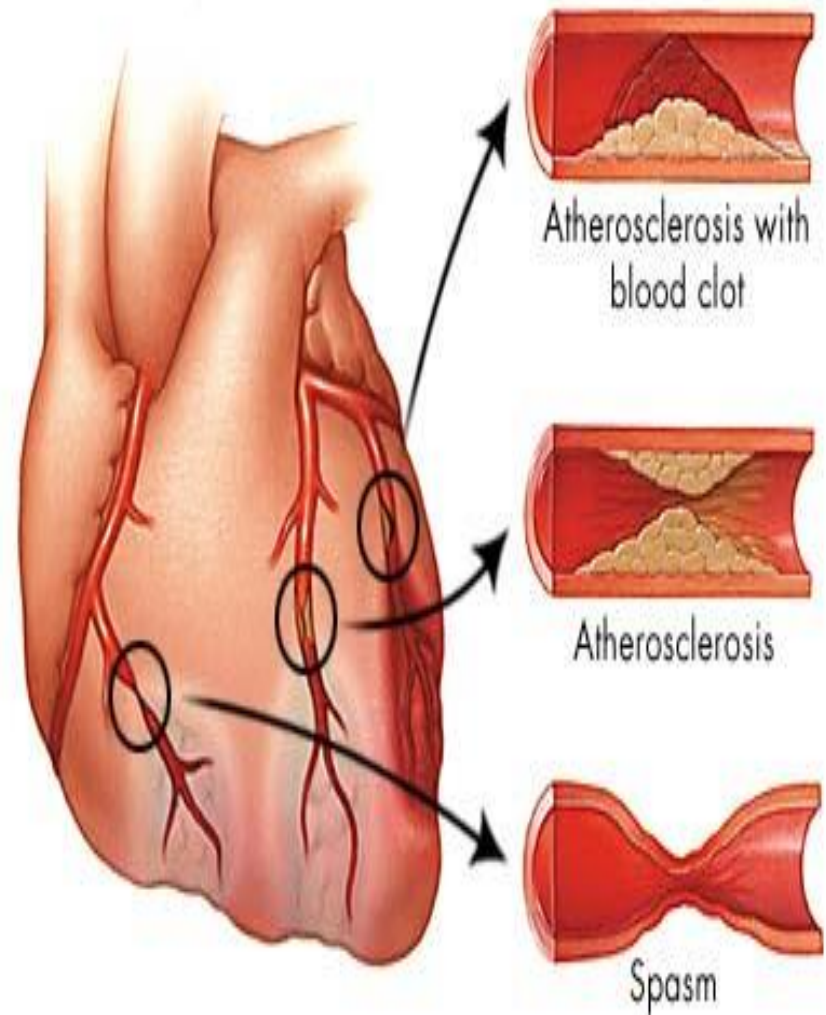
- Most organs receive more arterial blood flow when the **ventricles contract** than when they relax
- But the **opposite** is **true** in the **coronary arteries**: flow peaks when the heart relaxes
- There are three reasons for this:
 1. Contraction of the myocardium compresses the arteries and obstructs blood flow

Coronary Flow Cont...

2. When the ventricles contract, the aortic valve is forced open and its cusps cover the openings to the coronary arteries, blocking blood from flowing into them
3. When they relax, blood in the aorta briefly surges back toward the heart. It fills the aortic valve cusps and some of it flows into the coronary arteries

Coronary Artery Disease

- One of the most common and serious effects of aging
- **Atherosclerosis** often leads to eventual blockage of the coronary arteries and causes a **heart attack (myocardial infarction)**



Actions of The Heart

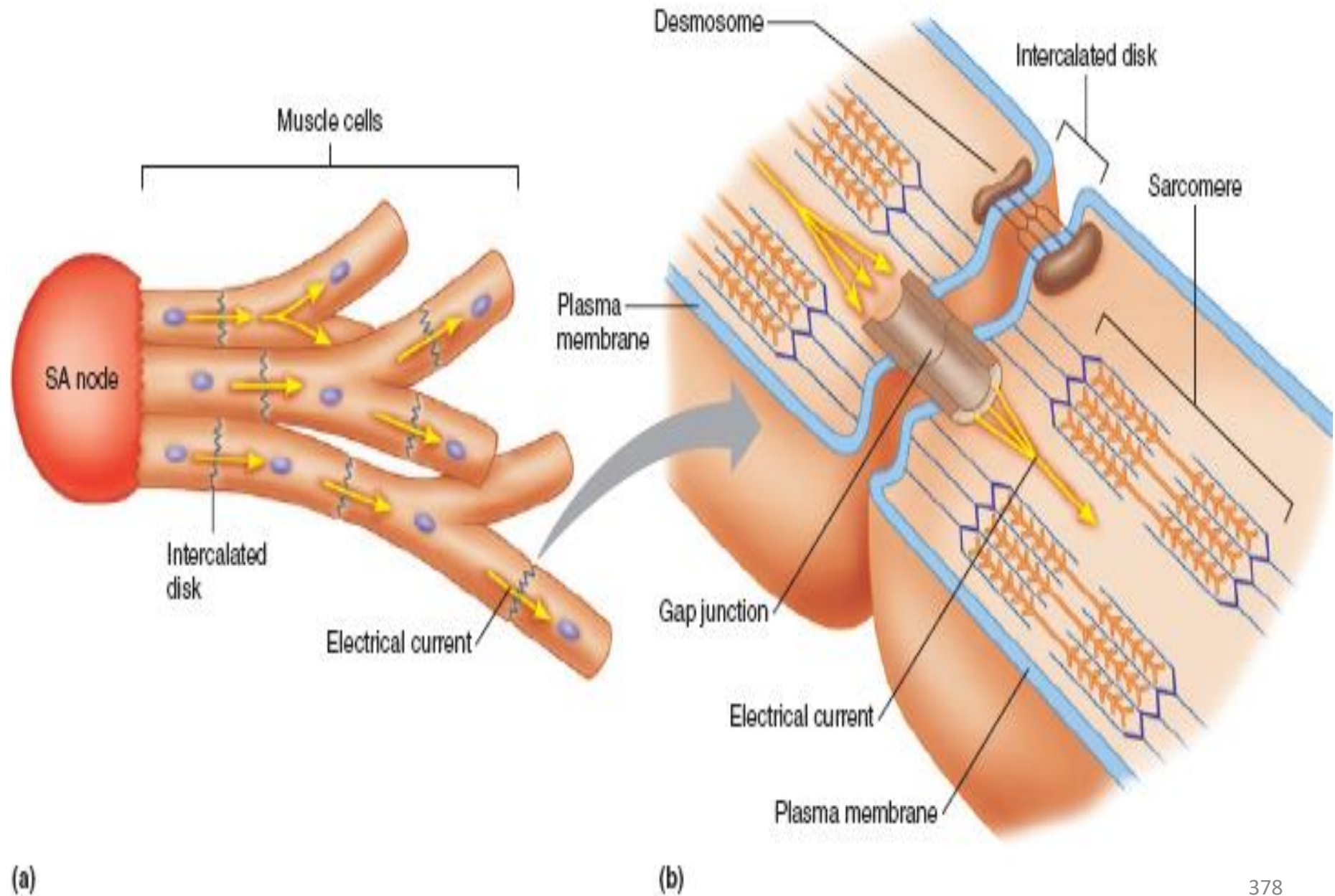
- Actions of the heart are classified into four types:
 1. Chronotropic action
 - The frequency of heartbeat
 2. Inotropic action
 - Force of contraction of heart
 3. Dromotropic action
 - The conduction of impulse through heart
 4. Bathmotropic action
 - The excitability of cardiac muscle

Cardiac Muscle

- The heart has 2 separate syncytium:
 - Atrial and Ventricular
- They are separated from each other by AV-fibrous tissue (electric resistant or insulator, surrounds valves)
- Action potential is conducted from atria to ventricles by way of atrio-ventricular bundle (A-V bundle) only

Cardiac Muscle Cont...

- Cardiac muscle fibers are connected in series with each other by intercalated discs
- Electric resistance through the intercalated disc is only 1/100 the resistance through the outside cell membrane
- Action potential spreads cell to cell, past the intercalated disc through the gap junctions



Properties of Cardiac Cells

Property	Ability
Automaticity	Generates electrical impulse independently, without involving the nervous system.
Excitability	Responds to electrical stimulation.
Conductivity	Passes or propagates electrical impulses from cell to cell.
Contractility	Shortens in response to electrical stimulation.

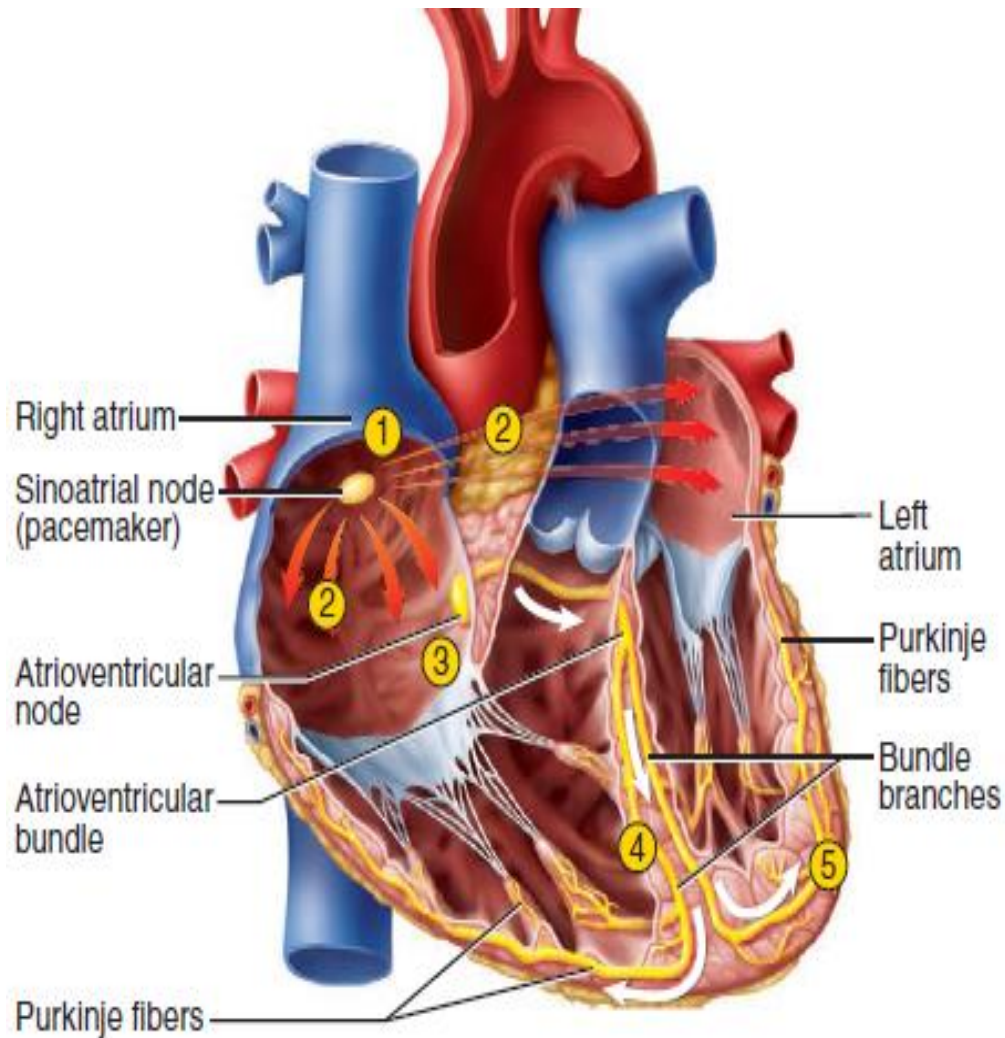
Cardiac Muscle Cont...

- In cardiac muscle, there are two types of cells:
 1. Contractile cells (**myocardium of atria and ventricles**)
 - Do not contract unless stimulated electrically by pacemaker tissue
 2. Autorhythmic (automatic) cells
 - Self-stimulating
 - Contract without any external stimulation

Cardiac Muscle Cont...

- Most of the muscle cells in the heart are contractile cells
- The **autorhythmic cells** are located in these areas:
 - Sinoatrial (SA) or sinus node
 - Atrioventricular (AV) node
 - Atrioventricular (AV) bundle (bundle of His)
 - Right & left bundle branches
 - Purkinje fibers

Cardiac Muscle Cont...



- ① SA node fires.
- ② Excitation spreads through atrial myocardium.
- ③ AV node fires.
- ④ Excitation spreads down AV bundle.
- ⑤ Purkinje fibers distribute excitation through ventricular myocardium.

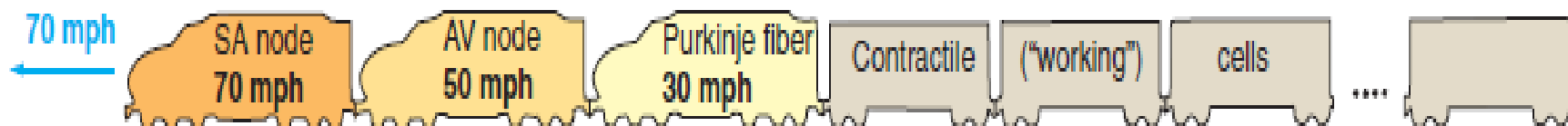
Fig. The cardiac conduction system

Cardiac Muscle Cont...

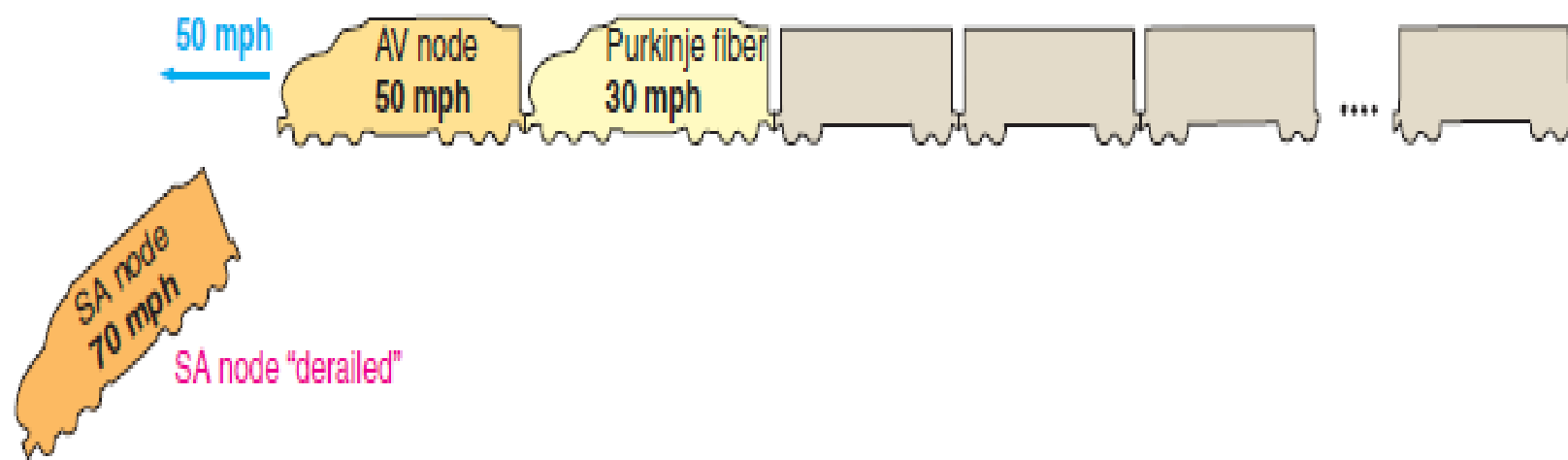
- Various automatic cells have different 'rhythms':
 - SA node - 60 – 100/minute
 - AV node & AV bundle - 40 – 60/minute
 - Bundle branches & Purkinje fibers - 20 – 40/ minute
- SA node has the highest or fastest rhythm & therefore sets the pace or rate of contraction for the entire heart
- As a result, the SA node is commonly referred to as the **pacemaker**

Overdrive Suppression

- Intrinsic rhythmicity of SA node is greater than other pacemaker sites
- Firing of SA node suppresses automaticity in other loci



- (a) Whole train will go **70 mph**
(heart rate set by SA node, the fastest autorhythmic tissue).



- (b) Train will go **50 mph**
(the next fastest autorhythmic tissue, the AV node, will set the heart rate).

Heart Rate

- The number of heart beat per minute
- The **normal heartbeat**, generated by the SA node, is called the **sinus rhythm** (60 to 100 beats per minute)
- Any region of spontaneous firing other than the SA node is called an **abnormal Pacemakers (Ectopic Pacemaker)**
- The most common ectopic pacemaker is the AV node, which produces a slower heartbeat of 40 to 50 bpm called a **nodal rhythm**

Electrical Behavior of Contractile Cells

- Cardiocytes have a stable resting potential of -90 mV and normally depolarize only when stimulated, unlike cells of the SA node
- A stimulus opens voltage gated sodium channels, causing a Na^+ inflow and depolarizing the cell to its threshold
- The threshold voltage rapidly opens additional Na^+ channels and triggers a positive feedback cycle like the one seen in the firing of a neuron
- The action potential peaks at nearly $+30$ mV.
- The Na^+ channels close quickly, and the rising phase of the action potential is very brief

Contractile Cells Cont...

- As action potentials spread over the plasma membrane, they open voltage-gated **slow calcium channels**, which admit a small amount of Ca^{2+} from the ECF into the cell
- This Ca^{2+} binds to ligand-gated Ca^{2+} channels on the sarcoplasmic reticulum (SR), opening them and releasing a greater quantity of Ca^{2+} from the SR into the cytosol
- This second wave of Ca^{2+} binds to troponin and triggers contraction in the same way as it does in skeletal muscle
- The SR provides 90% to 98% of the Ca^{2+} needed for myocardial contraction

Contractile Cells Cont...

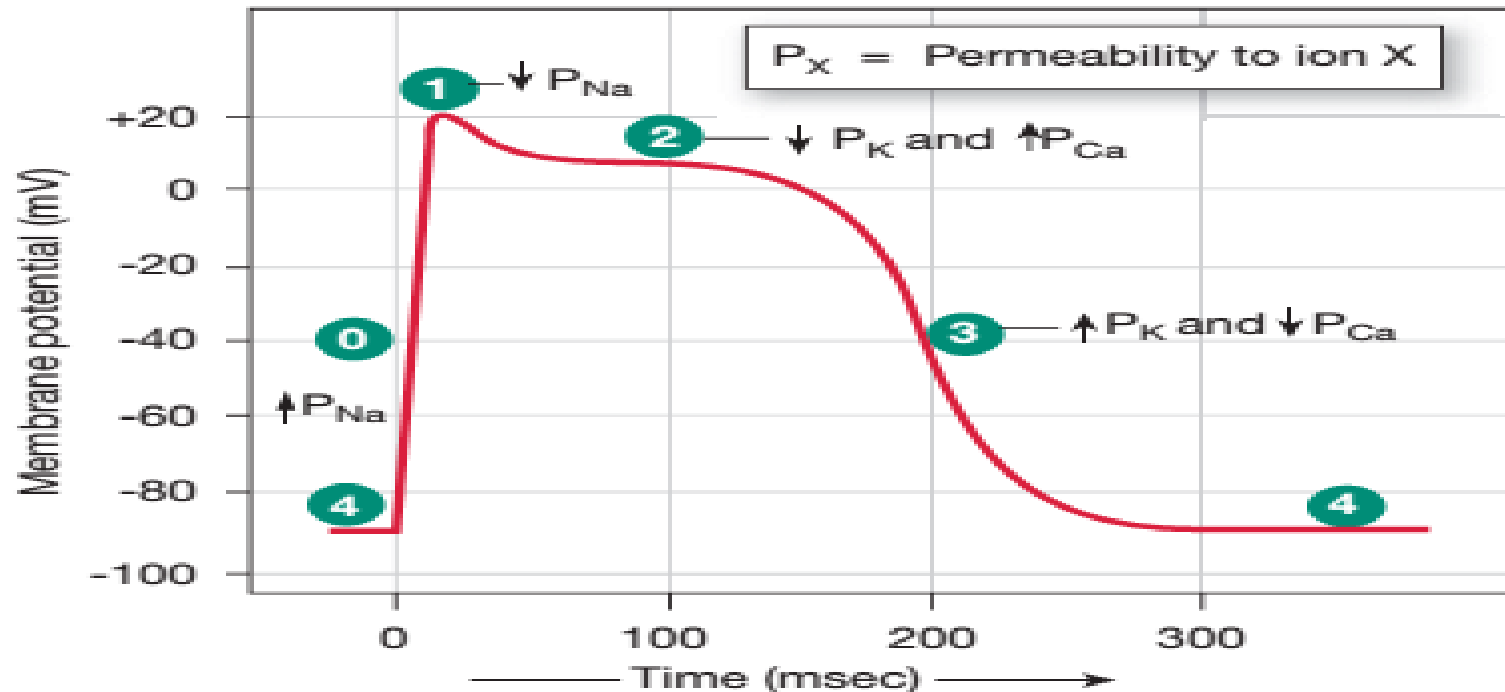
- In skeletal muscle and neurons, an action potential falls back to the resting potential within 2 ms
- In cardiac muscle, however, the depolarization is prolonged for 200 to 250 ms (at a heart rate of 70–80 bpm), producing a long plateau in the action potential—perhaps because the Ca^{2+} channels of the SR are slow to close or because the SR is slow to remove Ca^{2+} from the cytosol

Contractile Cells Cont...

- As long as the action potential is in its plateau, the cardiocytes contract
- Cardiac muscle has an absolute refractory period of 250 ms, compared with 1 to 2 ms in skeletal muscle
- This long refractory period prevents wave summation and tetanus, which would stop the pumping action of the heart

Contractile Cells Cont...

ACTION POTENTIAL OF A CARDIAC CONTRACTILE CELL



Phase*	Membrane channels
0	Na^+ channels open
1	Na^+ channels close
2	Ca^{2+} channels open; fast K^+ channels close
3	Ca^{2+} channels close; slow K^+ channels open
4	Resting potential

*The phase numbers are a convention.

Contractile Cells Cont...

- Compared to skeletal muscle, atrial and ventricular types of muscle:
 - Duration of contraction is **much longer**
 - The **T tubules** are much larger
 - **admit supplemental Ca^{2+}** from the ECF into the cell during excitation
 - No tetany due to long refractory period

1 Action potential enters from adjacent cell.

2 Voltage-gated Ca^{2+} channels open. Ca^{2+} enters cell.

3 Ca^{2+} induces Ca^{2+} release through ryanodine receptor-channels (RyR).

4 Local release causes Ca^{2+} spark.

5 Summed Ca^{2+} sparks create a Ca^{2+} signal.

6 Ca^{2+} ions bind to troponin to initiate contraction.

7 Relaxation occurs when Ca^{2+} unbinds from troponin.

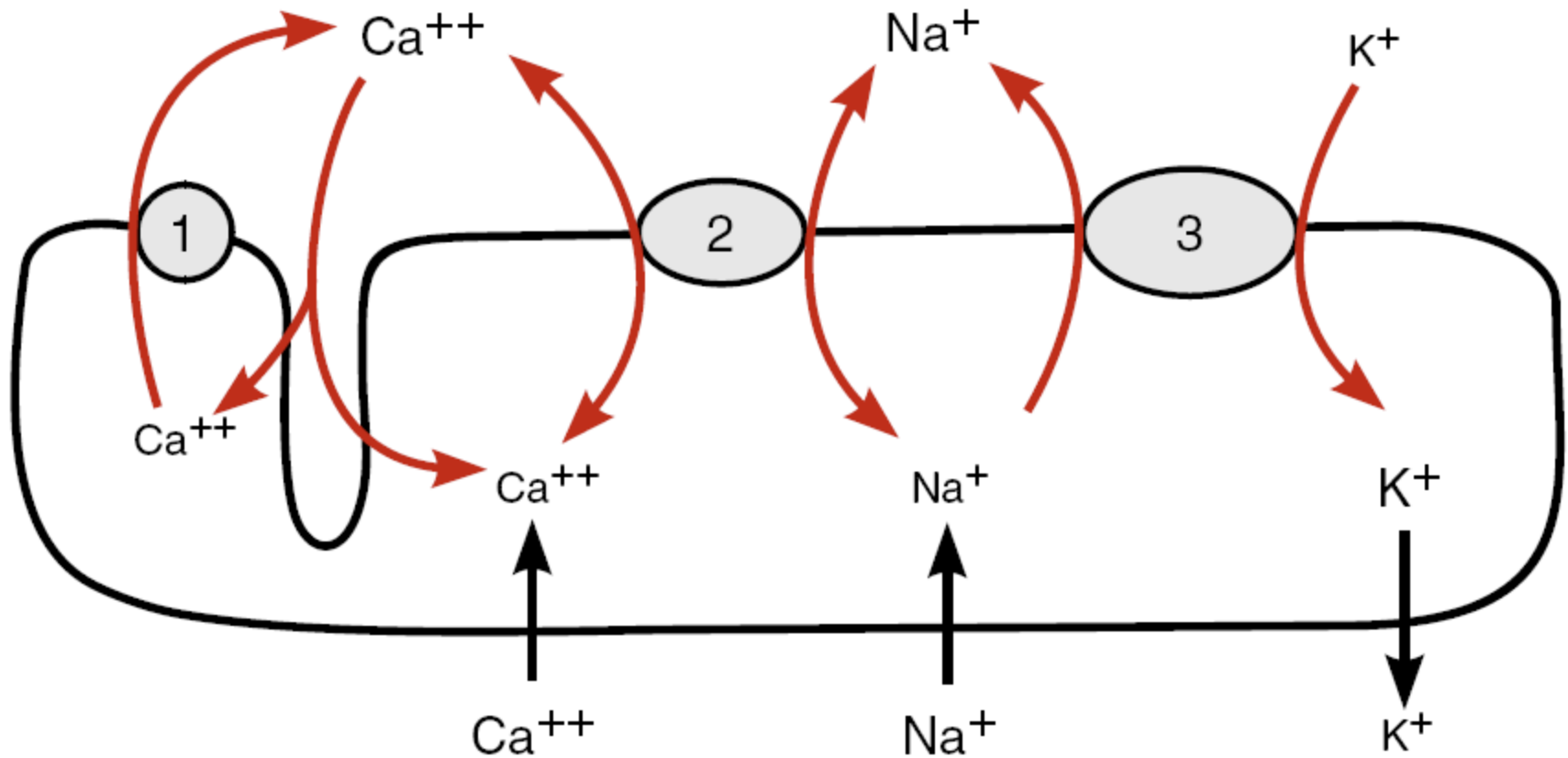
8 Ca^{2+} is pumped back into the sarcoplasmic reticulum for storage.

9 Ca^{2+} is exchanged with Na^{+} by the NCX antiporter.

10 Na^{+} gradient is maintained by the Na^{+} - K^{+} -ATPase.

Action Potential Cont...

- Relaxation(diastole) is as result of Ca^{++} removal
- Ca^{++} removed by:
 - Uptake by sarcoplasmic reticulum
 - Extrusion by Na^+ - Ca^{++} exchange
 - Ca^{++} pump (to limited extent)



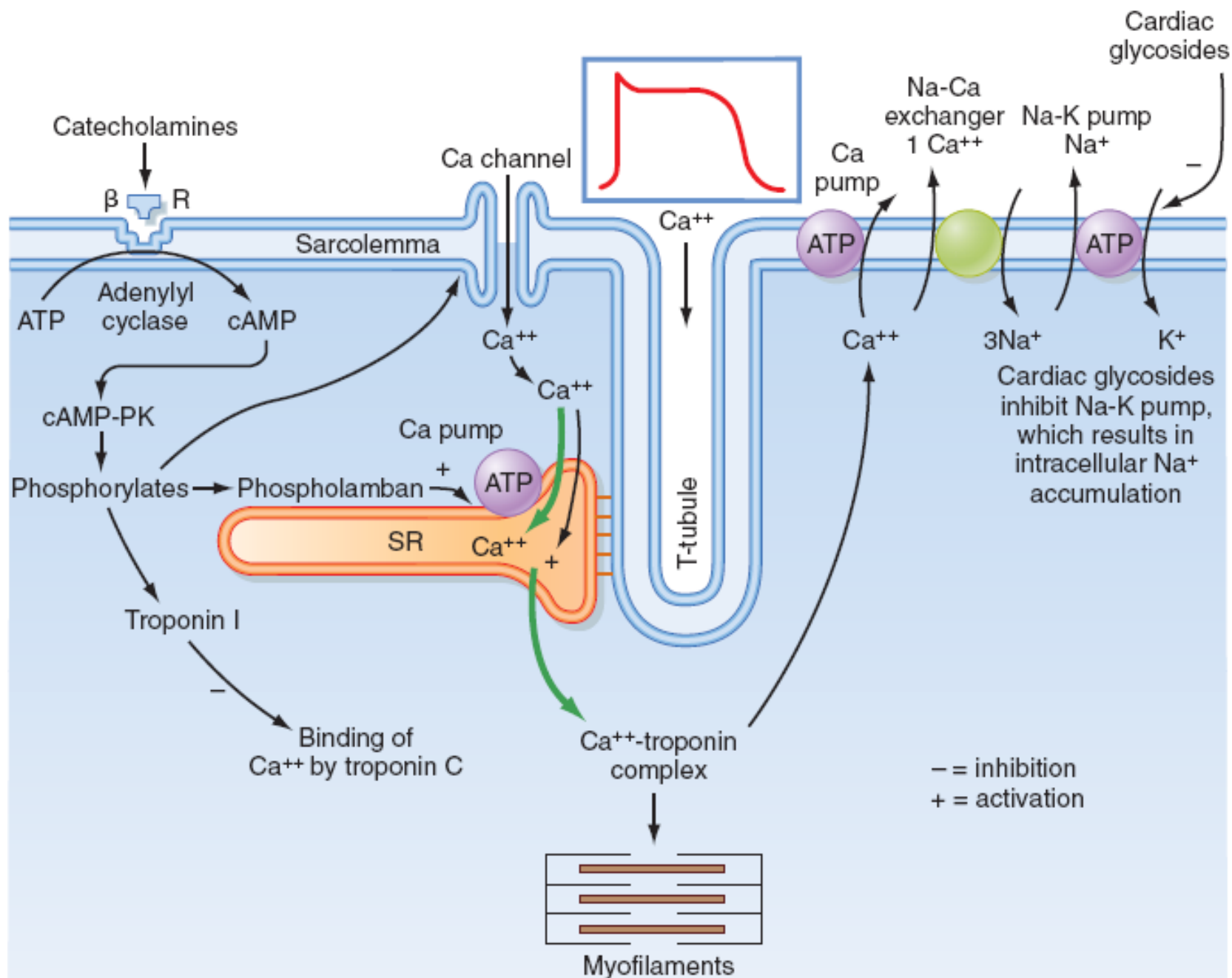
1 = ATP-dependent Ca^{++} pump

2 = $\text{Na}^+/\text{Ca}^{++}$ exchanger (3:1)

3 = Na^+/K^+ -ATPase pump (3:2)

Cardiac Glycosides

- Drugs that inhibit $\text{Na}^+/\text{K}^+-\text{ATPase}$
- Increase more Na^+ in and less Na^+ outside of the cell
- Leads to increase in intracellular Ca^{+2}
- Through the inhibiting $\text{Na}^+/\text{Ca}^{+2}$ exchange pump (by decreasing the availability of sodium to pump calcium out)
- Leads to enhanced contractility



Innervations of the Heart

- The heart is supplied with both sympathetic and parasympathetic nerves
- The **parasympathetic nerves** (the vagi nerves) are distributed mainly to the **SA** and **AV nodes**
- The **sympathetic nerves**, conversely, are distributed to **all parts of the heart**, with strong representation to the ventricular muscle as well as to all other areas
- Ventricles are not supplied by parasympathetic nerve

Innervations of the Heart

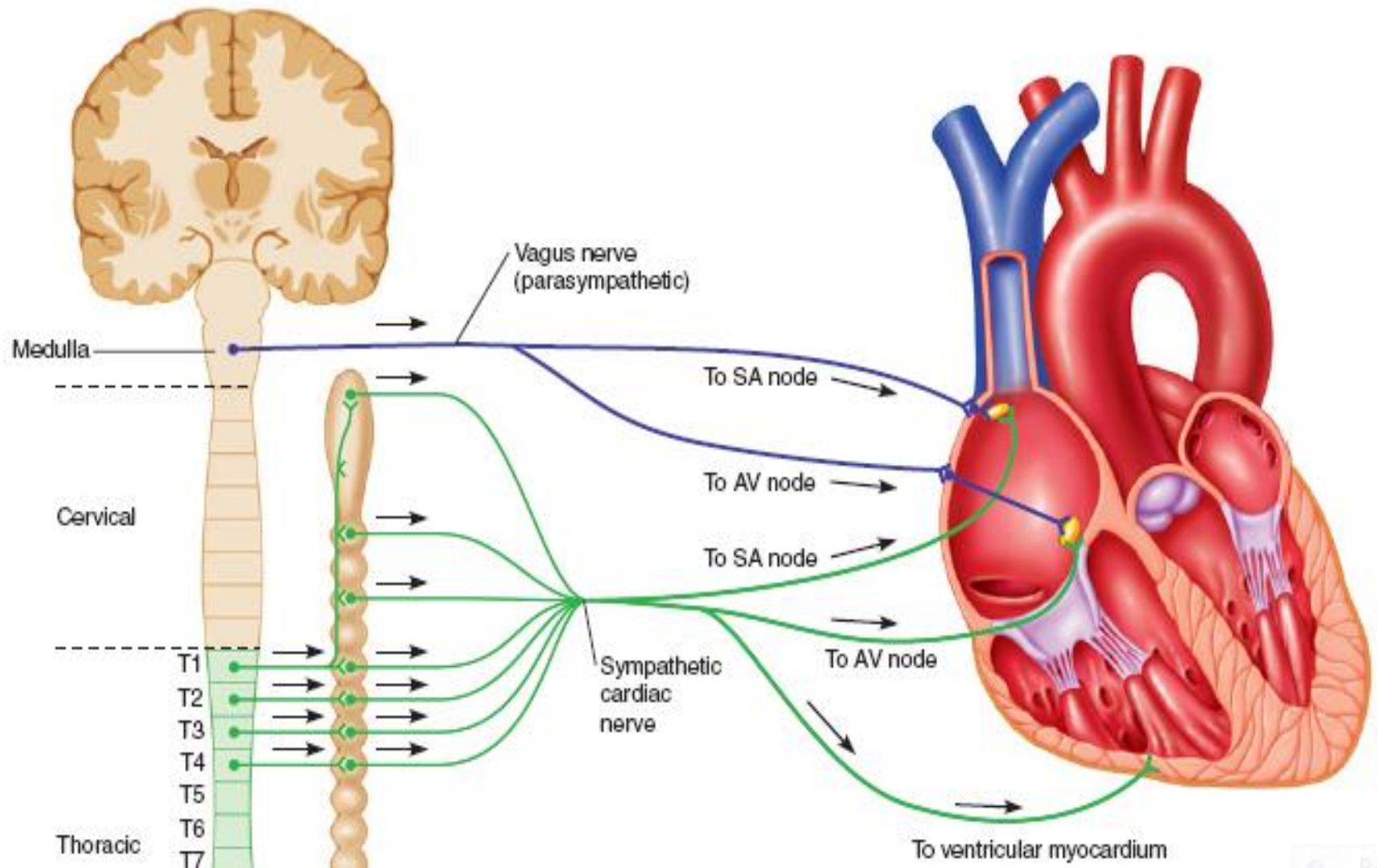


Fig. Parasympathetic & sympathetic innervation of heart

Innervations Cont...

Effects of Parasympathetic (Vagal) Stimulation

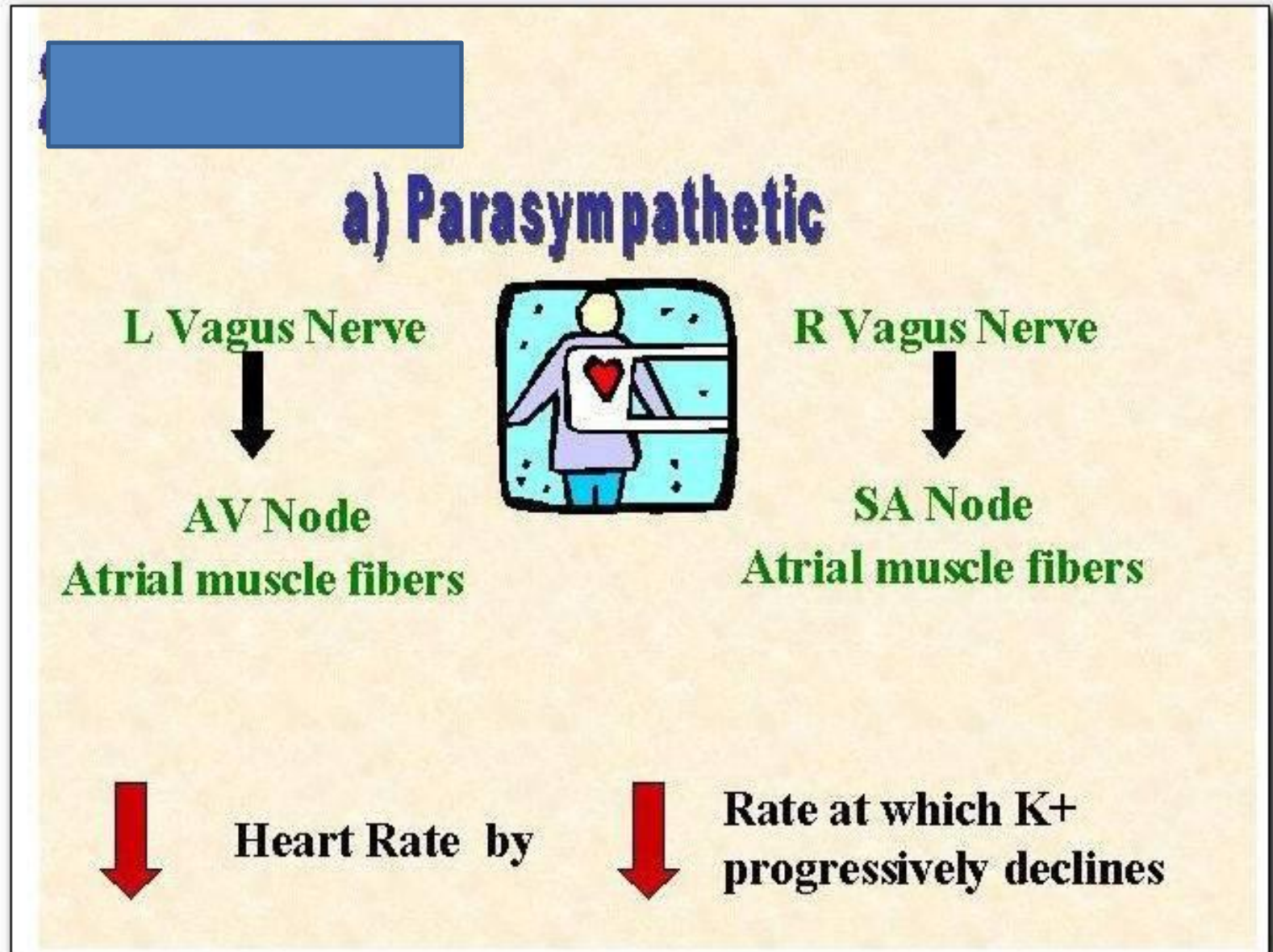
- Decreases the rate of rhythm of the sinus node
- Decreases the excitability of the A-V junction fibers between the atrial musculature and the A-V node
 - thereby slowing transmission of the cardiac impulse into the ventricles

Innervations Cont...

Effect of Sympathetic Stimulation

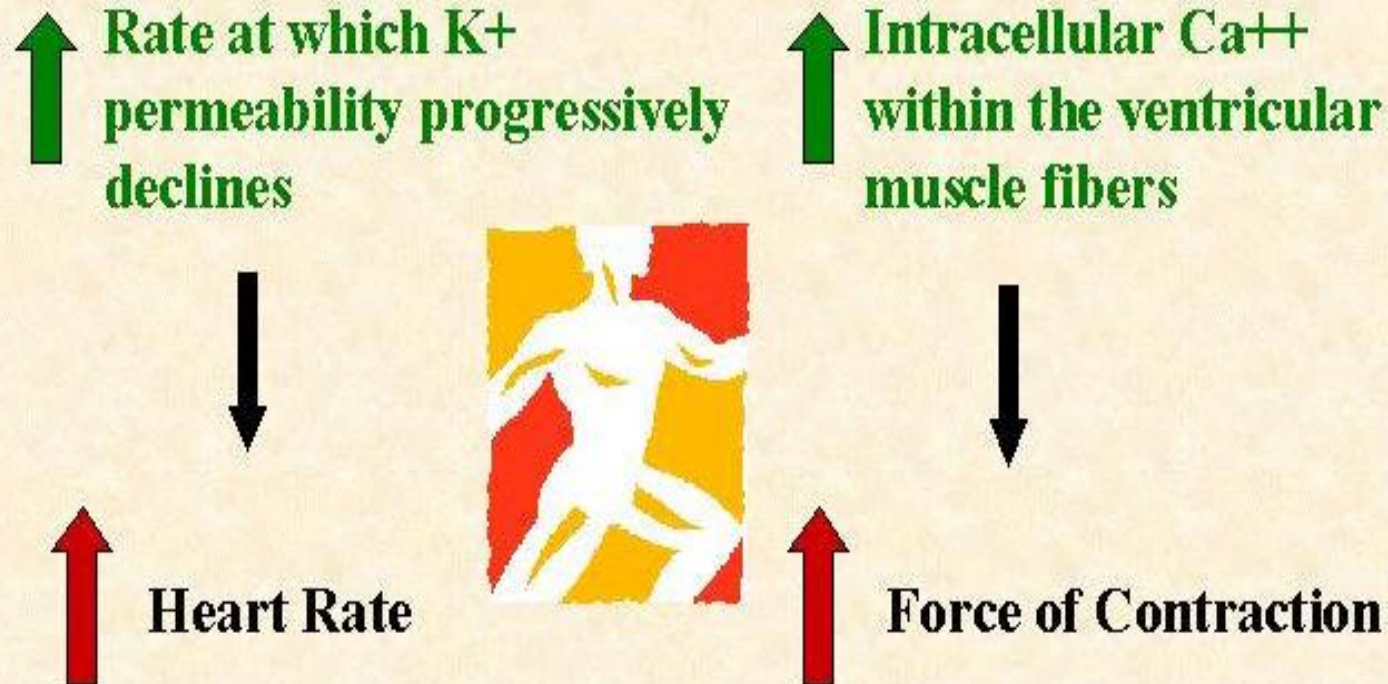
- Sympathetic stimulation increases the overall activity of the heart- HR - contractility, excitability
- **Maximal stimulation**
 - ✓ can almost **triple** the frequency of heartbeat and
 - ✓ can increase the strength of heart contraction as much as **two fold**

Factors Cont...



Factors Cont...

b) Sympathetic



Sympathetic and Parasympathetic effects

Sympathetic stimulation

- $\uparrow$ HR (+ve chronotropic)
- $\uparrow$ force of contraction (+ve Inotropic)
- Reduce slope of pacemaker potential
- Adrenergic transmitters and sympathetic stimulation increase slope of diastolic pacemaker depolarization $\rightarrow \uparrow$ **Heart rate**

Parasympathetic stimulation

- Ach opens K^+ channels
- Reduce slope of pacemaker potential $\rightarrow \downarrow$ **Heart rate**
- Also hyperpolarize pacemaker potential and reduce HR
- Ach and vagal stimulation increases the K^+ efflux, so slope reduced and $\downarrow$ heart rate

Effects of non-physiologic environment on myocardium

1. Body temperature:

- Rise (e.g. **Fever**): weak myocardial contraction (exhaust metabolic system)
- decrease chronotropic effect: decrease contractility

Effects Cont...

2. pH:

- **Acidosis:**

- Has - ve Inotropic effect due to depression of affinity of troponin C to Ca^{++}
- Severe acidosis stops heart in diastole

- **Alkalosis:**

- Has +inotropic effect due to increase affinity of troponin C to Ca^{++}
- Severe alkalosis stops heart in systole

Effects Cont...

3. Inorganic ions:

A. Na^+

- **Hypernatremia:**

- Has -ve inotropic effect
- Stimulate Na^+ - Ca^{++} exchanger to take Na^+ in, drive Ca^{++} out of cardiac myocyte
- Cytosolic Ca^{++} level decreases → decrease inotropy

- **Hyponatremia:**

- Has opposite effect to hypernatremia

Effects Cont...

B. Ca^{++}

- **Hypercalcemia:**
 - Increase cytosolic Ca^{++} level, stronger systole & incomplete diastole.
 - If level very high, heart stop in systole called Calcium Rigor
- **Hypocalcemia:** decrease myocardial contractility, but no serious effect

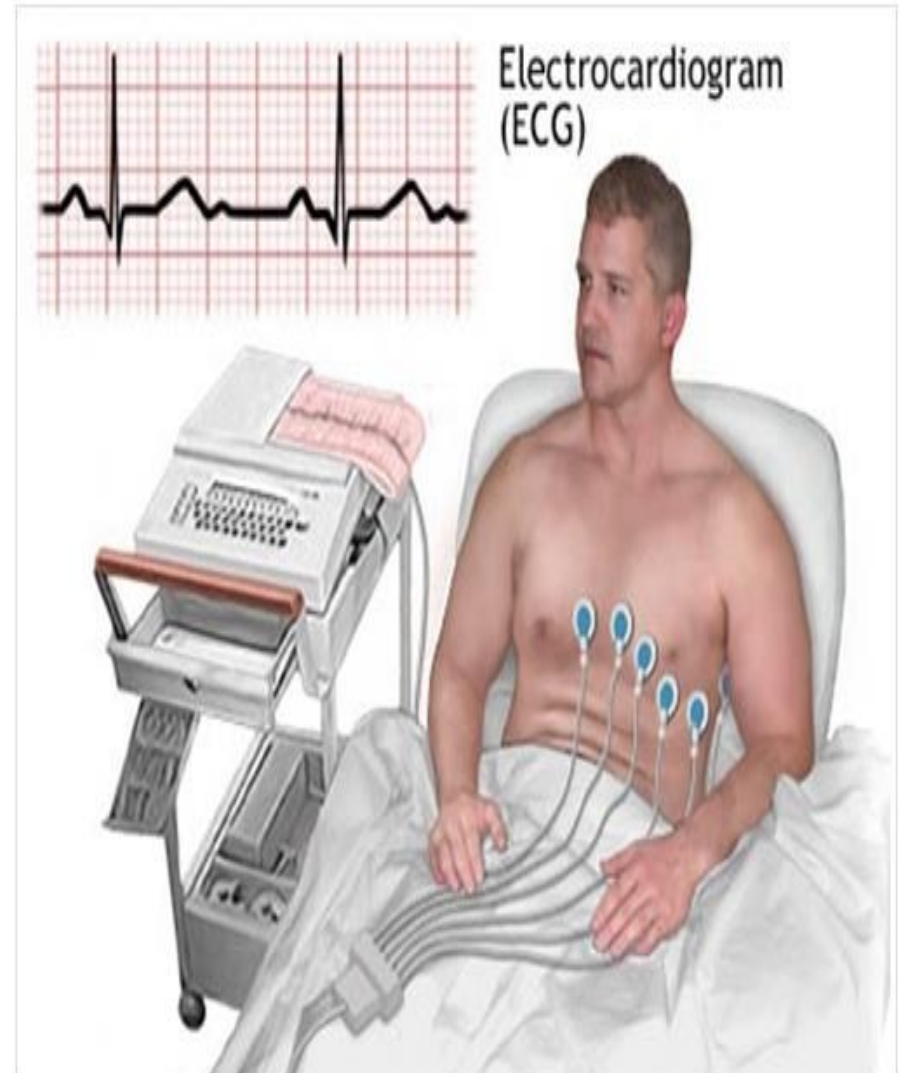
Effects Cont...

C. Potassium(K⁺):

- **Hyperkalemia:**
 - Negative inotropic effect
 - Low amplitude action potential → weak contraction
 - Marked hyperkalemia - heart stop in diastole
- **Hypokalemia:** has weak positive inotropic effect

Electrocardiography

- As the heart undergoes depolarization and repolarization,
 - the **electrical currents** that are generated spread not only within the heart, but also throughout the body
- This electrical activity generated by the heart can be measured by an array of electrodes placed on the body surface

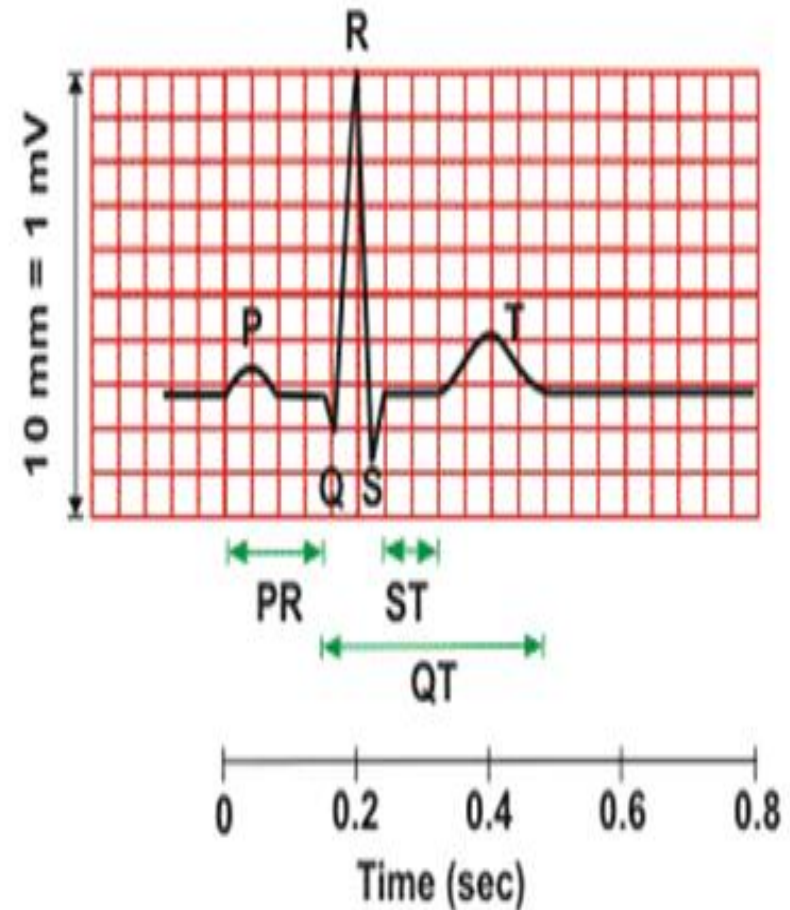


Electrocardiography Cont...

- Electrocardiography is a device that records the electrical activity of the heart muscle via electrodes placed on the chest and displays it as a visual record
- The recorded tracing (recorded copy made by the machine) is called an **electrocardiogram** (ECG, or EKG)

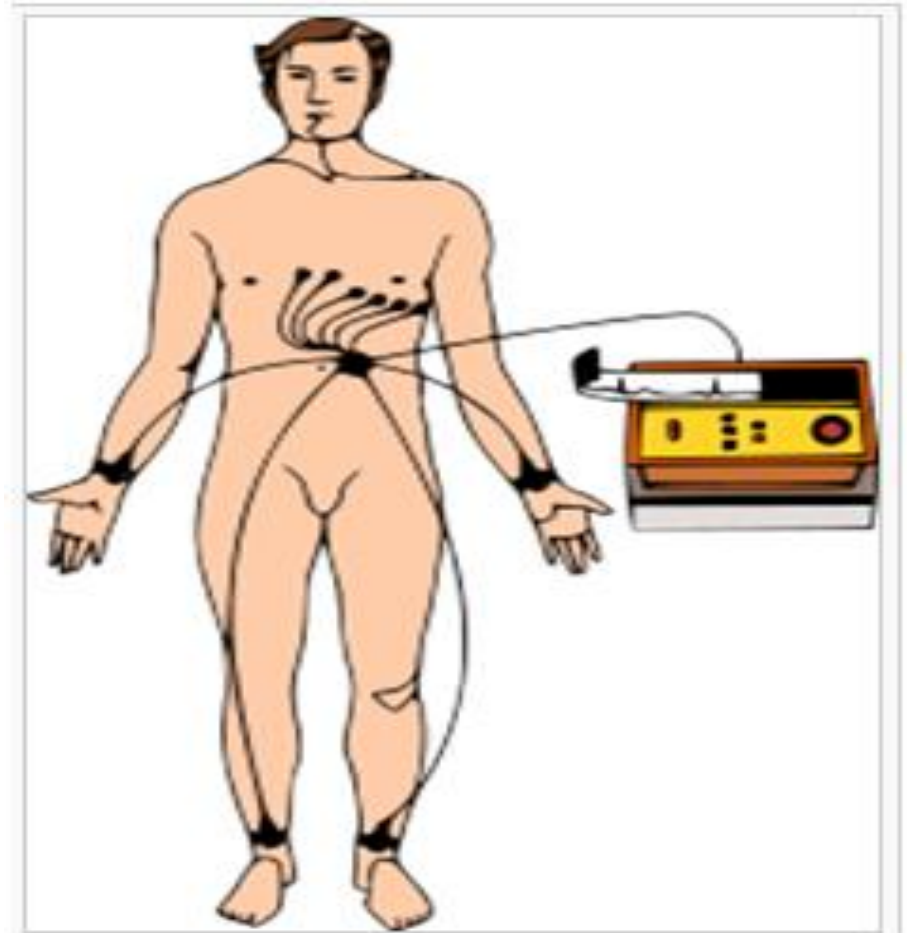
Electrocardiography Cont...

- The different waves that comprise the ECG represent the sequence of **depolarization** of the **atria & depolarization and repolarization** of the **ventricles**
- ECG is recorded from specific sites of the body in graphic form relating **voltage** (vertical axis) with **time** (horizontal axis)



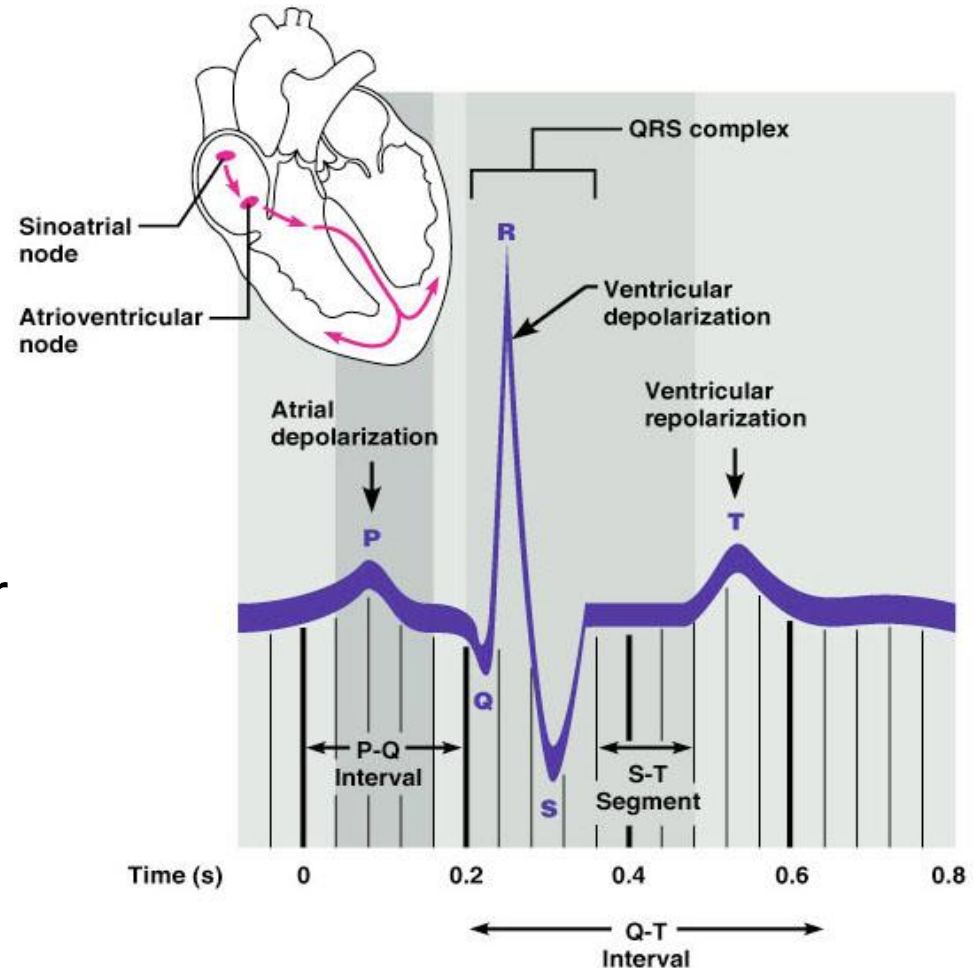
ECG Conventions

1. 1mV input → 10mm deflection
2. Paper speed = 25mm/sec
3. Recording points = wrist, ankle, skin on chest
4. Right leg = ground(earth)



Relation b/n cardiac Excitation and ECG waves

- There are three main deflections per cardiac cycle:
- **P wave**- corresponds to atrial depolarization
- **QRS complex**- corresponds to ventricular depolarization and
- **T wave**- corresponds to ventricular repolarization



Application of ECG

By analyzing electric potential fluctuations, some insight can be got relating to:

- Anatomical orientation of the heart
- Heart rate determination
- Relative size of heart chambers
- A variety of disturbances of rhythm and conduction arrhythmia and conduction block
- Extent, location and progress of ischaemic damage (myocardial infarction)

Cardiac Cycle

- Is the cardiac events that occur from the beginning of one heartbeat to the beginning of the next
- During this heartbeat, both atria simultaneously contract followed soon after by the contraction of the ventricles
- The cardiac cycle consists of a period of relaxation called **diastole**, during which the heart fills with blood, followed by a period of contraction called **systole**
- It consists of one complete contraction and relaxation of all four heart chambers

Cardiac Cycle Cont...

- During diastole,
 - normal filling of the ventricles increases the volume of each ventricle to about 110 to 120 milliliters
 - This volume is called the end-diastolic volume
- Then, as the ventricles empty during systole,
 - the volume decreases about 70 milliliters, which is called the stroke volume
- The remaining volume in each ventricle after systole, about 40 to 50 milliliters is called the end-systolic volume

Heart Sounds

- Sounds associated (usually) with valve closure
- Four heart sounds

1. First heart sound (S_1)

- Slightly prolonged “lub” sound
- Occurs at the beginning of ventricular systole
- Caused by sudden closure of AV-valves

Heart Sounds Cont...

2. Second heart sound (S_2)

- Shorter, high pitched “dub” sound
- Occurs at the beginning of ventricular diastole
- Caused by sudden closure of semi-lunar valves

3. Third heart sound (S_3)

- due to rapid ventricular filling

Heart Sounds Cont...

4. Fourth heart sound (S4)

– during atrial contraction

Third and fourth sounds occur:

- Normally in children
- **Abnormal in adult**

Cardiac Output (CO)

- Is the volume of blood ejected from the heart per minute

$$CO = HR \times \text{Stroke volume}$$

- The usual resting values of CO
 - for young, **healthy men**, resting cardiac output averages about 5.6 L/min.
 - for **women**, this value is about 4.9 L/min

Cardiac Output Cont...

- Cardiac output is not constant but varies with the body's state of activity
- Vigorous exercise
 - increases CO to as much as 21 L/min in a person in good condition and
 - up to 35 L/min in world-class athletes

Cardiac Output Cont...

- The difference between the **maximum** and **resting** cardiac output is called **cardiac reserve**
- **Cardiac Reserve**
 - = CO during maximal exercise - CO at rest
 - E.g. 35L - 5 L = 30L
- **Cardiac Index**
 - = Cardiac output ÷ body surface area
 - = about 3 L/min/m² of body surface area

Factors Influencing CO

- **Intrinsic:**
 - Arterial pressure (afterload)
 - filling pressure(preload)
- **Extrinsic:**
 - Parasympathetic and sympathetic effects

Factors Cont...

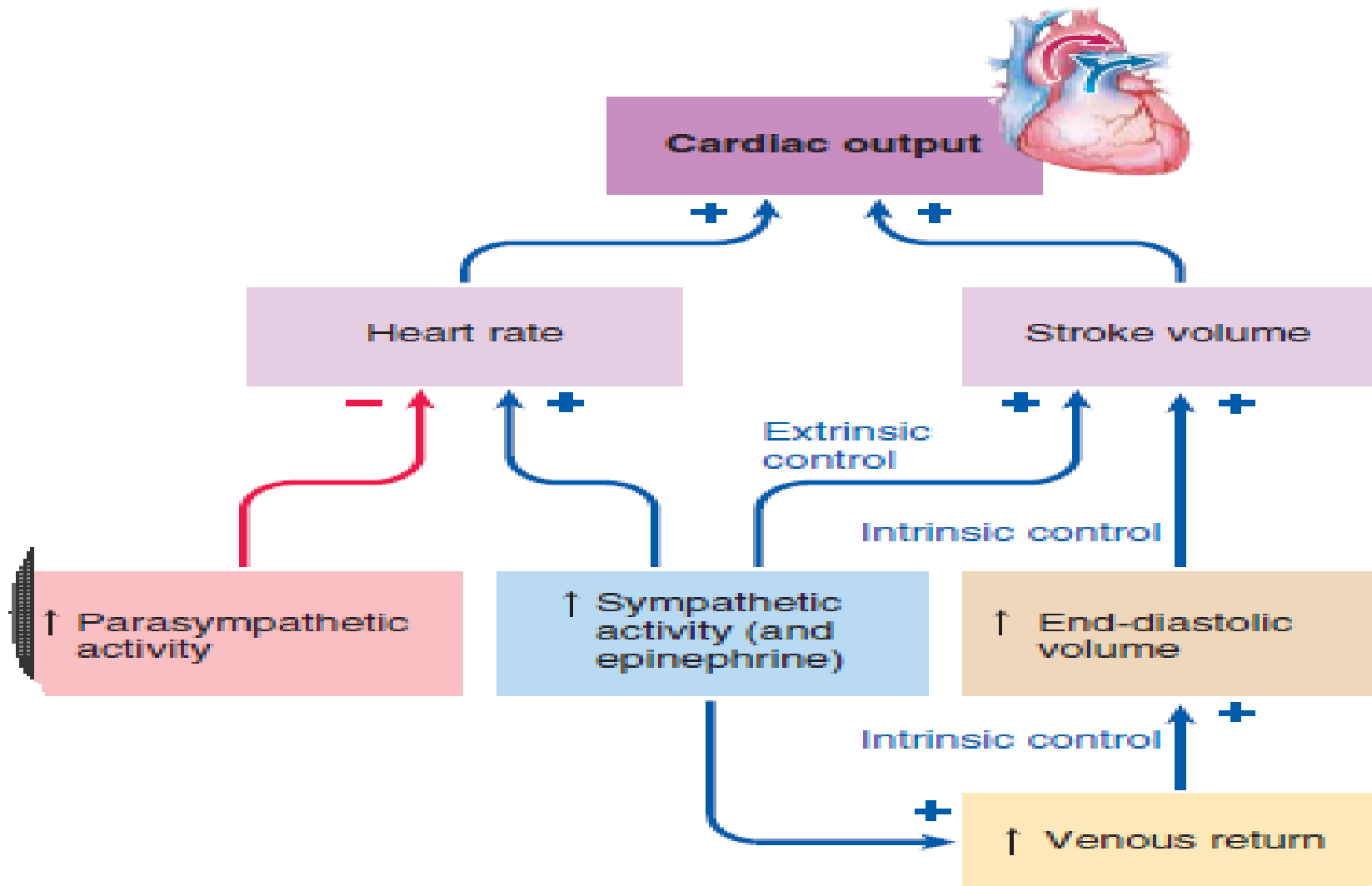
Preload:

- The initial stretching of the cardiac myocytes prior to contraction; therefore, it is related to the sarcomere length at the end of diastole

Afterload:

- The “load” against which the heart must contract to eject blood
- A major component is aortic pressure on left ventricle during diastole
 - i.e. the greater the aortic pressure, the greater the afterload on the left ventricle

Factors Cont...



Control of cardiac output

Circulatory System

- The combined function of the heart, blood, and blood vessels
- Important to transport oxygen and nutrients to organs and tissues throughout the body and carry away waste products

Basic Principles of Circulatory Function

- Three basic principles underlie all functions of the system
 1. Blood flow to most tissues is controlled according to the tissue need
 - When tissues are active, they need a greatly increased supply of nutrients and therefore much more blood flow than when at rest
 - The microvessels of each tissue continuously monitor tissue needs, such as the availability of oxygen and other nutrients

2. Cardiac output is the sum of all the local tissue flows
3. Arterial pressure regulation is generally independent of either local blood flow control or cardiac output control

Divisions of Circulation

1. Pulmonary circulation:

- The blood flow within the lungs that is involved in the exchange of gases between the blood and alveoli

2. Systemic circulation:

- Comprised of all the blood vessels within and outside of organs excluding the lungs

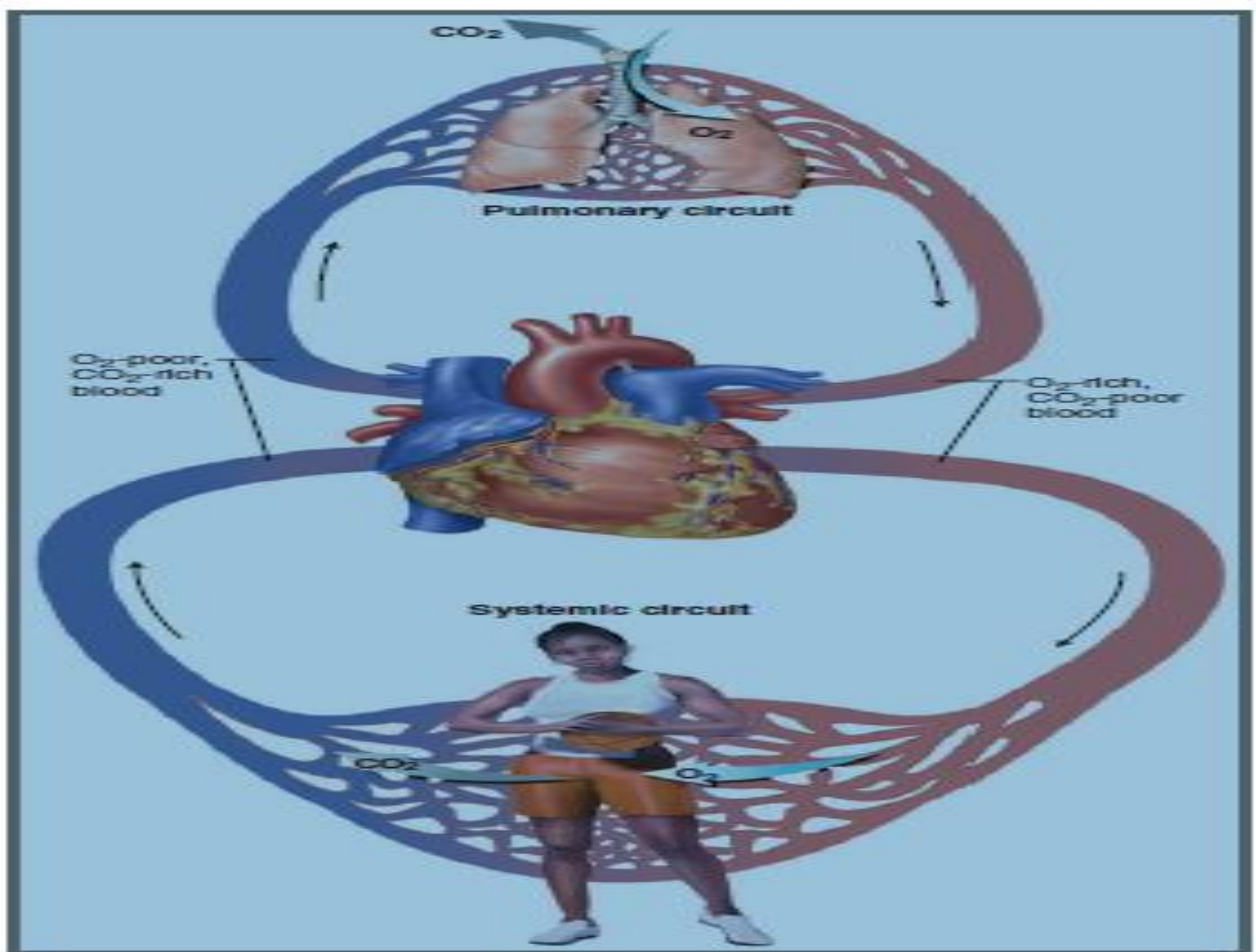
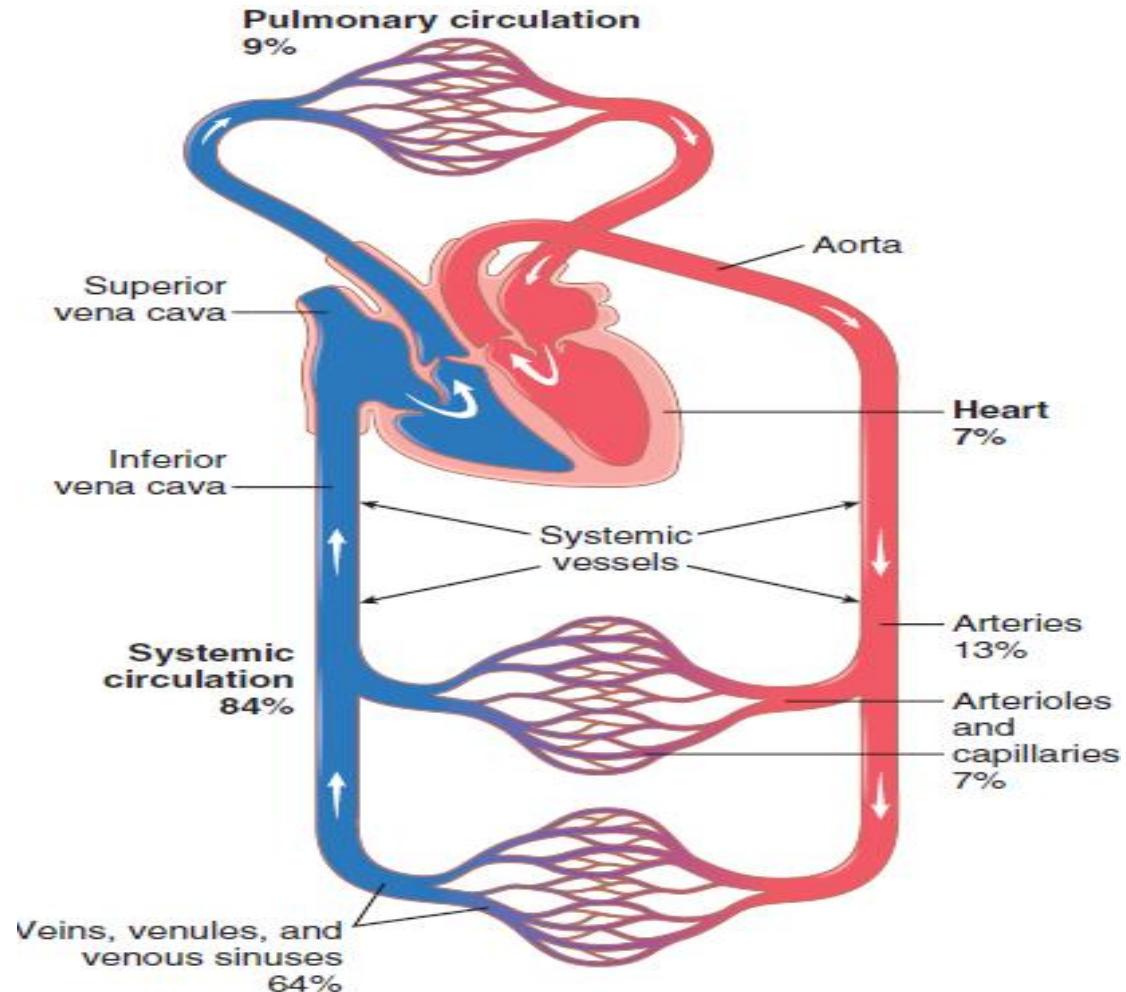


Fig. Division of circulation

Distribution of Blood to the Body Organs

- 64% in veins/venules
- 13% in the arteries
- 7% in capillaries
- 7% in the heart
- 9% in the lung



Circulatory Routes

- The **usual route** of blood flow is:
Heart → arteries → arterioles → capillaries →
venules → veins → heart
- Blood usually passes through only one network of capillaries, but there are **exceptions**, particularly:
 - Portal systems and
 - Anastomoses

Circulatory Routes Cont...

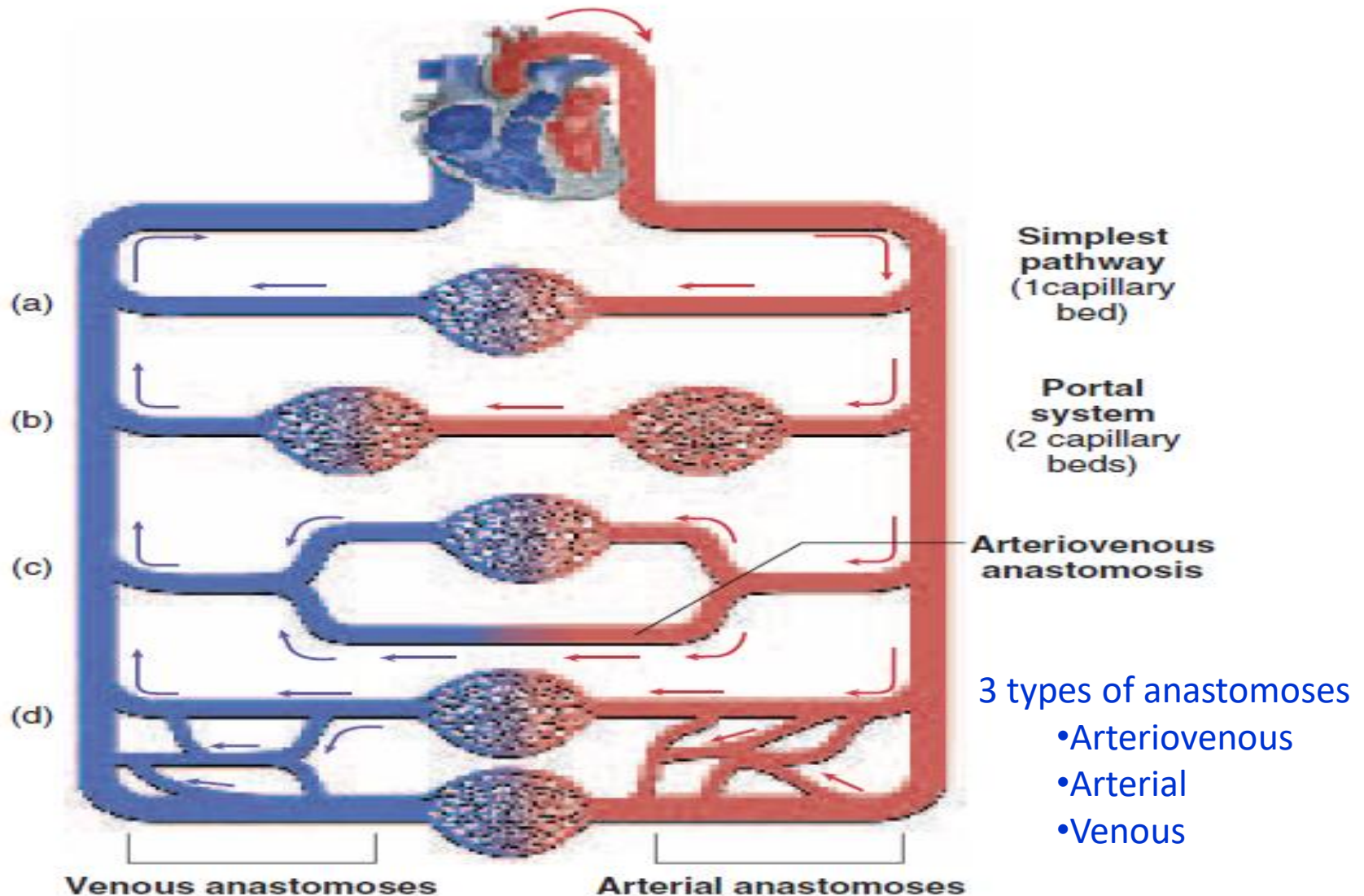


Fig. Portal circulation and anastomosis

Blood Vessels

- A tube with a space in the centre, called the lumen that transport blood through the body
- Mammals have **three types of blood vessels**
 - ✓ **Arteries** carry blood away from the heart
 - ✓ **Veins** carry blood towards the heart
 - ✓ **Capillaries** exchange media

Arterioles are small arteries

Venules are small veins which collect blood after it has flowed through a capillary bed

Blood Vessels Cont...

- The **smaller arteries** and **arterioles** are more **muscular** and can contract and relax to close off and to open up the capillary beds
- No exchange of materials takes place in the arteries and veins, whose walls are too thick and impermeable
- Exchange of materials takes place in capillaries only

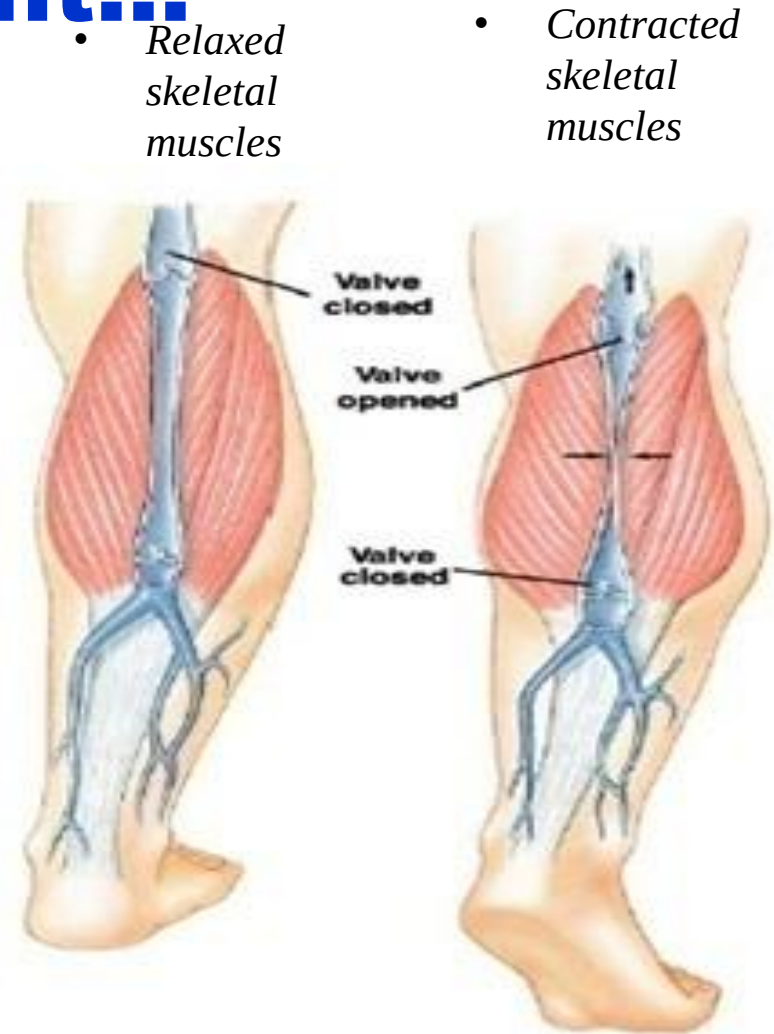
Blood Vessels Cont...

Veins

- Extend b/n smallest venules (>10 mm Hg) and largest terminal veins (venae cavae = 0 mmHg)
- High capacitance vessel
- Has great distensibility
- Has **one-way valve** to prevent excessive venous distension
- In the venous circulation, blood flows from smaller vessels into progressively larger ones
- The upward flow of blood depends in part on the **massaging action** of **skeletal muscles**

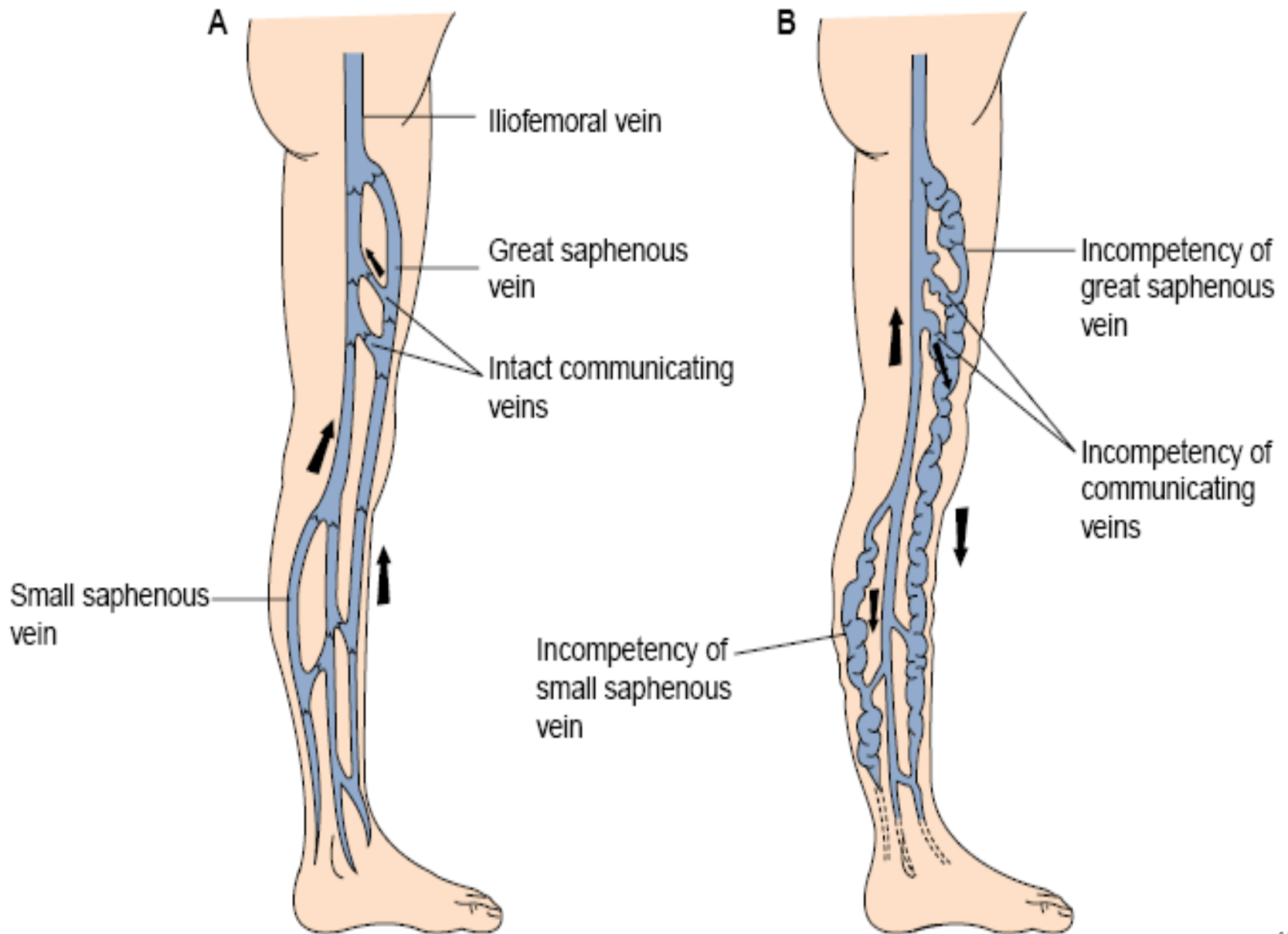
Blood Vessels Cont...

- The **presence of one-way venous valves** that keep the blood from dropping down again when the muscles relax
- **Varicose veins** result in part from the failure of venous valves



Varicose Veins

- Dilation and valvular insufficiency of **dependent veins** as a result of familial, occupational predisposition or both and prolonged obstruction as in pregnancy
- **Venous pulse:**
 - Pressure and volume fluctuation in veins near heart due to retrograde transmission



Microcirculation

- Includes arterioles, metarterioles, capillaries and venules
- The microcirculation of each organ is organized to serve that organ's specific needs
- In general, each nutrient artery entering an organ branches six to eight times before the arteries become small enough to be called *arterioles*
- The arterioles themselves branch two to five times, and form capillaries

Microcirculation Cont...

- Precapillary sphincter can open and close the entrance to the capillary
- The arterioles are highly muscular, and their diameters can change manyfold
- The metarterioles (the terminal arterioles) do not have a continuous muscular coat, but smooth muscle fibers encircle the vessel at intermittent points

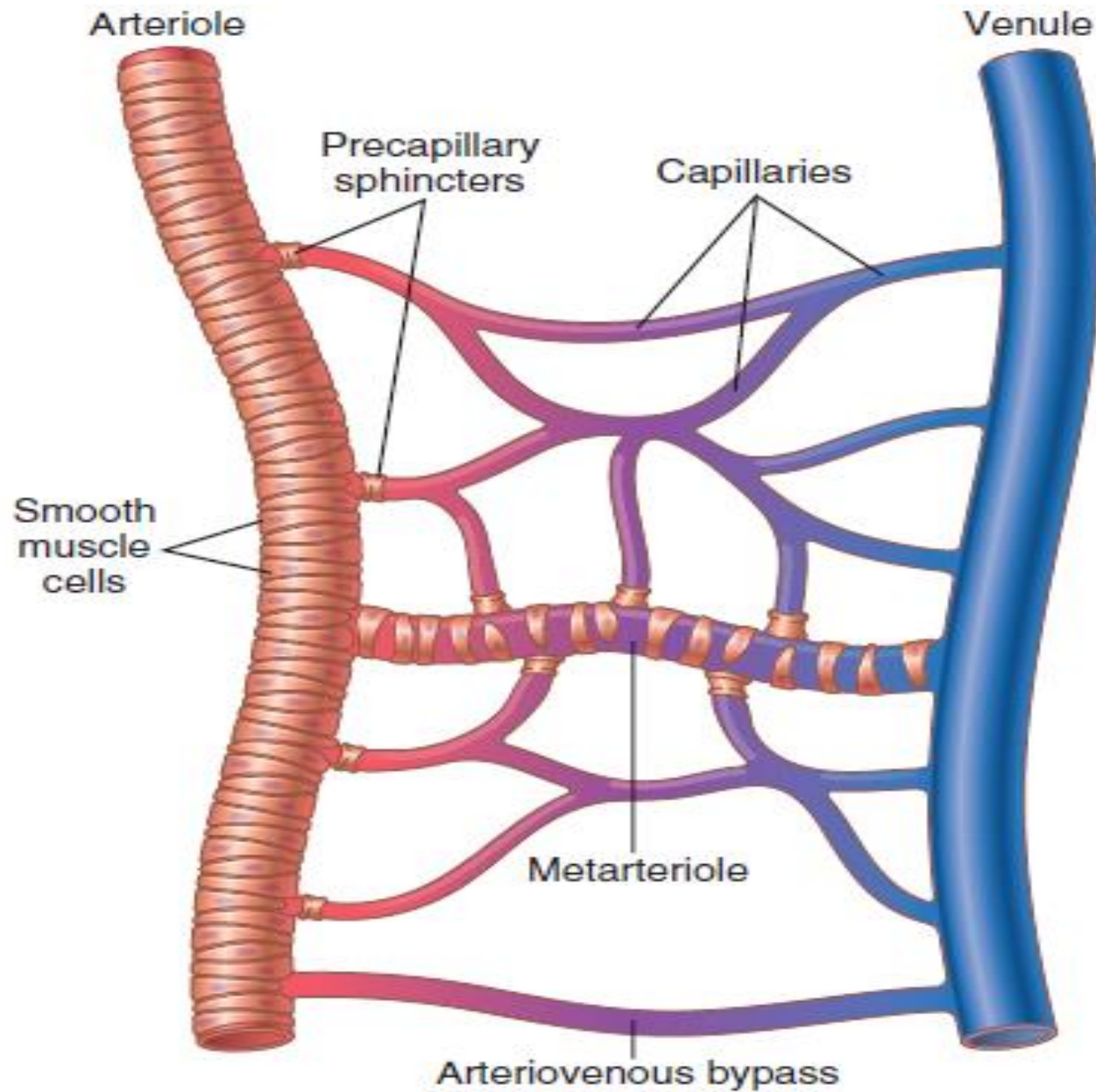


Fig. Components of the microcirculation

Types of capillaries

1. Continuous capillaries

- Have tight junctions, their endothelial are joined
- Form blood -brain barrier
- Abundant in skin and muscles

2. Fenestrated capillaries

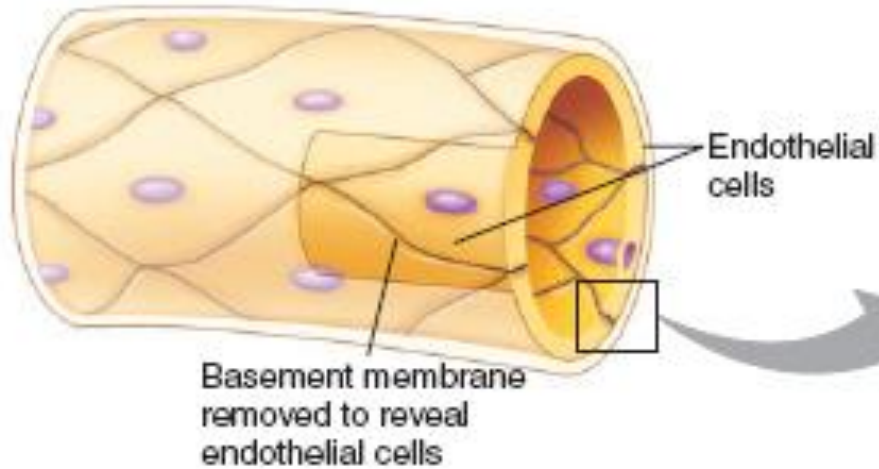
- Riddled with oval pores
- Found in organs that transport lots of water-
bowels, glomerular capillaries of kidney, pancreas
and salivary glands)
- Fenestrate keep plasma proteins back

Types Cont...

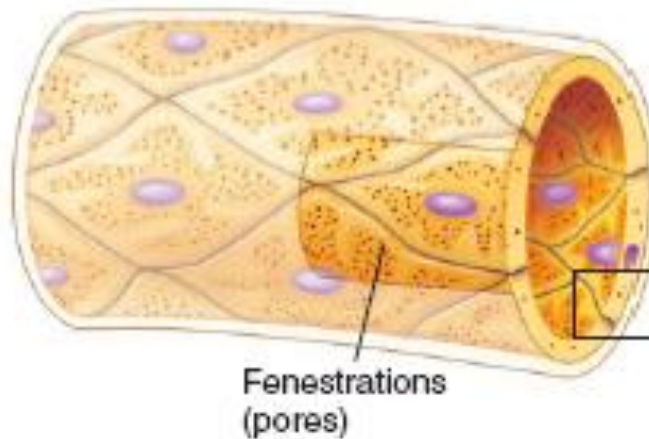
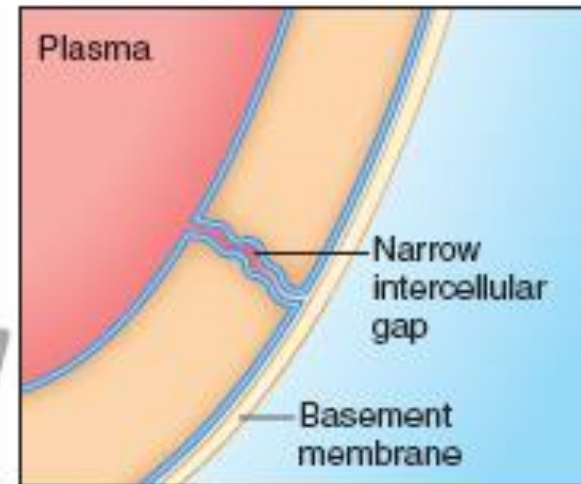
3. Sinusoid capillaries

- Have broad openings between endothelial cells
- Found in tissues bathed in plasma (liver, spleen, and bone marrow)
- Allow large molecules & even blood cells to pass

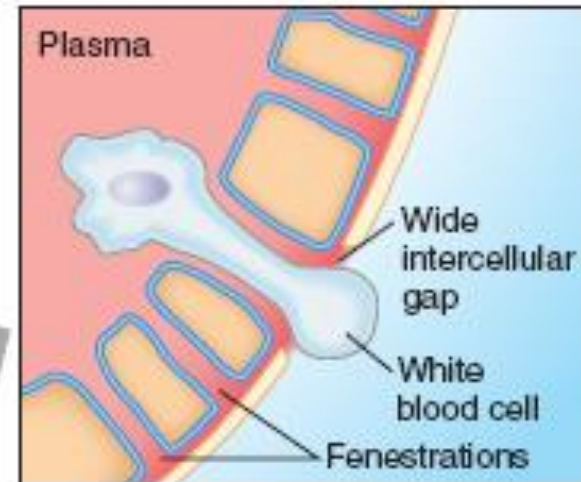
Types Cont...



(a) Continuous capillary



(b) Fenestrated capillary



Transcapillary Exchange

(Starling's law)

- Movement across capillary
- Influenced by:
 - Nature of substance (size, shape, lipid solubility)
 - Balance between hydrostatic and colloid osmotic pressure force across membrane.
 - Capillary surface area available for exchange
 - Physical characteristics of capillary membrane (continuous, fenestrated, discontinuous)

Methods of exchange

General methods of exchange:

1. Diffusion:

- E.g. lipid soluble substances O_2 , CO_2 , certain anesthetic agents diffuse with little hindrance through membrane.

2. Filtration-absorption

- Determined by hydrostatic and osmotic pressure on each side of membrane

Exchange Cont...

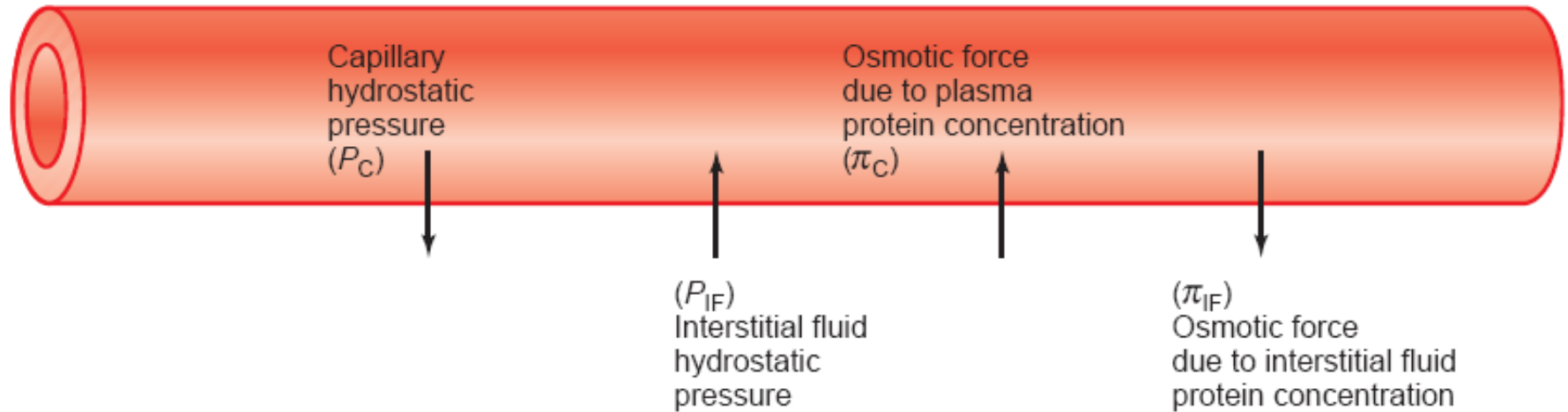
- **Arterial end:** hydrostatic pressure $>$ osmotic pressure = filtration
- **Venous end:** osmotic pressure $>$ hydrostatic pressure = reabsorption
- **Intermediate:**
 - Declined filtration
 - Increased reabsorption

$$P_{\text{eff}} \text{ (effective filtration pressure)} = \Delta P \text{ (hydrostatic pressure difference)} - \Delta \pi \text{ (oncotic pressure difference)}$$

= internal/external pressure difference

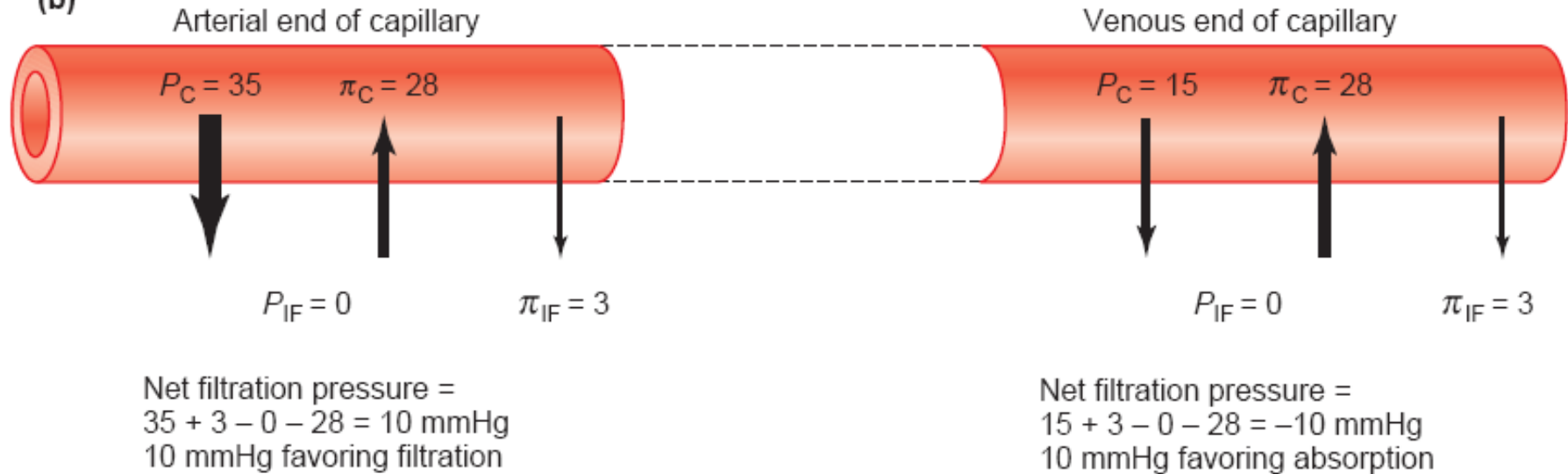
Exchange Cont...

(a)

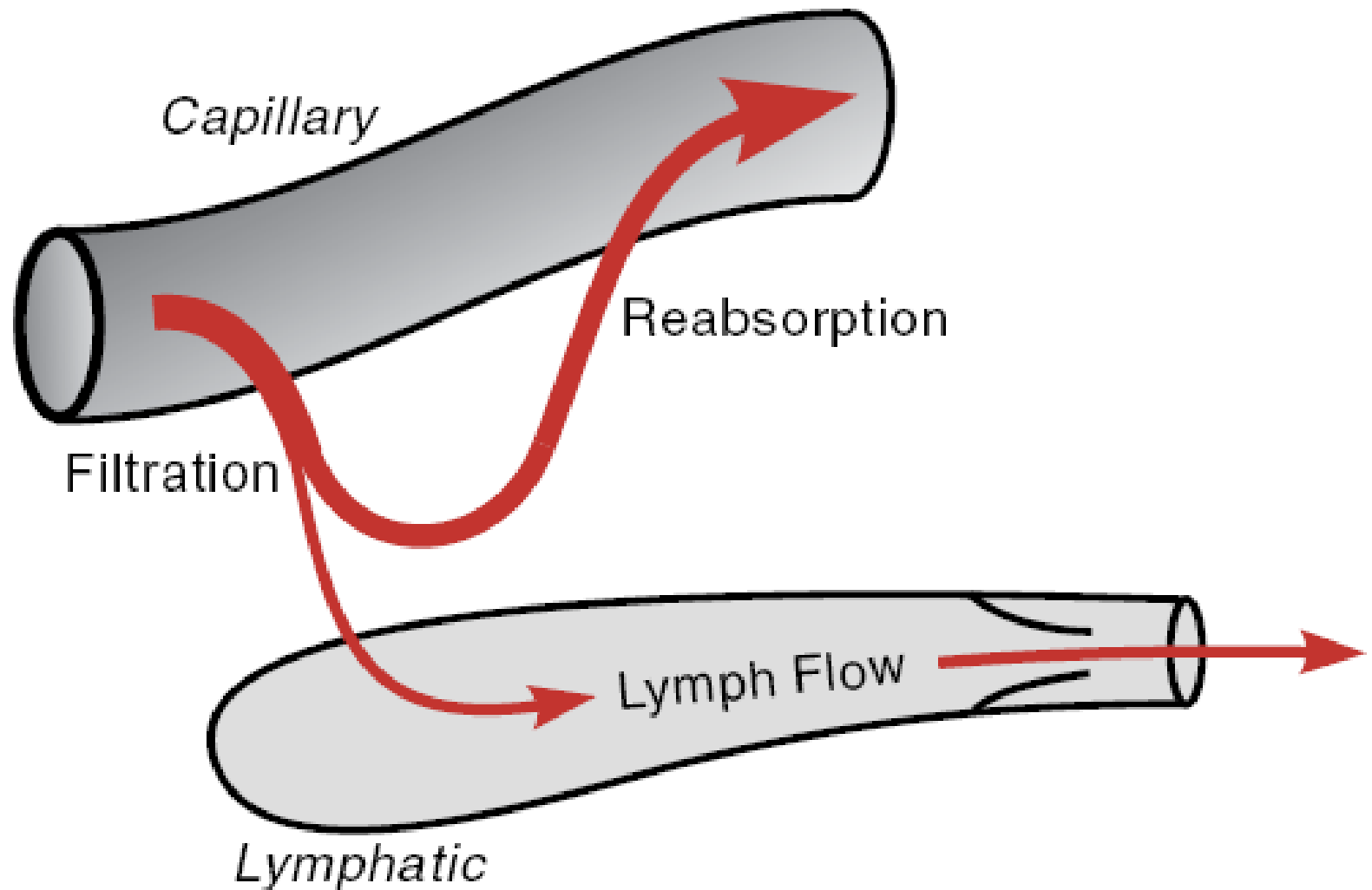


$$\text{Net filtration pressure} = P_C + \pi_{IF} - P_{IF} - \pi_C$$

(b)

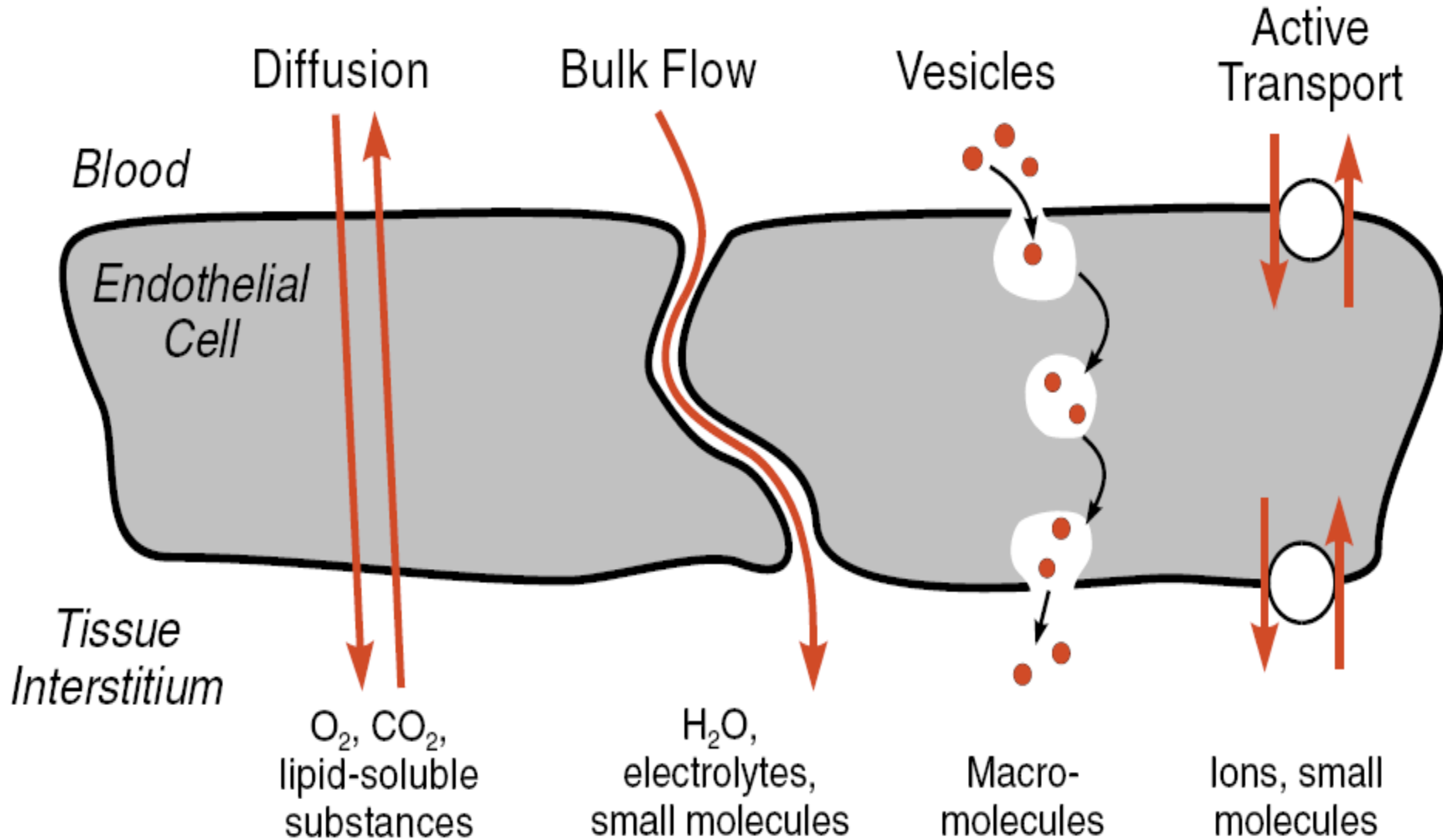


Exchange Cont...



$$\text{Filtration} = \text{Reabsorption} + \text{Lymph Flow}$$

Exchange Cont...



Blood Pressure (BP)

- The force that the blood exerts against a vessel wall
- Can be measured by **manometer** (pressure-measuring device)
- Two pressures are recorded: **systolic pressure (SBP)** and **diastolic pressure (DBP)**

Blood Pressure Cont...

- For a healthy adult person, average blood pressure is 120/80 mmHg
- The difference between systolic and diastolic pressure is called **pulse pressure**
- Pulse pressure is an important measure of the stress exerted on **small arteries** by the pressure surges generated by the heart

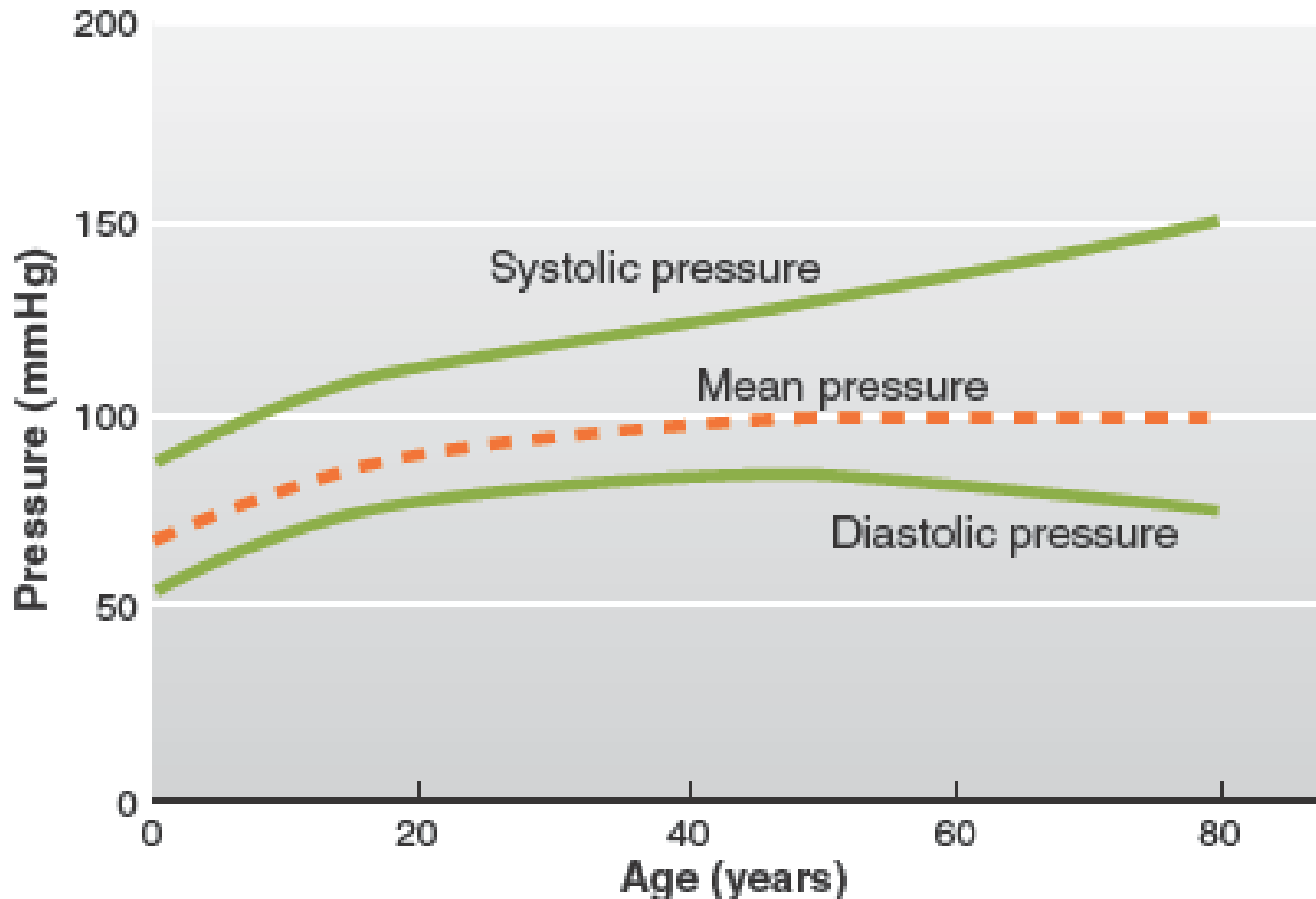
Blood Pressure Cont...

Mean arterial pressure (MAP)

- Since diastole lasts longer than systole, MAP is not simply the **average** of systolic and diastolic pressures
- The best estimate of MAP is the sum of diastolic pressure and one-third of the **pulse pressure**

$$\text{MAP} = \text{DP} + 1/3(\text{SP} - \text{DP})$$

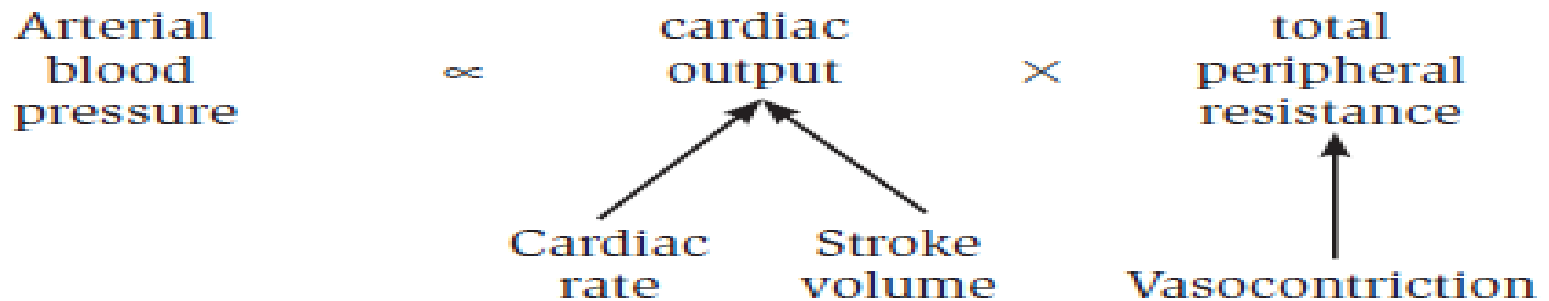
- MAP varies, however, with the influence of gravity



Changes in blood pressure with age

Blood Pressure Cont...

- Mean arterial pressure (MAP) is proportional to cardiac output (CO) times resistance (R) of the arterioles:



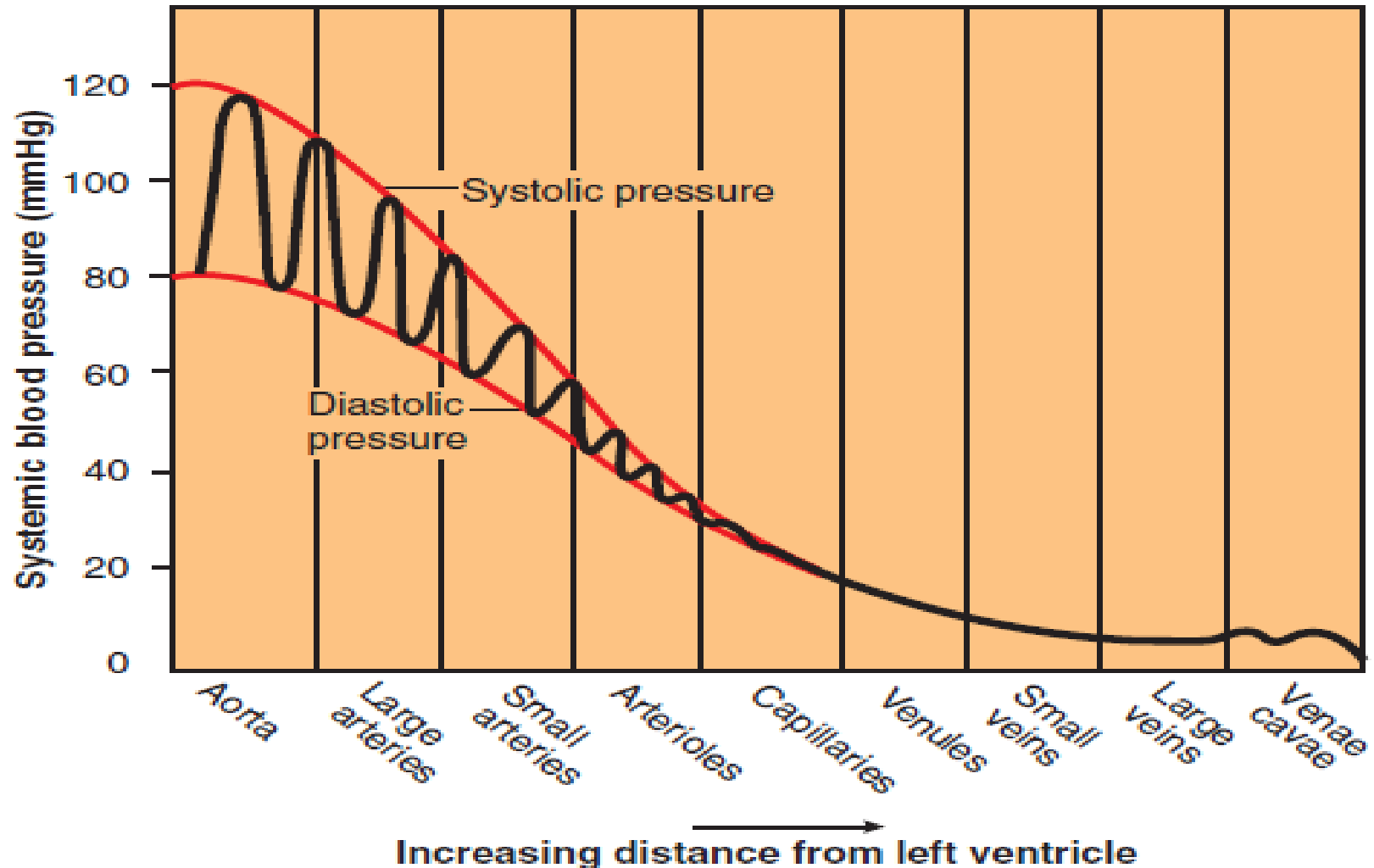
Blood Pressure Cont...

- Blood pressure rises with age as the arteries become less distensible and absorb less systolic force
- Atherosclerosis also stiffens the arteries and leads to a rise in BP

Changes in BP Related to Distance from the Heart

- All measures of blood pressure (SBP, DBP, Pulse P, and MAP) decline from heart to vein because of arterial elasticity and the effect of friction against the vessel wall
- There is no pulse pressure beyond the arterioles, but there are slight pressure oscillations in the venae cavae caused by the respiratory pump

Changes in BP Cont...



Rregulation of Blood Pressure

- Regulatory processes classified into 3 groups according to time of action.
 1. Short term control mechanisms
 2. Intermediate-term control mechanisms
 3. Long-term control mechanisms

Short-term Control Mechanisms

- Predominantly vasomotor adjustment and neuronal control
- Include:
 - Baroreceptor (stretch) reflexes:
 - Chemoreceptor reflexes
 - Ischemic reflexes of CNS

Short-term Cont...

Common characteristics:

- **Rapid onset of action** (within few sec.)
- **Response vigorous**, but if activated continuously, within a few days, it either dies out completely - (baroreceptors) or attenuated - (chemoreceptors, CNS Ischemic response)
- **Vasomotor responses** supplemented by hormonal mechanisms (noreadrenalin, adrenalin), and with delayed action; vasopressin

Baroreceptor Reflexes

- Location mainly on **aortic arch** and **carotid sinus**
- Convey information about:
 - Mean arterial pressure (MAP)
 - Amplitude of pressure fluctuation (pulse pressure)
 - Steepness of pressure rise (rate of pressure change)
- More sensitive to decrease than increase pressure
- More sensitive to sudden change

Baroreceptor Cont...

Glossopharyngeal nerve

Vagus nerve

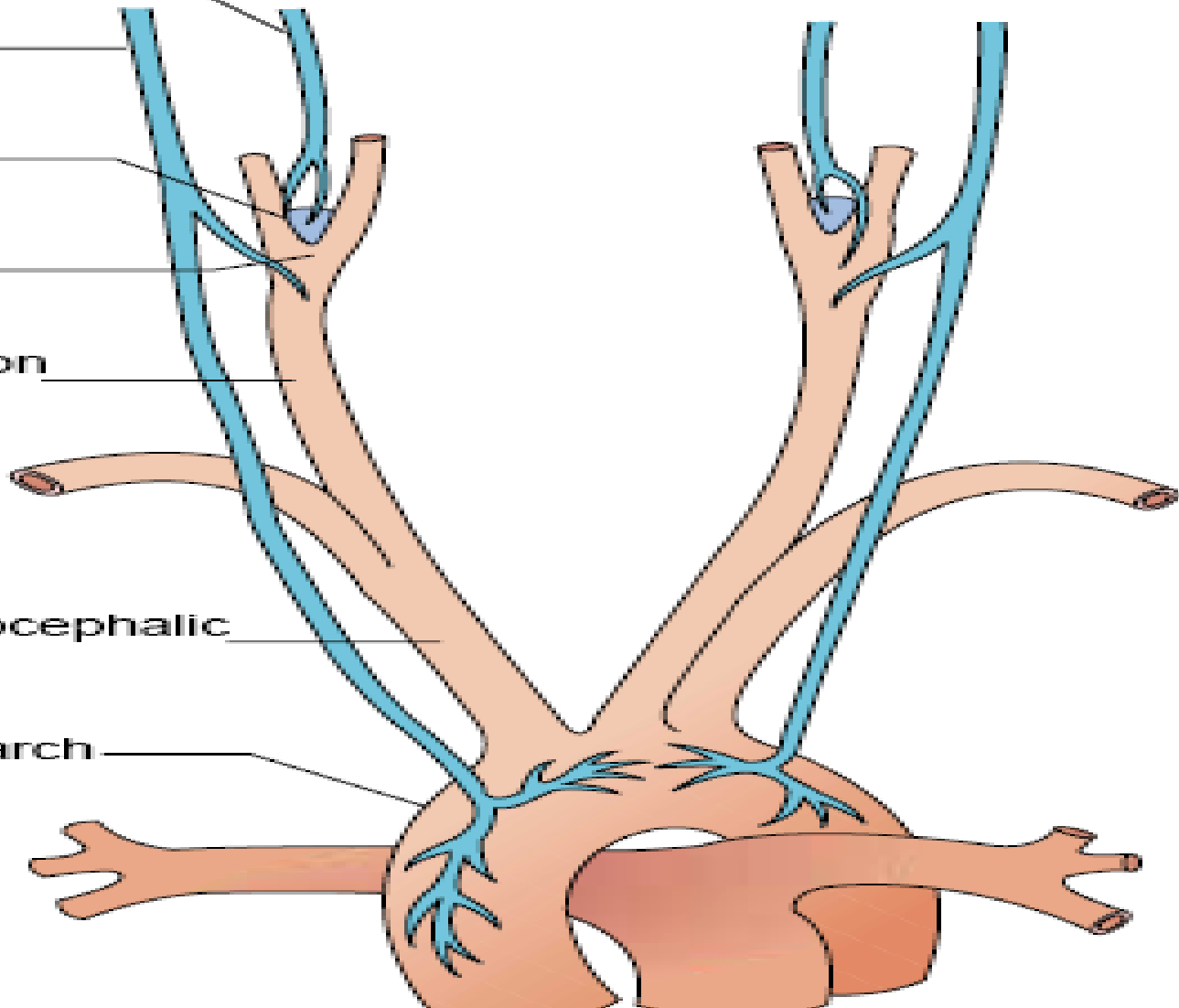
Carotid body

Carotid sinus

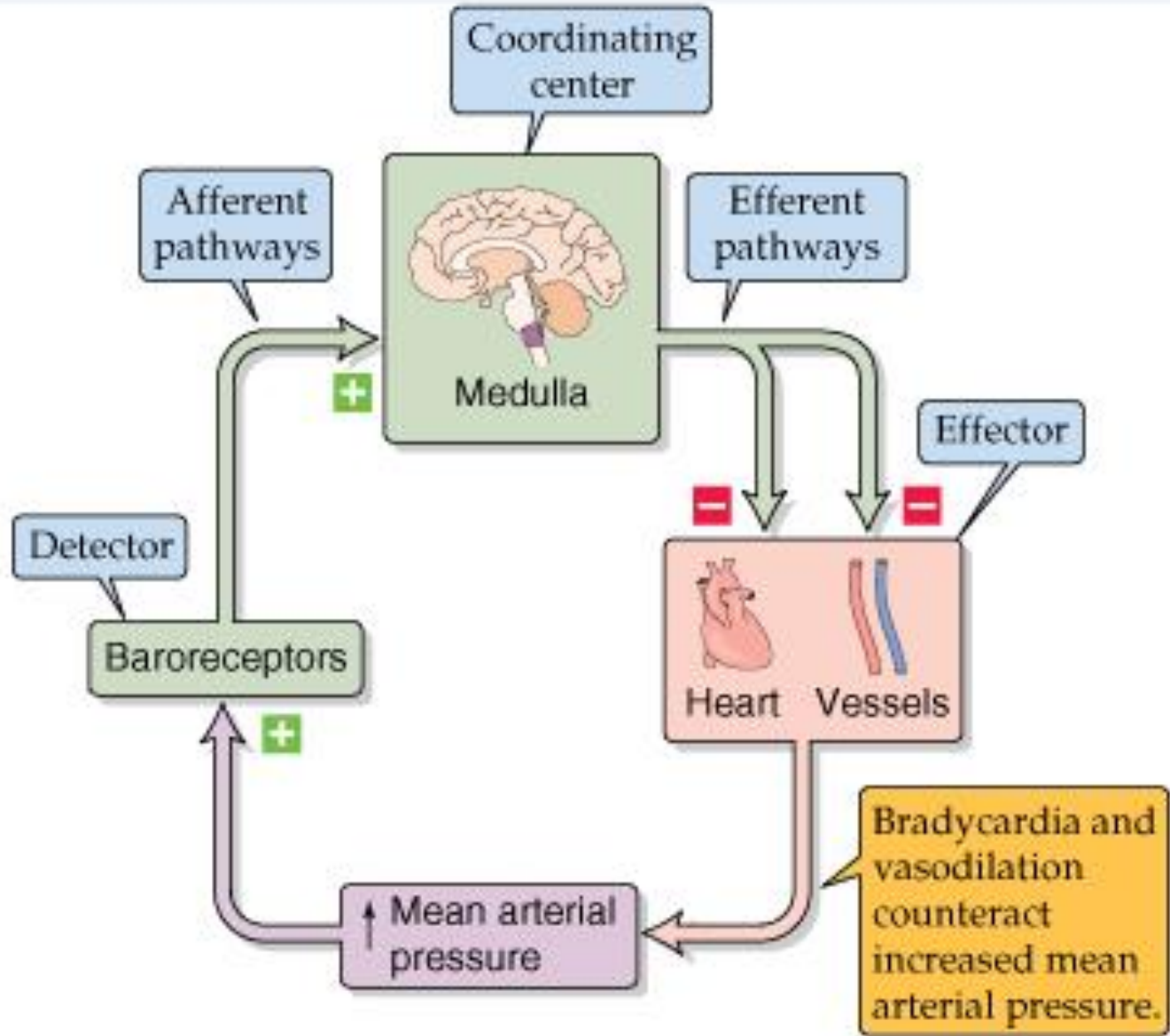
Common carotid artery

Brachiocephalic artery

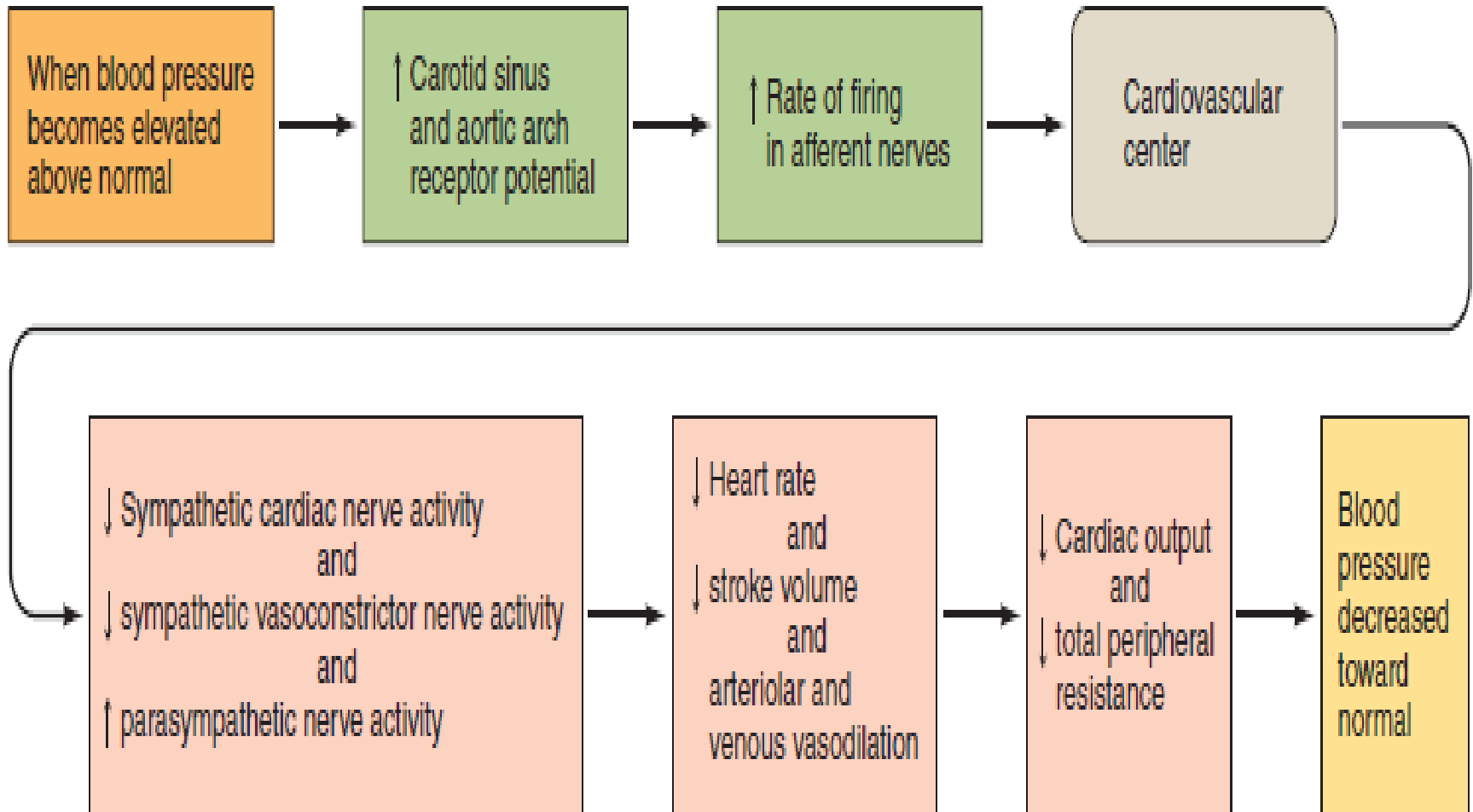
Aortic arch



Baroreceptor Cont...



Baroreceptor Cont...



(a)

CNS Ischemic Response **(Cerebral ischemia)**

- When arterial pressure falls below 40mmHg (as result of blood loss), cerebral ischemia activates sympathadrenal system
- Vasoconstriction and increased myocardial contractility pronounced
- This causes increase in arterial pressure (as high as heart can pump)

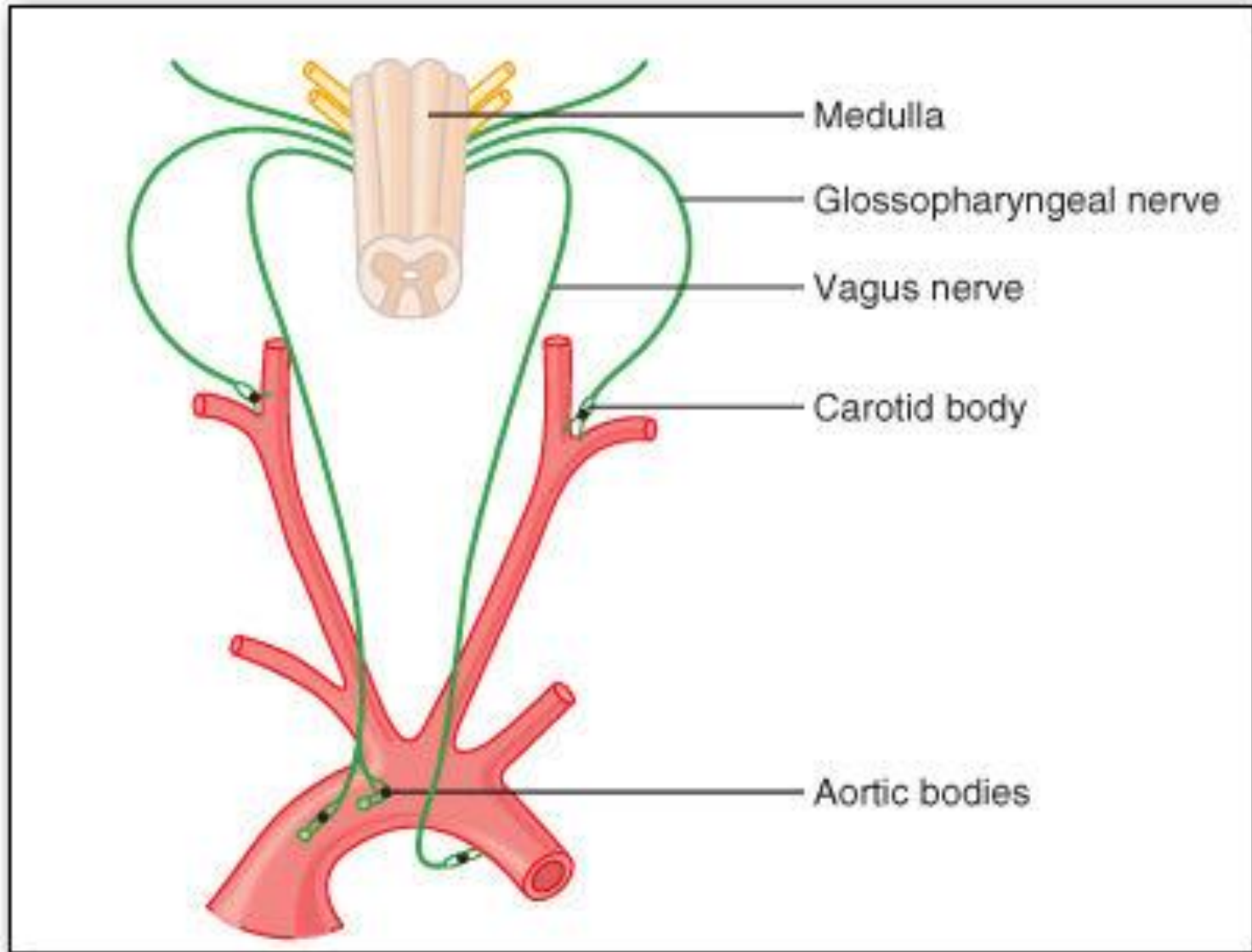
CNS Ischemic Cont...

- This system is emergency arterial pressure control system i.e. acts rapidly and very powerfully
- Thus prevent further decline in arterial pressure when blood flow to brain decreases dangerously
- This control system is “last ditch” mechanism for blood pressure control

Arterial Chemoreceptors

- Location:- carotid and aortic bodies (near aortic sinus and carotid sinus)
- Stimulus:
 - Decreased PO_2 (hypoxia)
 - Increased PCO_2 (hypercapnia) and
 - Increased H^+ (acidosis)
- Response: hyperventilation (increased minute ventilation)

Chemoreceptors Cont...



Chemoreceptors Cont...

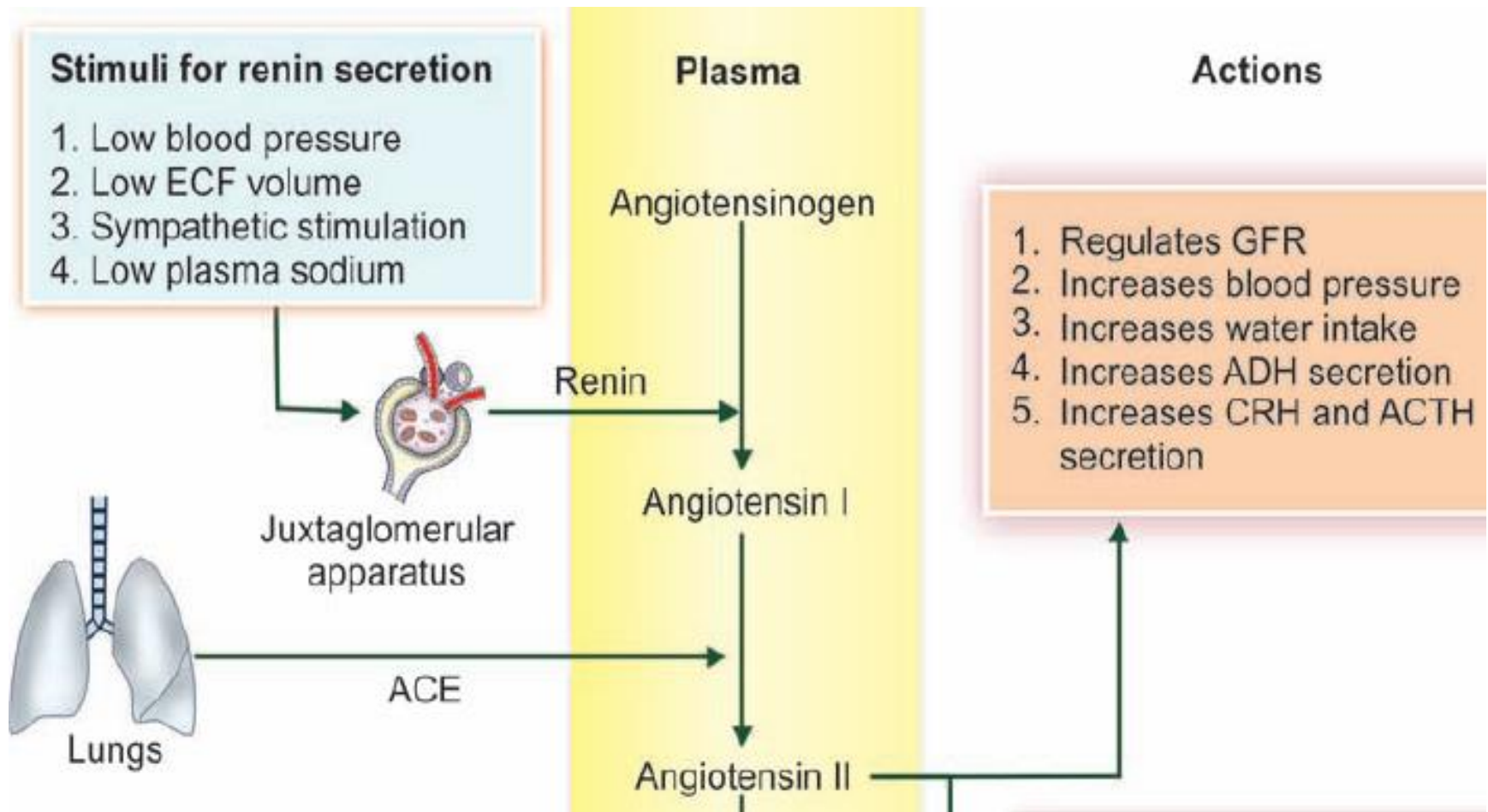
- Secondary effect: increased O₂ delivery to tissues (heart, brain)
 - general vasoconstriction
 - increased arterial pressure
- Chemoreceptor reflex protective in:
 - hypoxia due to altitude (low arterial PO₂)
 - circulatory shock (peripheral ischemia)

Intermediate Term Control

- Transcapillary volume shifts in response to changes in capillary pressure
 - $\uparrow$ Pressure $\rightarrow$ $\uparrow$ stress on veins $\rightarrow$ veins relax & $\downarrow$ pressure (stress relaxation)
 - $\downarrow$ intravascular volume $\rightarrow$ opposite effect
- Beginning of arteriolar vasoconstriction by angiotensin II

Long-term Control

Works by renin- angiotensine - aldosterone system (RAAS)



Hormonal Control

- Part of short term or intermediate term control

Angiotensin II

- Potent vasoconstrictor → ↑ blood pressure

Aldosterone

- Na⁺ retention by the kidneys → water follows sodium → ↑ blood volume and pressure

Hormonal Cont...

Natriuretic peptides (atrial natriuretic peptide and brain natriuretic peptide)

- $\uparrow \text{Na}^+$ excretion by the kidneys $\rightarrow$ $\downarrow$ blood volume & pressure

Antidiuretic hormone

- Primarily promotes water retention
 - vasoconstrictor at pathologically high concentrations
- 
- $\uparrow$ blood pressure

Methods for Measuring Blood Pressures

- Primary method:
Catheter, flexible tube that is inserted in the blood vessel
- Secondary method:
Auscultatory Method
(sphygmomanometer)



Fig. Measuring BP by sphygmomanometer

Hypertension (high BP)

- A chronic resting blood pressure higher than 140/90mmHg
- Causes of hypertension
 - **Primary Hypertension:** Cause unknown in 90 to 95% of cases
 - **Secondary Hypertension** = 5 to 10% of cases
 - Kidney Abnormalities
 - Narrowing of certain arteries
 - Adrenal gland abnormalities

Hypotension- abnormally low blood pressure

Hypertension Shortens Life

- Hypertension shortens life expectancy in at least 3 ways
 1. Excessive workload on heart and elevated arterial pressure
 - Coronary artery disease(CAD)
 - Congestive heart failure(CHF)
 2. Rupture of major vessel in brain
 3. Damage to kidneys, leading to renal failure

Some Anti-hypertensive Drugs

- β -adrenergic receptor blockers:-
 - reduce cardiac function and BP
 - E.g. propranolol
- Angiotensin Converting Enzyme (ACE) inhibitors:
 - e.g. enalapril
- Calcium channel blocking agents
e.g nifedipine

Venous Return

- The volume of blood flowing from veins in to right atrium per min
- It is equal to cardiac output
- It is influenced by right atrial pressure

Venous Return Cont...

Factors that affect venous return:

1. Contraction or compression of veins returning blood to the heart (the skeletal muscle pump)
2. Pressure changes in the abdomen and thorax during breathing (the respiratory pump)
3. Sympathetic innervations of veins
4. Blood volume

Blood Flow

- The amount of blood that moves to a particular organ in a given time
- Total blood flow is equal to CO; 5-6 L/min
- Determined by 2 factors:
 1. Pressure difference b/n two ends of the vessel i.e., the force that pushes blood through vessels
 2. Resistance of flow, hindrance to flow through vessels

Blood Flow Cont...

$$Q = \Delta P / R$$

Where Q = Blood flow

ΔP = Change in pressure

R = Resistance

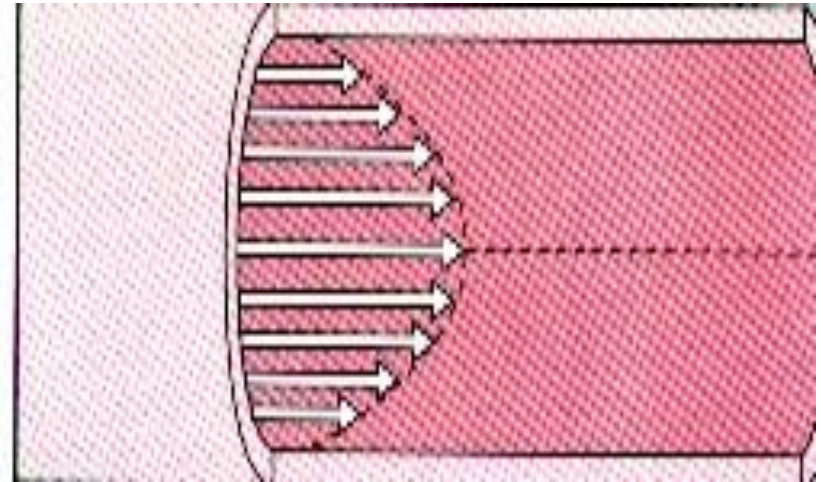
- According to Ohms Law: BF is directly proportional to the ΔP but inversely proportional to resistance (R)

Types of Blood Flow

There are two types of blood flow inside the vessels

1. **Laminar blood flow (streamline flow)**

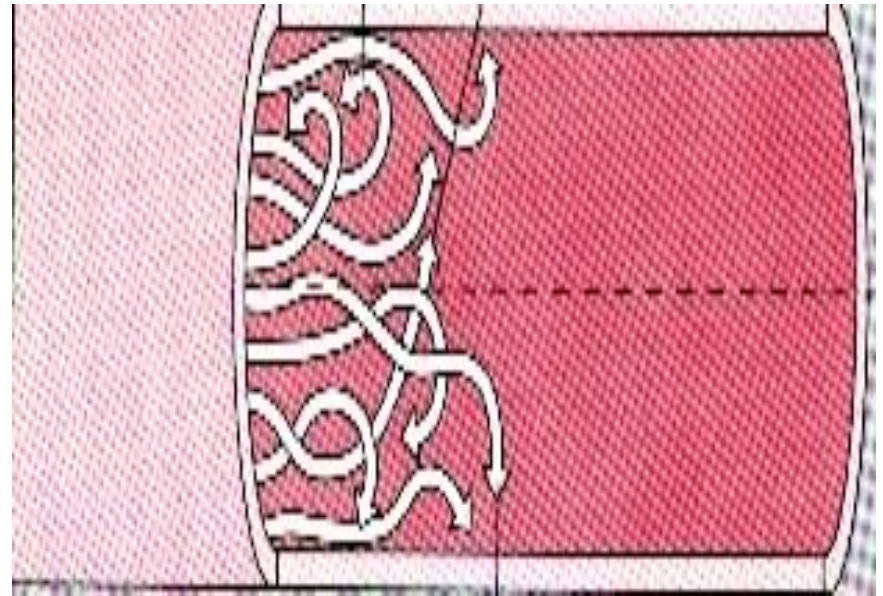
- Blood flows in a steady rate through long smooth vessels
- Blood cells move in a straight line
- Blood cells at the centre of the vessel move faster
- Laminar flow is silent



Types Cont...

2. Turbulent flow

- Blood flows in all directions in a vessel, continuously mixed
- Turbulent blood flow produces sound
- Occurs at blood vessels with high elastic content and during high velocity



Regulation of Blood Flow

Short term regulatory mechanisms:

- Minute by minute adjustment of local BF according to metabolic demand by producing vasodilators.
 - a. **Metabolic auto-regulation:** is the ability of tissues to regulate their own blood supply
 - b. **Nervous regulation:** ANS
 - c. **Humoral regulation:** vasoactive substances

Long term regulatory mechanism:

- mechanisms that adjust blood flow over long time
E.g. Angiogenesis (formation of new blood vessels) or decrease blood supply

- Some of the different vasodilator substances include:
 - Adenosine
 - Carbon dioxide
 - Adenosine phosphate compounds,
 - Histamine
 - Potassium ions
 - Hydrogen ions

- Vasodilator substances may be released from the tissue in response to oxygen deficiency
- For instance, decreased availability of oxygen can cause both adenosine and lactic acid (containing hydrogen ions) to be released into the spaces between the tissue cells
- Adenosine and lactic acid then cause intense acute vasodilation

Autoregulation of Blood Flow

- The capacity of tissues to regulate their own blood flow
- Most vascular beds have an intrinsic capacity to compensate for moderate changes in perfusion pressure by changes in vascular resistance, so that blood flow remains relatively constant
- It is probably due in part to the intrinsic contractile response of smooth muscle to stretch (**myogenic theory of autoregulation**)

Autoregulation Cont...

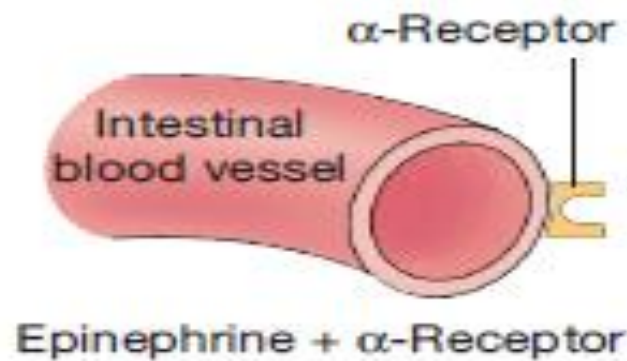
- Vasodilator substances tend to accumulate in active tissues, and these “metabolites” also contribute to auto-regulation (**metabolic theory of autoregulation**)
- When blood flow decreases, metabolites accumulate and the vessels dilate
- When blood flow increases, metabolites tend to be washed away

Neuronal Regulation of Blood Flow

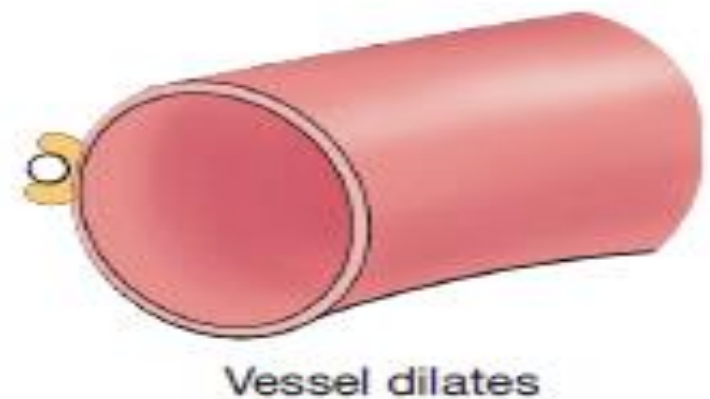
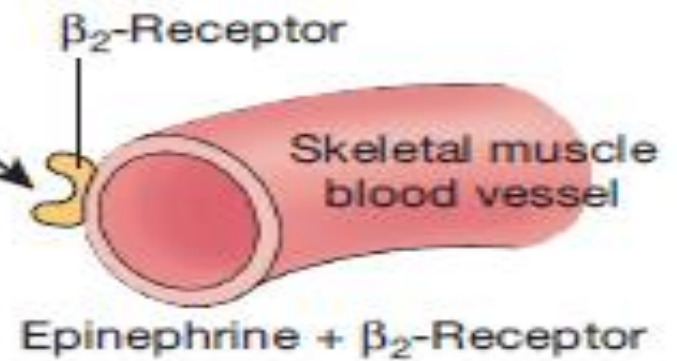
- **Parasympathetic supply:**
 - Generally has no effect
- **Sympathetic supply**
 - Releases norepinephrine
 - Acts on α receptors
 - Causes arteriolar constriction
 - Sometimes causes vasodilation

○ Epinephrine can bind to different isoforms of the adrenergic receptor.

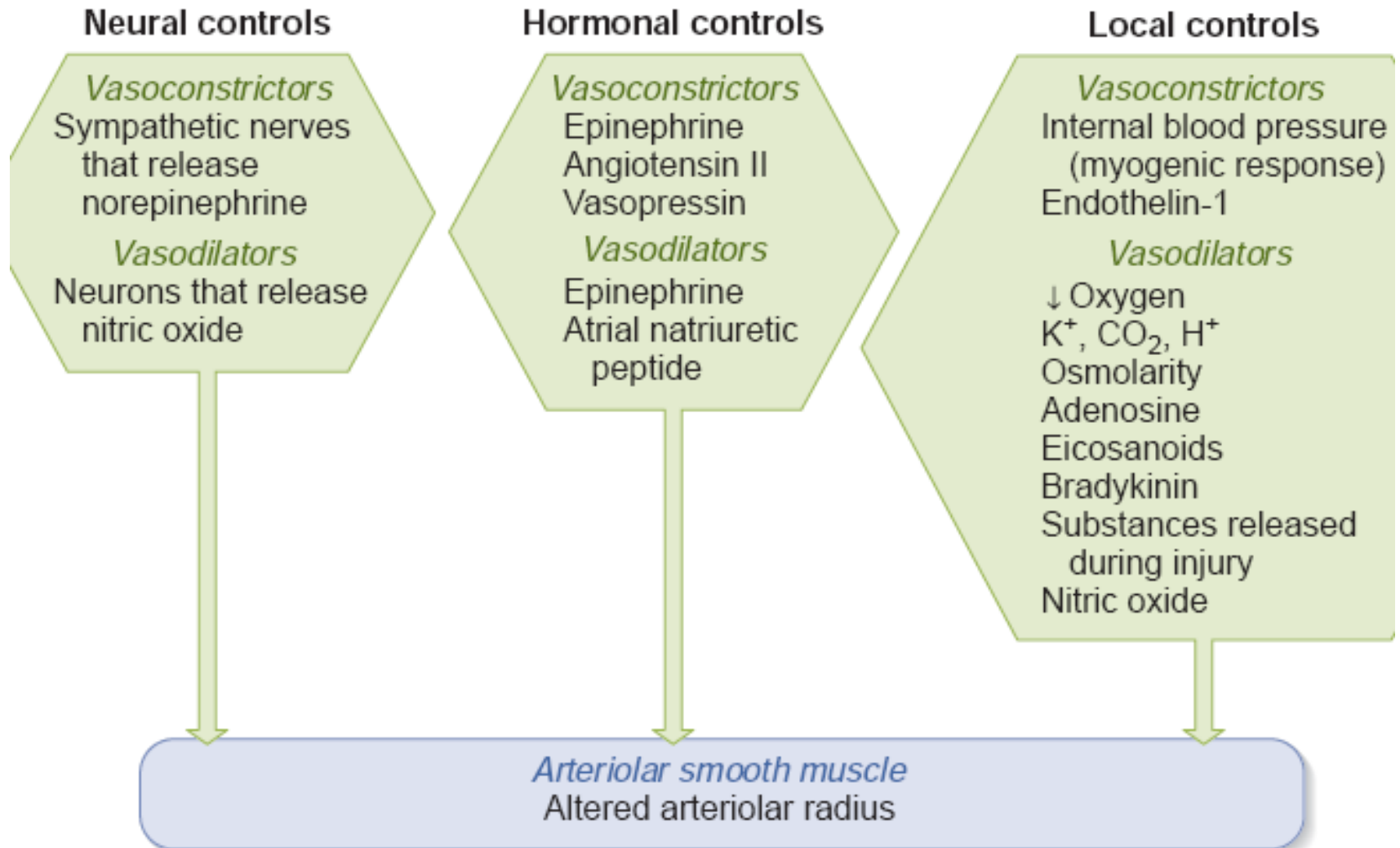
α -Receptor response



β_2 -Receptor response



Summary of Acute Blood Flow Control



Major factors affecting arteriolar resistance, and therefore blood flow

Shock

- General circulatory insufficiency (fall in arterial pressure)

Causes:

- **Disorders in the heart**
 - Cardiogenic shock can be caused by restricted filling (e.g. AV stenosis), myocardial disorders (e.g. Infarctions), restricted(ineffective) ventricular ejection

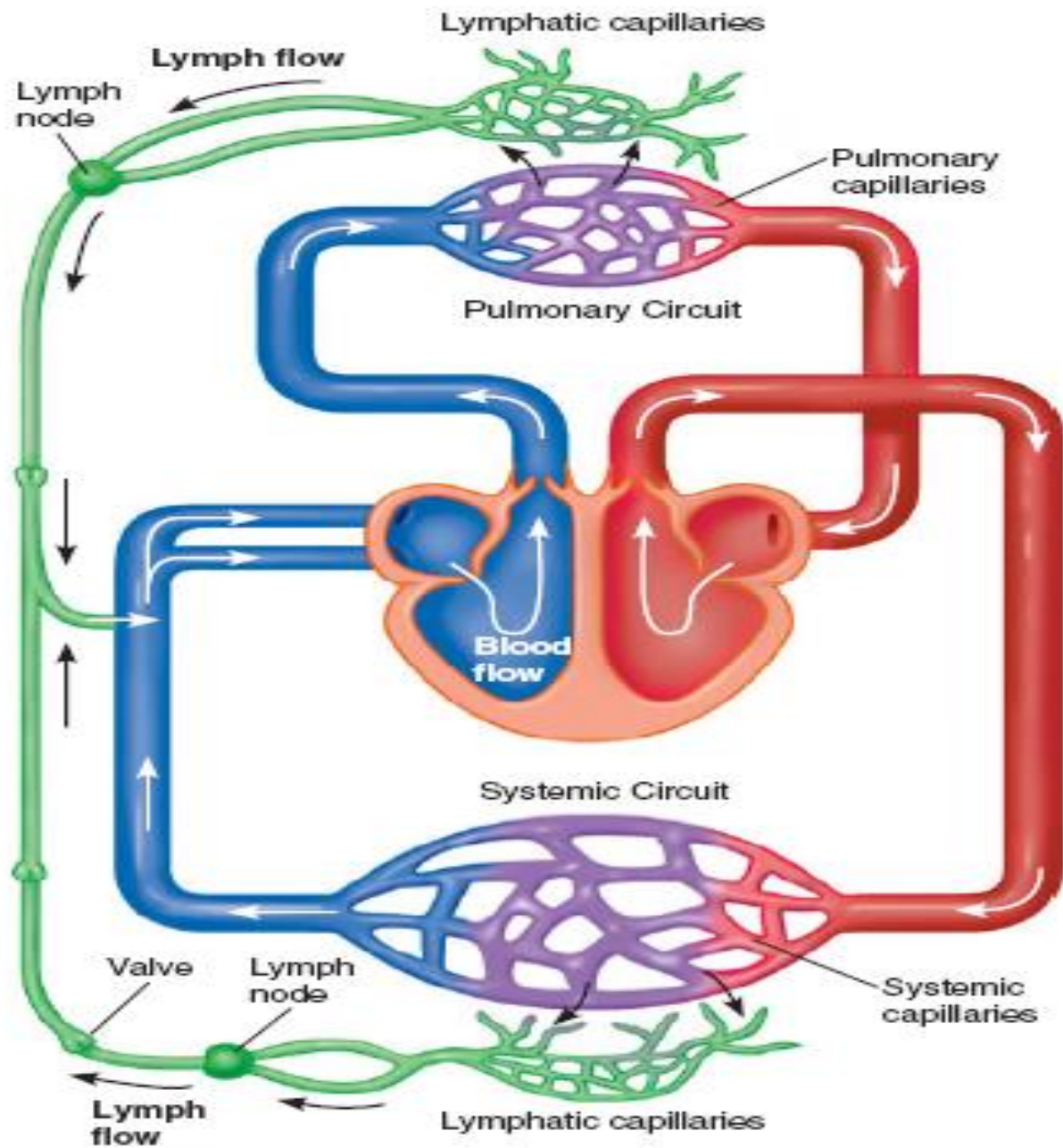
Shock Cont...

Causes Cont...

- **Disorders in vessels** (vascular insufficiency developing into vascular shock)
- **Hypovolemia**
 1. Absolute hypovolaemia:
 - Blood loss, plasma loss, dehydration
 2. Relative hypovolaemia:
 - Due to Vasodilation

Lymphatic System

- A network of organs and vein like vessels that recover tissue fluid, inspect it for disease agents, activate immune responses, and return the fluid to the bloodstream
- Components:
 - lymph, the recovered fluid
 - lymphatic vessels
 - lymphatic tissue, composed of aggregates of lymphocytes and macrophages
 - lymphatic organs, in which these cells are especially concentrated



The lymphatic system. **Daily lymphatic volume= 3-5 L(10%)**

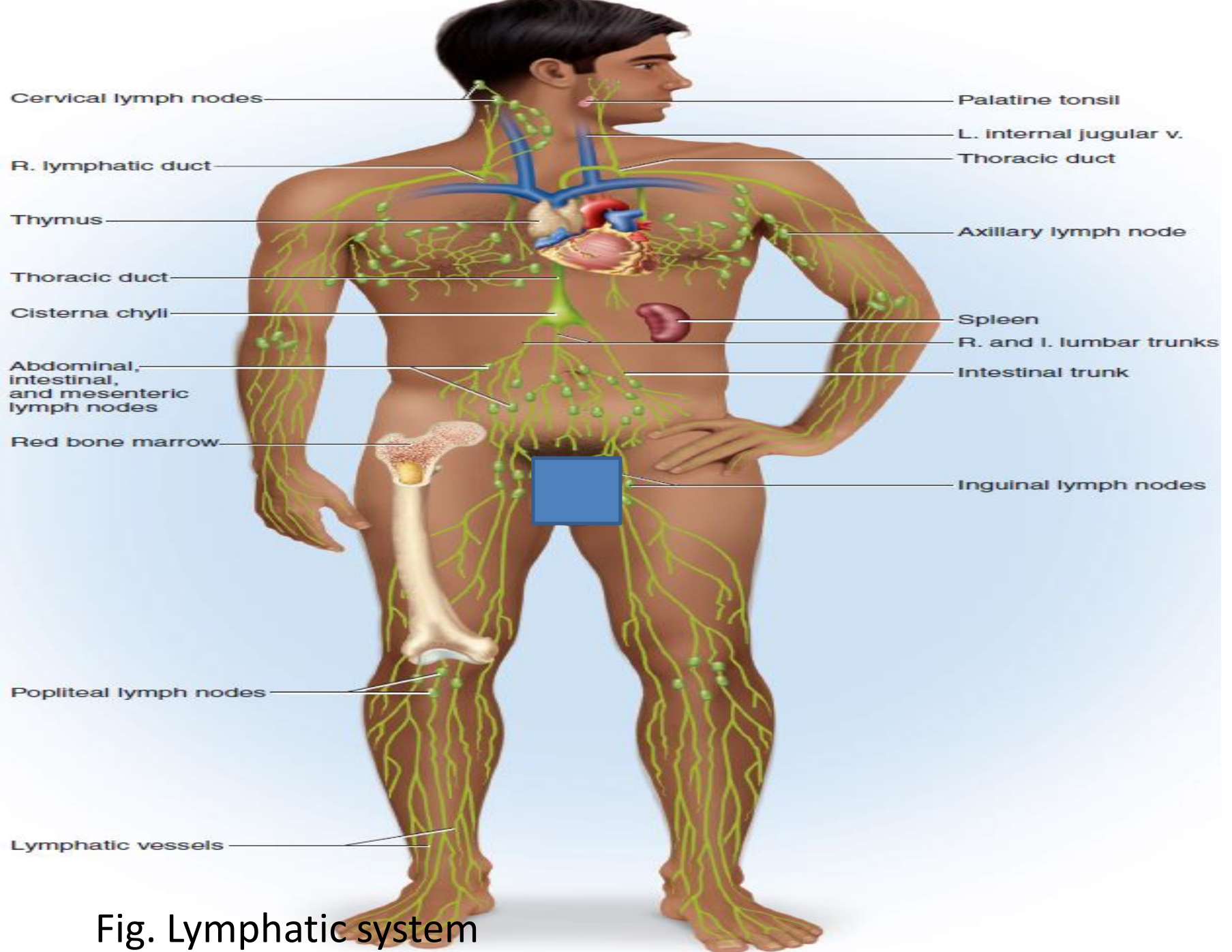


Fig. Lymphatic system

Functions of lymphatic system

1. Fluid recovery

- Absorbs excess fluid from ECF and returns it to the bloodstream

2. Immunity

- As the lymphatic system pull through excess tissue fluid, it also picks up foreign cells and chemicals from the tissues
- On its way back to the bloodstream, the fluid passes through lymph nodes, where immune cells stand guard against foreign matter
- When they detect it, they activate a protective immune response

Function cont...

3. Lipid absorption

- In the small intestine, special lymphatic vessels called *lacteals* **absorb dietary lipids** that are not absorbed by the blood capillaries

4. Controlling the Interstitial Fluid Pressure

- The lymphatic system functions as
 - an “**overflow mechanism**” to return to the circulation **excess proteins** and **excess fluid volume** from the tissue spaces

Lymph

- A clear, colorless fluid, similar to blood plasma but low in protein
- Composition varies substantially from place to place
 - Lymph leaving the lymph nodes contains a large number of lymphocytes
 - this is the main supply of lymphocytes to the blood stream
 - Lymph leaving the GIT contains a large number of fat substance

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THANK YOU