Debre Markos university
School of medicine
Physiology Unit

Module: Musculoskeletal and integumentary System

Target group: Medicine; PC-I

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Semester: 2nd

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Musculoskeletal and Integumentary Physiology

- ❑ **At the end of this module students will be able to;**
- ❑ **Understand the** functions, characteristics & classification of muscles
- ➢ **Discuss the physiological features of skeletal muscle and other properties like:**

- ✓ Molecular basis of skeletal muscle contraction
- ✓ Motor Unit
- ✓ Physiology of the neuromuscular junction (NMJ)
- ✓ The sliding filament hypothesis
- ✓ Excitation-contraction coupling
- ✓ Muscle energetics
- ✓ Muscle contraction kinetics (types of contraction, summation, tetanus fatigue
- ✓ Types of skeletal muscle fibers

Musculoskeletal and integumentary physiology

- **Explain about Smooth Muscle**
  - ✓ Smooth muscle classification
  - ✓ Excitation-Contraction Coupling
  - ✓ Slow wave/pacemaker potentials & action potentials
- **Understand and analyze about Cardiac Muscle**
  - Cardiac muscle Action Potenitals & Pacemaker potentials
  - Excitation - Contraction coupling
- **Discuss about Integumentary System**
  - Skin functions, receptors in the skin…
  - Bone Physiology
  - Calcium homeostasis

1. Introduction

- ***"A muscle is an engine, capable of converting chemical energy into mechanical energy.***

- ***It is quite unique in nature, for there has been no artificial engine devised with the great versatility of living muscle".***

— Ralph W. Stacy and John A. Santolucito, in *Modern College Physiology,* 1966

Introduction…..

General points:

a. Can be excited chemically, electrically + mechanically

b. Contractile mechanisms (actin + myosin) that can be activated by **Action Potential.**

Mass:

- 45-50% of the total human body mass (≈ 600 muscles)
- 40% skeletal+ 10% cardiac and smooth muscles (45-50%).

O_2 consumption

- 25% total bodily O_2 consumption at rest.
- During strenuous exercise it can increase as much as**10-20** times.

Introduction….

2. Functions, properties, and classifications of muscular tissue

2.1. Functions of muscles

❑ **Four key functions of muscular tissue for homeostasis**

1. Producing body movements

- **Muscle** contractions pull on tendons, which are attached to bones.

2. Stabilizing body positions

- Skeletal muscle contractions stabilize joints and help maintain body positions.

3. Storing of substance within the body

- Sustained contractions of ring like bands of smooth muscle (sphincters), prevent outflow of the contents of a hollow organ.

4. Generating heat

- As muscular tissue contracts, it produces heat; **thermogenesis.**

Introduction….

2.2. Properties of muscular tissue

1. **Excitability:** Respond to certain stimuli by producing electrical signals (action potentials).
   - ✓ a property of both muscle and nerve
2. **Contractility:** Contract forcefully when stimulated by AP.

3. **Extensibility:** Stretch without being damaged
4. **Elasticity:** Return to its original length and shape after contraction or extension.

2.3. Classification of muscles

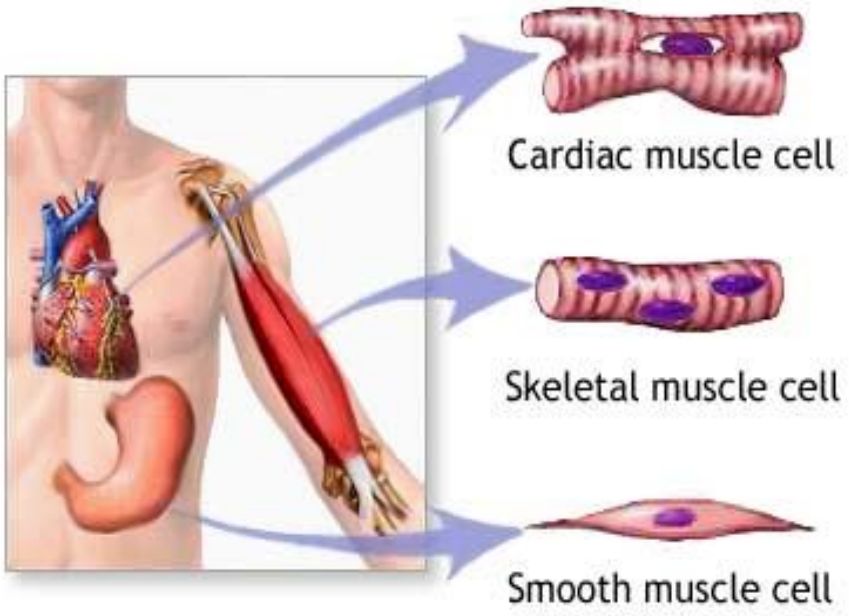
I. Anatomical classification

1. Striations

➢ Presence of alternating light and dark bands on the sarcolemma.

a. Skeletal

b. Cardiac



2. Non Striation

c. Smooth muscles

II. Physiological classification

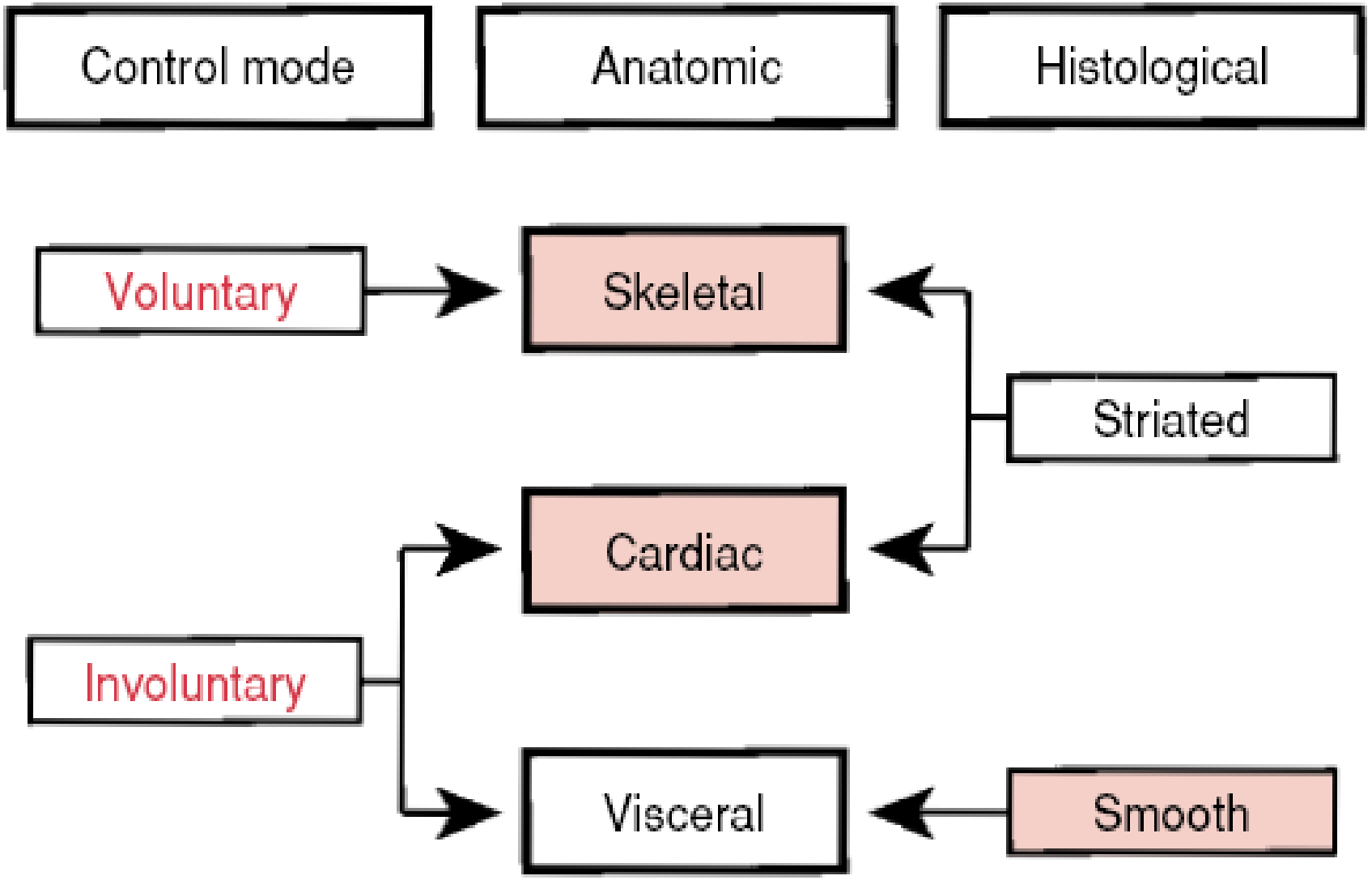
1. Voluntary Muscle

- Skeletal muscle (CNS, somatic neurons).

2. Involuntary muscle

- Cardiac muscle (Intrinsic + extrinsic factors, ANS + hormonal)
- Smooth muscle (Intrinsic + extrinsic factors, ANS + hormonal)

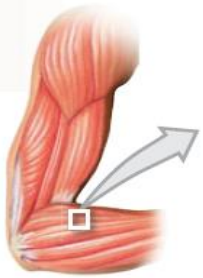
Classification of muscle…..

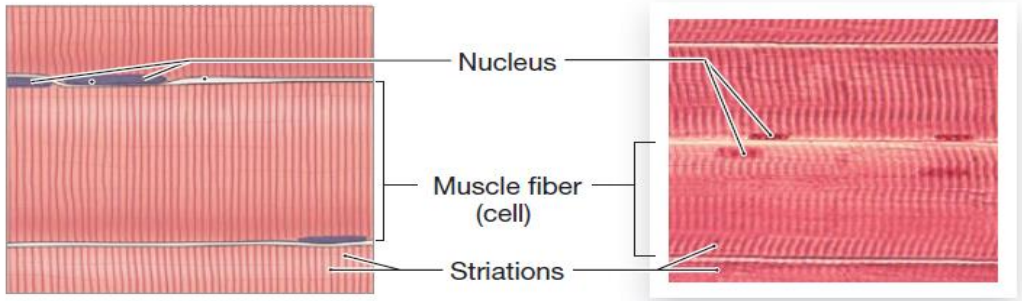


Classification….

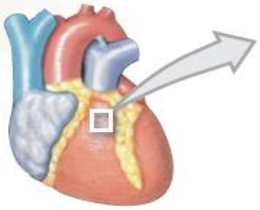
THE THREE TYPES OF MUSCLES

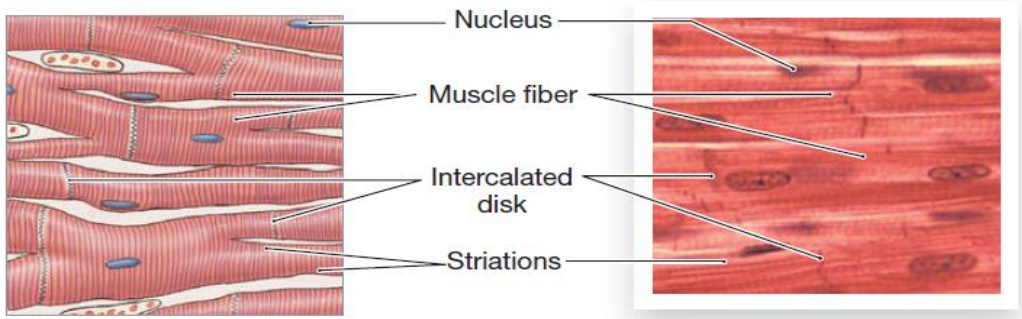
(a) Skeletal muscle fibers are large, multinucleate cells that appear striped or striated under the microscope.



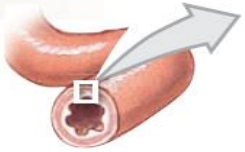


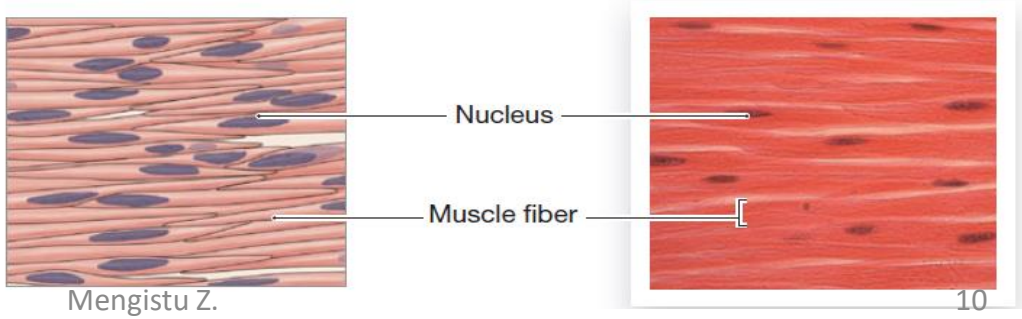
(b) Cardiac muscle fibers are also striated but they are smaller, branched, and uninucleate. Cells are joined in series by junctions called intercalated disks.





(c) Smooth muscle fibers are small and lack striations.





Classification…..

- The human body has three types of muscle tissue:
  - ✓ **skeletal muscle, cardiac muscle and smooth muscle.**

❖ **Skeletal Muscles:** **most** are attached to the bones of the skeleton, enabling these muscles to control body movement.

- Skeletal muscles are unique in that they contract only in response to a signal from a somatic motor neuron.
- They cannot initiate their own contraction, and their contraction is not influenced directly by hormones.

❖ **Cardiac muscle** {*kardia,* heart} is found only in the heart and moves blood through the circulatory system.

NB: Skeletal and cardiac muscles are classified as **striated muscles** {*stria,* groove} because of their alternating light and dark bands seen under the light microscope

Classification….

- **Smooth muscle:** is the primary muscle of internal organs and tubes, such as the stomach, urinary bladder, and blood vessels.

❖ Its primary function is to influence the movement of material into, out of, and within the body.

- An example is the passage of food through the gastrointestinal tract.

- Viewed under the microscope, smooth muscle lacks the obvious cross-bands of striated muscles.
- Its lack of banding results from the less organized arrangement of contractile fibers within the muscle cells.

3.Types of Muscles

3.1. Skeletal muscle

- Skeletal muscles make up the bulk of muscle in the body and constitute about 40% of total body weight.
- They position and move the skeleton, as their name suggests.
- Skeletal muscles are usually attached to bones by **tendons** made of collagen.
- The **origin** of a muscle is the end of the muscle that is attached closest to the trunk or to the more stationary bone.
- The **insertion** of the muscle is the more *distal* or more mobile attachment.
- When the bones attached to a muscle are connected by a flexible joint, contraction of the muscle moves the skeleton.
- The muscle is called a **flexor** if the centers of the connected bones are brought closer together when the muscle contracts, and the movement is called *flexion*.
- The muscle is called an **extensor** if the bones move away from each other when the muscle contracts, and the movement is called *extension*.

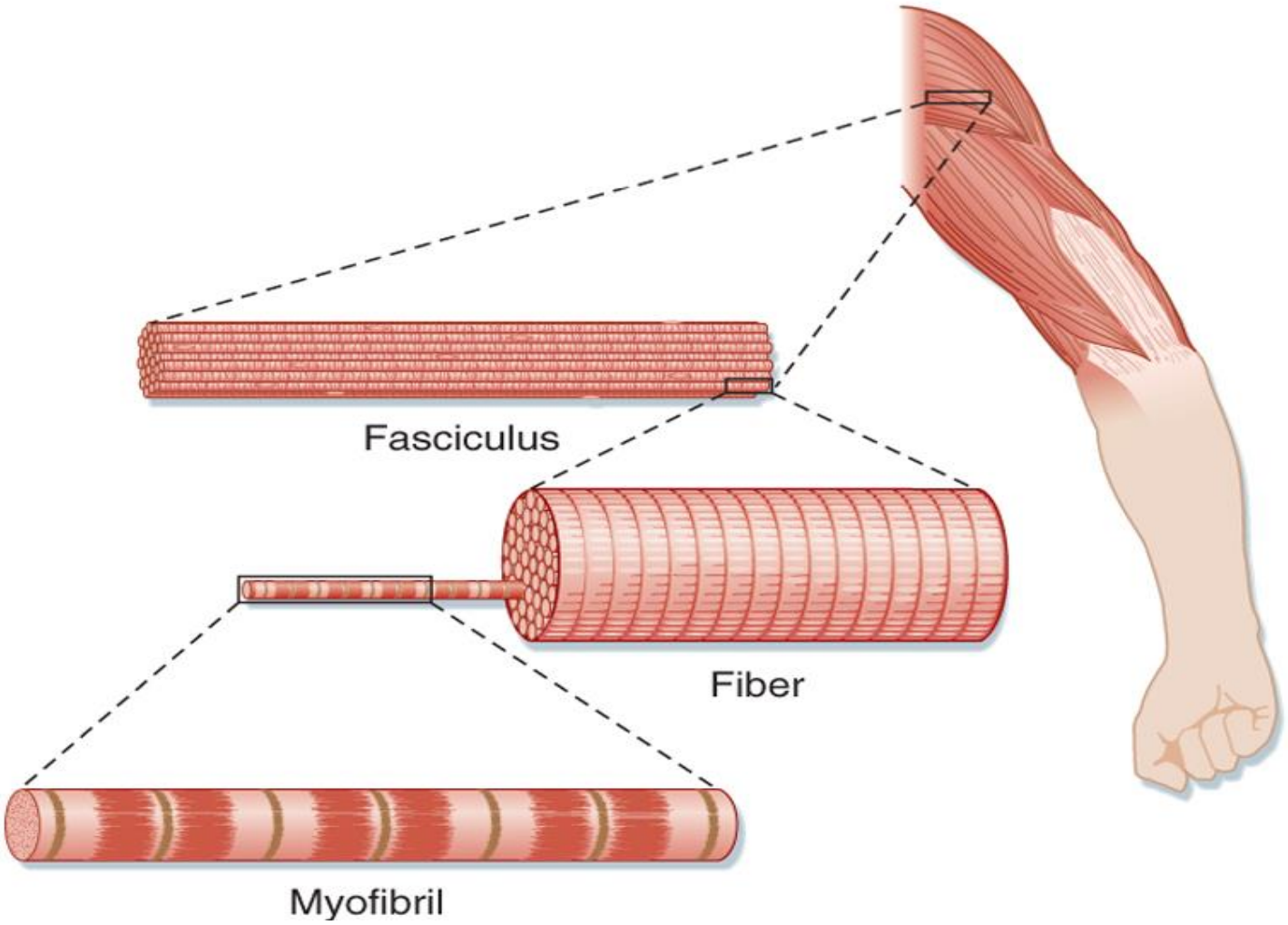
Skeletal Muscle….

- Does not contract in the absence of nervous stimulation, lacks anatomic and functional connections between individual muscle fibers, and is generally under voluntary control.

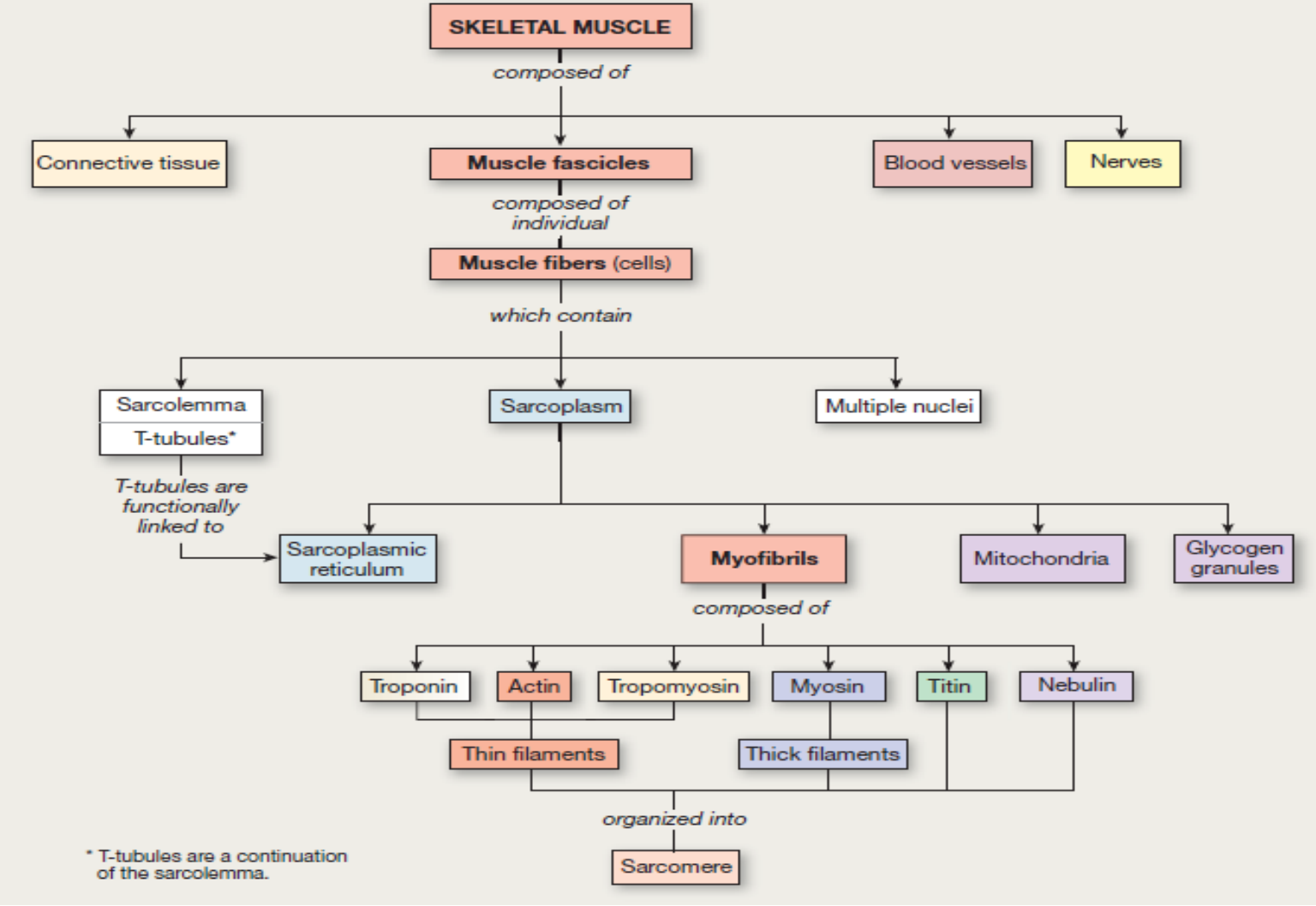
- Skeletal muscle is made up of individual muscle fibers that are the "building blocks" of the muscular system in the same sense that the neurons are the building blocks of the nervous system.
- Each muscle fiber is a single cell that is multinucleated, long, cylindrical, and surrounded by a cell membrane, the **sarcolemma.**

- The muscle fibers are made up of myofibrils, which are divisible into individual filaments.
- These myofilaments contain several proteins that together make up the contractile machinery of the skeletal muscle.
- Depends on the proteins **myosin-II, actin, tropomyosin & troponin.**

Skeletal Muscle Structure



Skeletal Muscle……



Structural organizations of skeletal muscle

Skeletal muscle…

- **Skeletal Muscles Are Composed of Muscle Fibers:** Muscles function together as a unit.
- A skeletal muscle is a collection of muscle cells, or **muscle fibers**, just as a nerve is a collection of neurons.
- Skeletal muscle fibers are the largest cells in the body, created by the fusion of many individual embryonic muscle cells.

- Committed stem cells called **satellite cells** lie just outside the muscle fiber membrane.
- Satellite cells activate and differentiate into muscle when needed for muscle growth and repair.

Structural arrangement and contractile unit of skeletal muscle

Muscle

↓ *epimysium*

Fasciculus (*20 muscle fibers*)

↓ *perimysium*

Muscle fiber (ɵ=*10-100 µm, L=30cm, multinucleated*)

↓ *endomysium*

Myofibril (ɵ= *1-2µm, longitudinal, Sarcomere, 75% muscle vol., Z-line, α-actinin,*)

Myofilaments

Thick filaments
1500 molecules, myosin

Thin filaments
3000 molecules, actin

Structure of Skeletal muscle…..

- **Terminologies**

1. Epimysium: a connective tissue which ensheaths the entire muscle.
2. Perimysium: a connective tissue that ensheaths the fascicles
3. Endomysium: a sheath that covers each muscle fiber.

NB: Each one is the continuation of the other.

4.Sarcoplasmic Reticulum (SR):a tubular network divides the individual skeletal muscle fiber into myofibrils.

✓ Function as Ca+2 stores and regulates excitation contraction coupling.

5. Sarcolemma: a true plasma membrane of skeletal muscle fiber.
6. α-actinin: a protein that connects **actin to the z-line**.
7. Myoplasm: cytoplasm of the muscle cell.

Anatomy of Skeletal Muscle……

8. Myosin: the thick contractile protein.

9. Actin: the thin contractile protein.

10. Dystropin: actin binding protein linking transmembrane protein

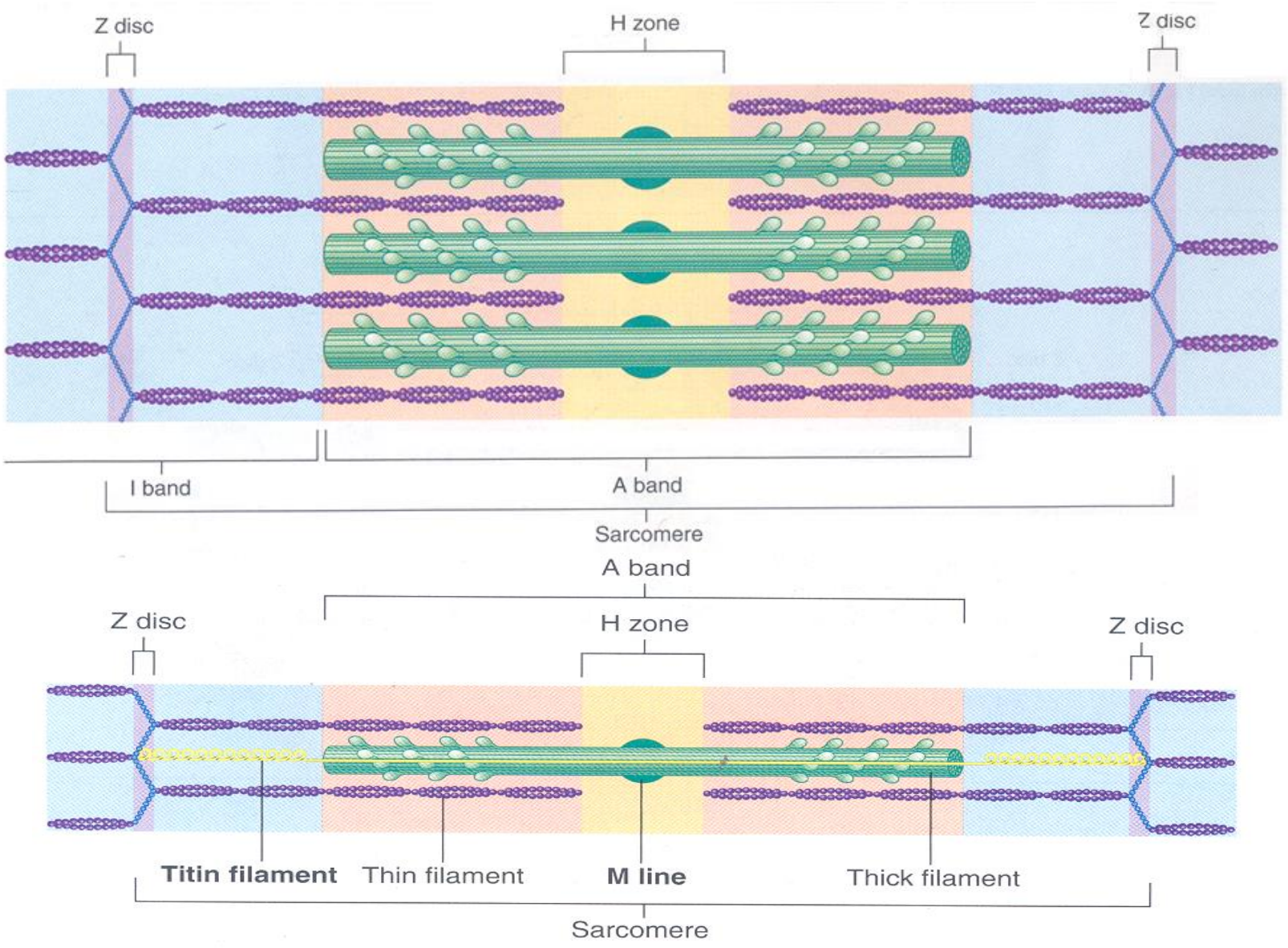
11. Titin: tethers myosin to z lines, serves as a scaffold for sarcomere.

- ✓prevents overstretching of sarcomere, Stretch sensor.
- ✓Responsible for passive elasticity of muscles.
- ✓ Composed of 244 individually folded **protein.**

12. Nebulin: a template protein, determines the precise size of actin.

- ***The main intracellular structures in striated muscles are myofibrils {myo-, muscle}, highly organized bundles of contractile and elastic proteins that carry out the work of contraction.***

Geometrical orientation of the contractile elements



Components of Muscle

- **Functional unit is sarcomere**

a. It is the distance between two z-lines.

b. Responsible for the striated appearance.

c. Dimensions: The resting length of a sarcomere is 2-2.2µm.

▪**SR – highly organized Structure.**

- - contain high concentration of calcium ions (Ca^{2+}).

- a. It is an internal tubular structure that runs between the myofibrils.
- b. It is closed at both ends.
- c. It is not continuous with the sarcolemma.
- **d. *Functions:***
- i. Stores Ca^{2+} in the terminal cisternae (lateral sacs, 1*calsequestrin* = 43 Ca^{2+})
- ii. Uptake and release of Ca^{2+}

NB: Calsequestrin is sarcoplasmic protein that binds Calcium.

Molecular geometry

A-Band (A= Anisotropisch)*

a. The darker area in the center of the sarcomere.

b. It is due to the orderly arrangement of thick filaments.

c. Thin filaments may extend into the A-band.

❖ **A –band** – actin and myosin filaments overlap for some distance

H-Band (H = Hensen's disc, ?Hell*?)

a. Contains only myosin tails (no myosin heads/no cross-bridges)

b. There are no thin filaments

c. When the muscle is relaxed

NB: * Germanic words

Molecular geometry…..

- **M-line (M= Mittelmembran)**)*

a. Site of the reversal polarity of the myosin molecules in each of the thick filaments.

b. It vertically bisects the H-Band

c. It contains 2 important proteins:

- Myomesin: a structural protein that links neighboring thick filaments
- Creatinine Phosphokinase: an enzyme that maintains adequate ATP conc. in working muscle fibers.

Molecular geometry….

I-Band (I= Isotropisch))*

a. The lighter area on either side of the z-lines.

b. Each sarcomere contain half of the two I-bands.

c. Thin filaments

Z-Line/Disc (Z = Zwischenscheibe))*

a. Dense line in the center of each light band.
b. Separates one sarcomere from the next.
c. It is the attachment site for the thin filaments.

3.1. 1. Molecular mechanisms of muscle contraction

❑ Sliding-Filament Model

- This model theorizes that sliding of actin inward to myosin initiated by the cross-bridge from myosin to actin filaments.
- In the contracted state, the actin filaments have been pulled inward among the myosin filaments, so their ends overlap one another to their maximum extent.

- **The force generated by interaction of the cross-bridge from the myosin filaments with the actin filaments causes the actin filaments to slide inward among the myosin filaments.**

- To trigger the interaction of Actin and Myosin; AP travelling along muscle fibers and causes SR to release Ca+2; Ca+2 activate the force of interaction between Actin and Myosin.

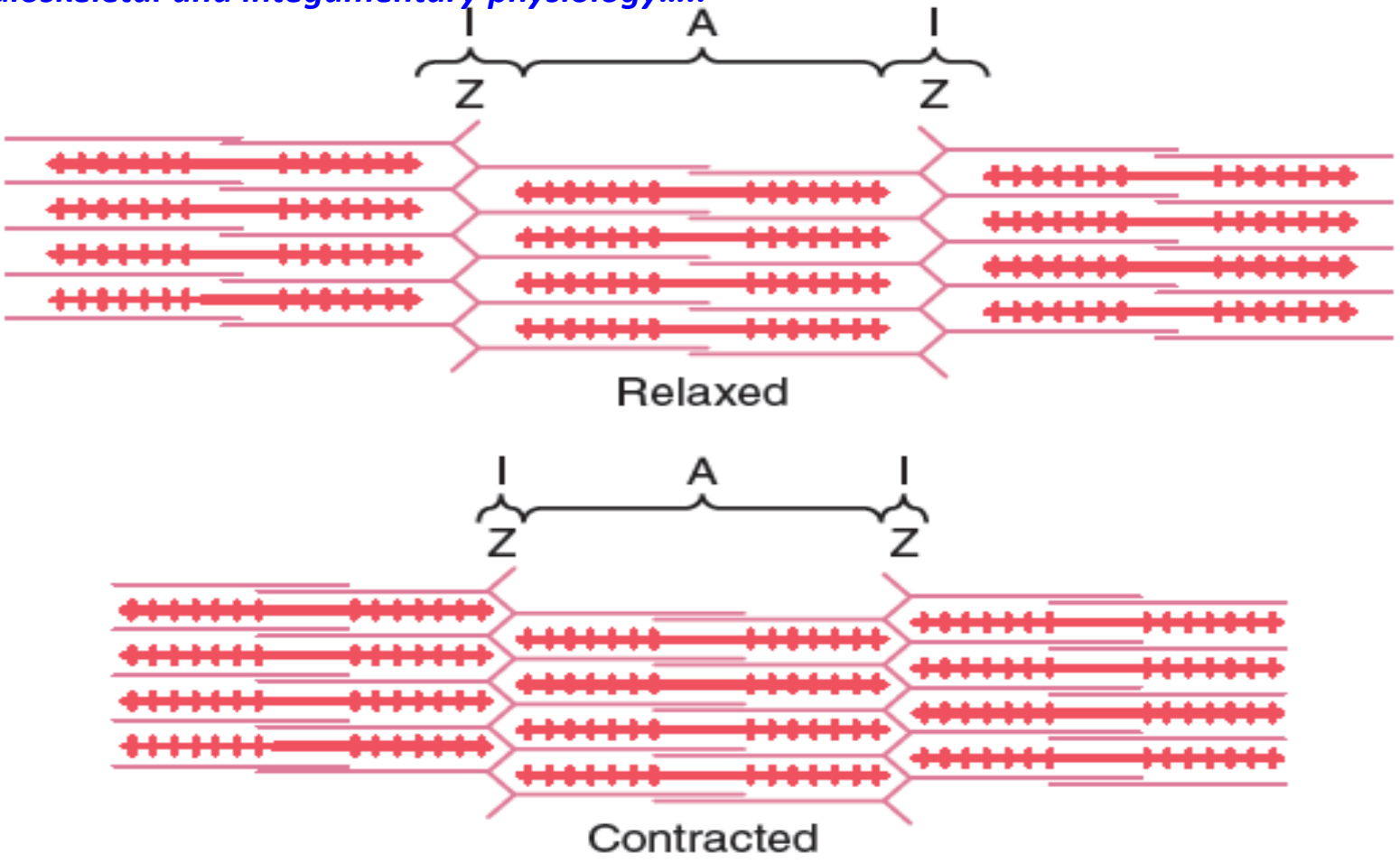


Figure 6-5. Relaxed and contracted states of a myofibril showing (*top*) sliding of the actin filaments (*pink*) into the spaces between the myosin filaments (*red*) and (*bottom*) pulling of the Z membranes toward each other.

I. Regulatory Role of Troponin-Tropomyosin System

a. Resting state

- Troponin I and Tropomyosin covers the sites where myosin heads bind to actin.

  (At rest: interaction of thick and thin filaments is inhibited).

- ❑ Troponin-Tropomyosin complex is called "Relaxing-Protein" because it inhibits the interaction between myosin and actin.

b. Contractile state

- The invading action potential to T-Tubule → Ca^{2+} released from SR → binds to troponin C → binding of troponin I to actin is weakened → tropomyosin moves laterally → uncovers binding sites for myosin heads → contraction *(in the presence of ATP).*

- Seven myosin-binding sites are uncovered for each molecule of **troponin that binds a Ca^{2+}.**

II. Regulatory action of calcium

- 2 tubular networks (Sarcotubular system) that are involve with Ca^{2+}

1. Transverse Tubule (T-tube)

a. It is an invagination of the surface of the muscle membrane (sarcolemma).

b. It is found at the junction of A-band and I-band.

c. One end of the tube is open to the extracellular space, but it other end is closed.

d. **Function:** Rapid transmission of the AP from the cell membrane to all the fibers on the muscle.

III. Regulation of ATP

a. When Actin binds with myosin: ATP + Ca^{2+} → CONRACTION

b. When Actin binds with myosin: ATP - Ca^{2+} → RELAXATION

c. ATP is also needed for relaxation.

d. 3 ATP molecules are needed:

i. For the formation of the actin-myosin complex

ii. For the initiation of relaxation.

iii. To pump out Ca^{2+} from the sarcoplasm to sequester it into **SR** (Ca^{2+} - Mg^{2+} pump/**SERCA**).

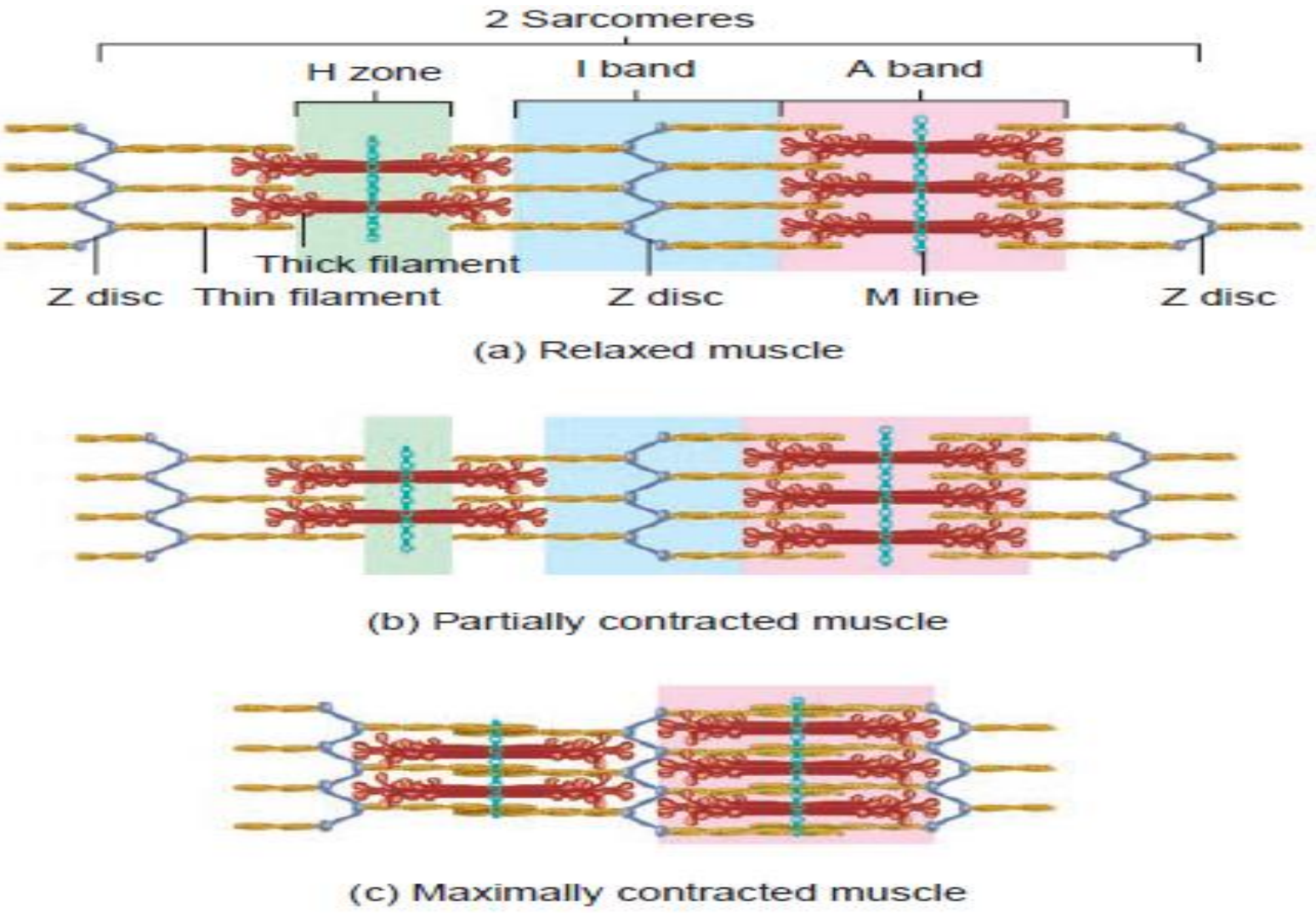
e. In the absence of Ca^{2+} ATP is not hydrolyzed.

❑ During muscular contraction

- There is NO CHANGE in length of either the thick or the thin filaments.
- Z-line gets considerably darker.

- There is shortening of the sarcomere.
- A decrease of **I-band** *and* **H zone**.
- **A-band** remains **κ**.

NB: The length of thick & thin filaments is identical in a neonate & adult muscle.



- **During muscle contractions, thin filaments move toward the M line of each sarcomere.**

Contractile and Regulatory proteins

A. Contractile proteins

1. Actin/thin filaments/: composed from Actin, Tropomyosin Troponin.

•The back bone for actin filament is F- Actin (composed from G-actin)

a. Globular proteins

i. Actins: Globular –Actin (G-actin) & Fibrillar- Actin (F-actin)

ii. Troponin

b. Non-Globular proteins: Tropomyosin

Actin: actin, tropnin and tropomyosin filaments

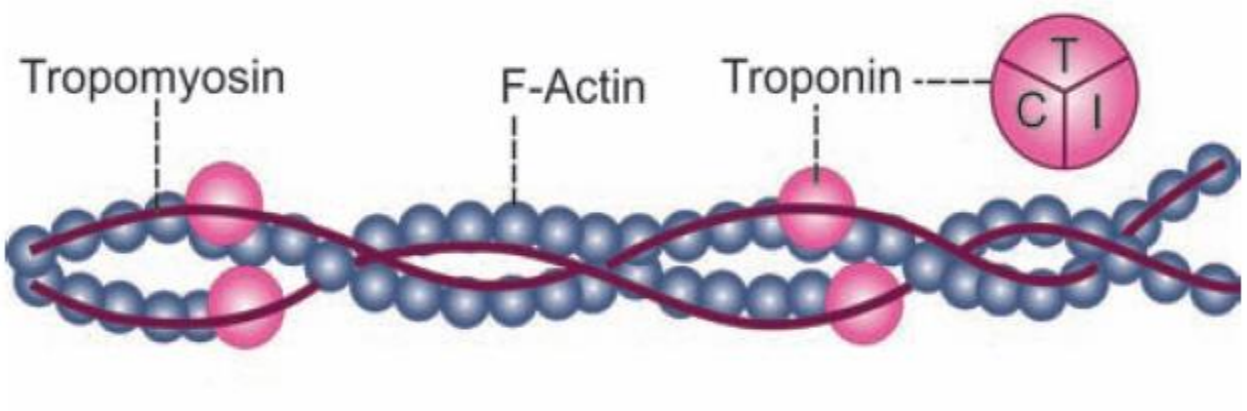
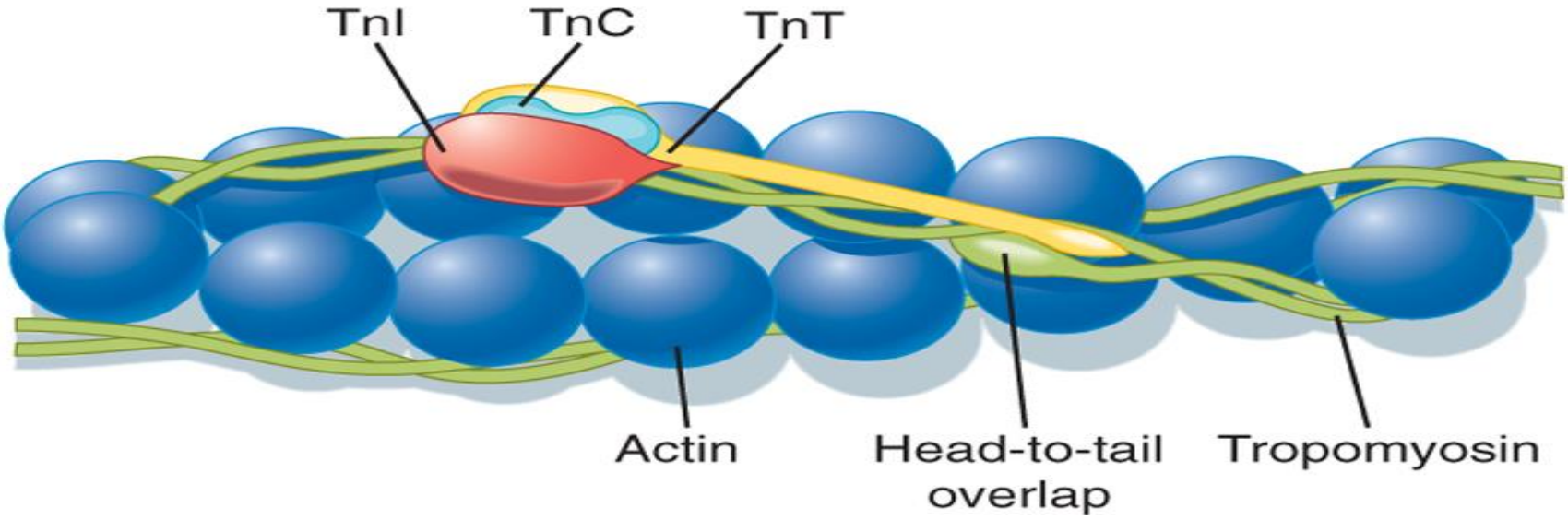
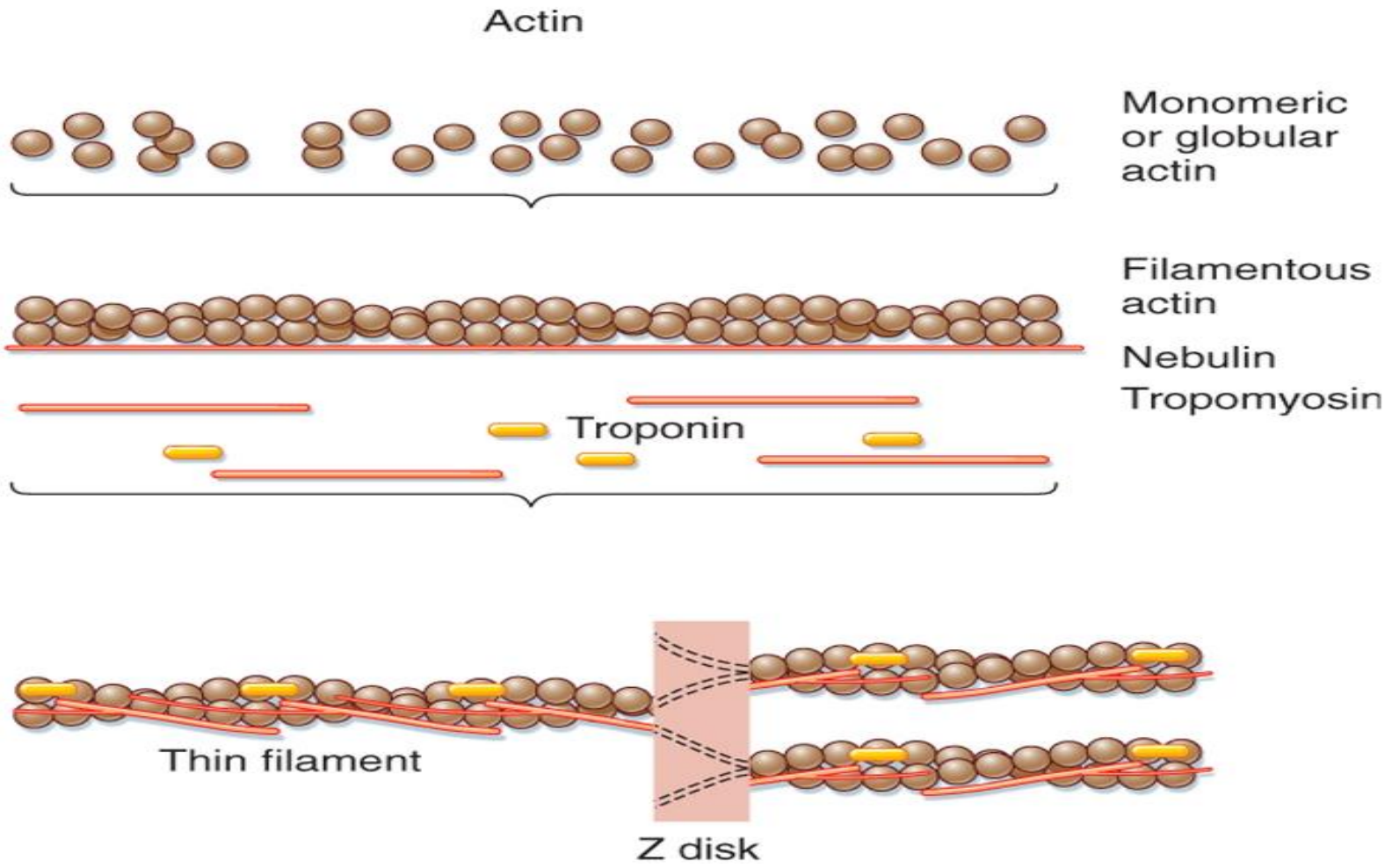


FIGURE 29.8: Part of actin filament.
Troponin has three subunits, T, C and I.





Actin Filaments

2. Thick Filament/ myosin/ (an actin-binding protein).

a. Dimensions: has a width of 11-18 nm & Length of 1.6 µm.

b. Composition of Myosin: has

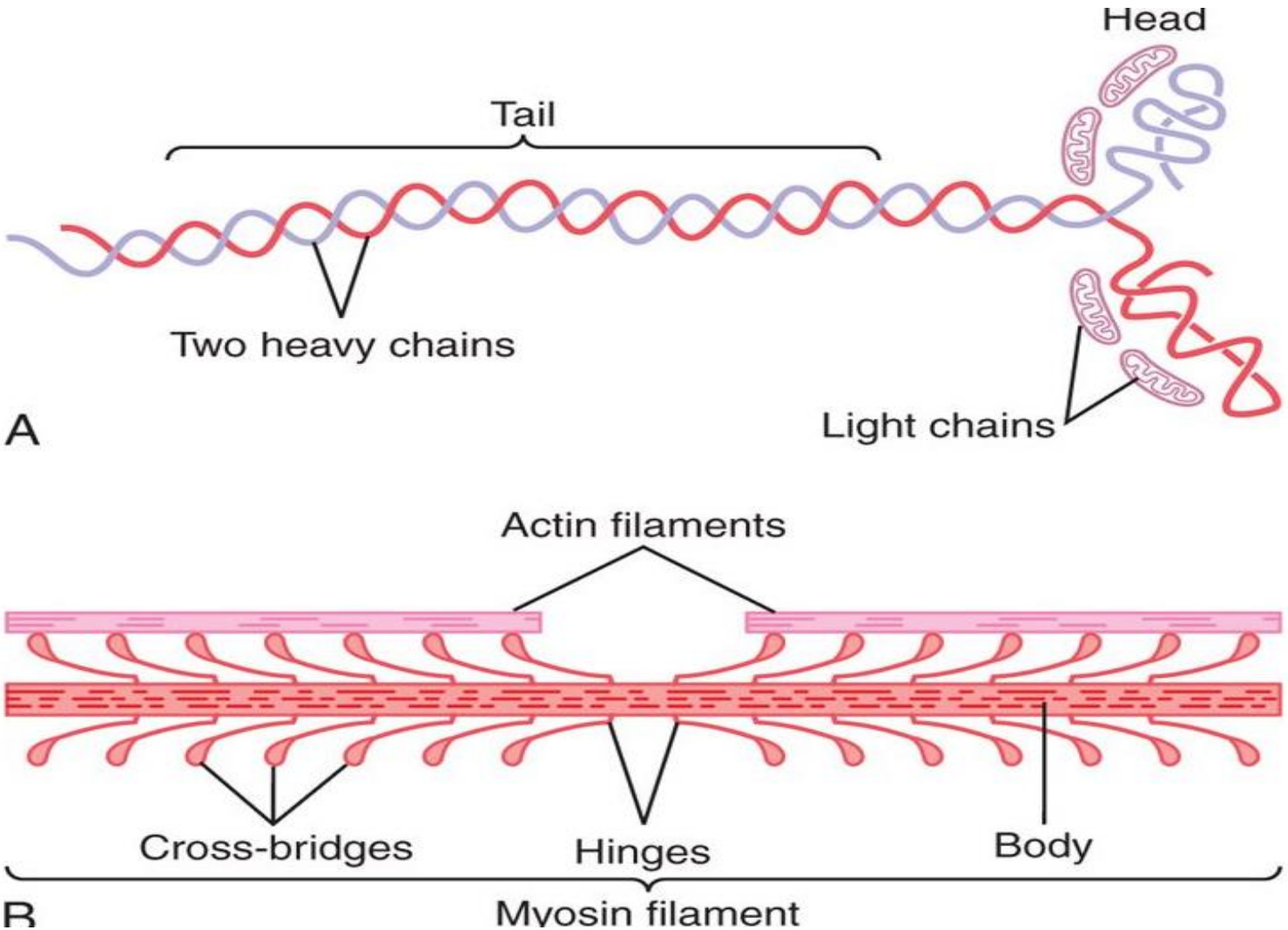
2 heavy chains

4 light chains

- 2 heads: Myosin head (cross-bridge) which is an actin-binding site & ATP-binding site (ATPase) where Hydrolyzes ATP.

- 1 long tail : form core of the thick filament.

- Composition of Myosin/thick/ filament



B. Regulatory proteins

i. Tropomyosin

a. A rod-shaped molecule stretched along each strand of thin filament.

b. 1tropomyosin molecule covers seven actin monomers in an actin filament.

c. It blocks the binding sites of myosin on actin; at rest it lie on the top of the active sites of the actin, so no attraction between actin and myosin;

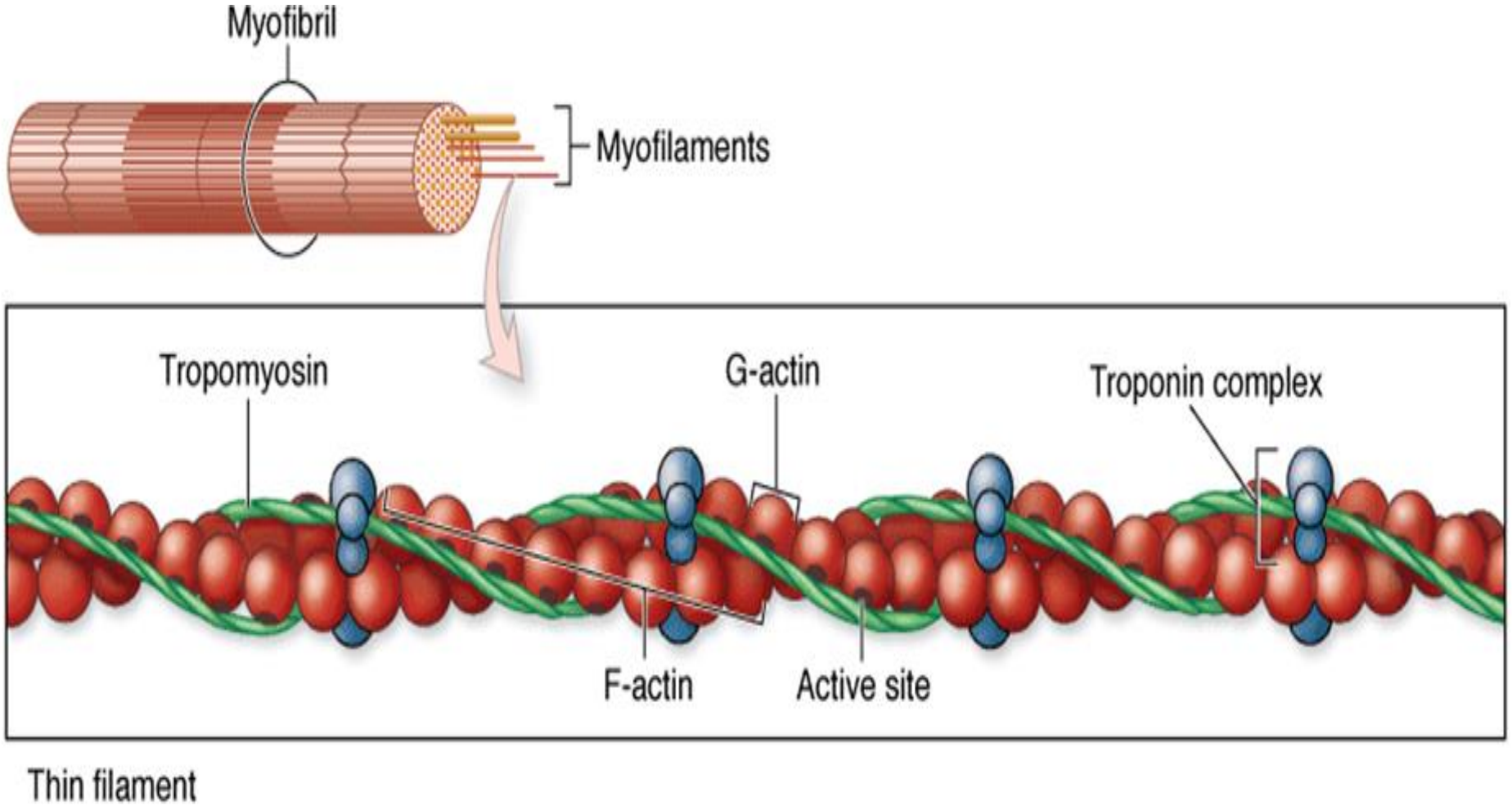
ii. Troponins

~ Small globular units located at intervals along the tropomyosin molecules.

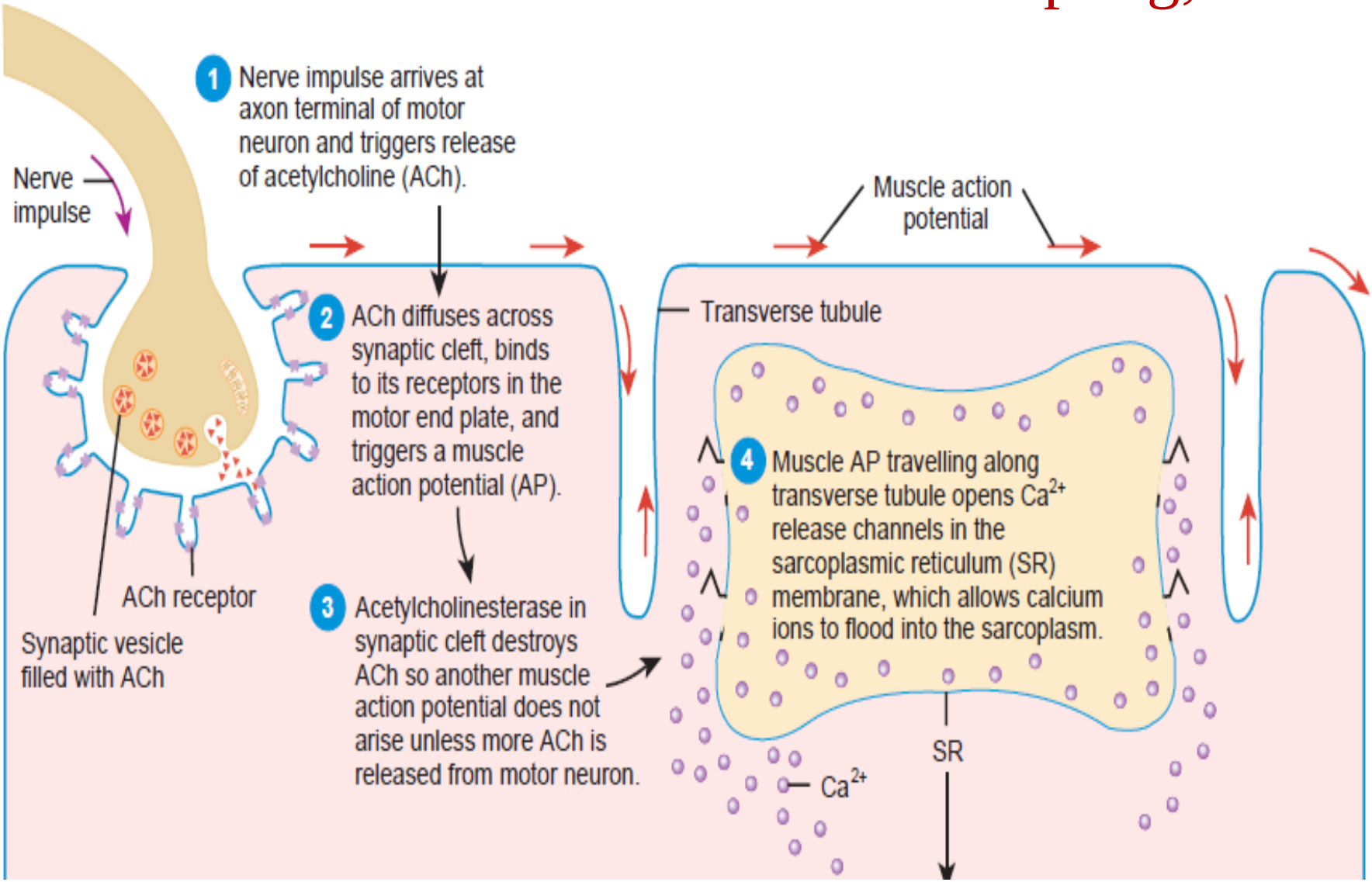
a. Troponin T: it binds other troponin components to tropomyosin.

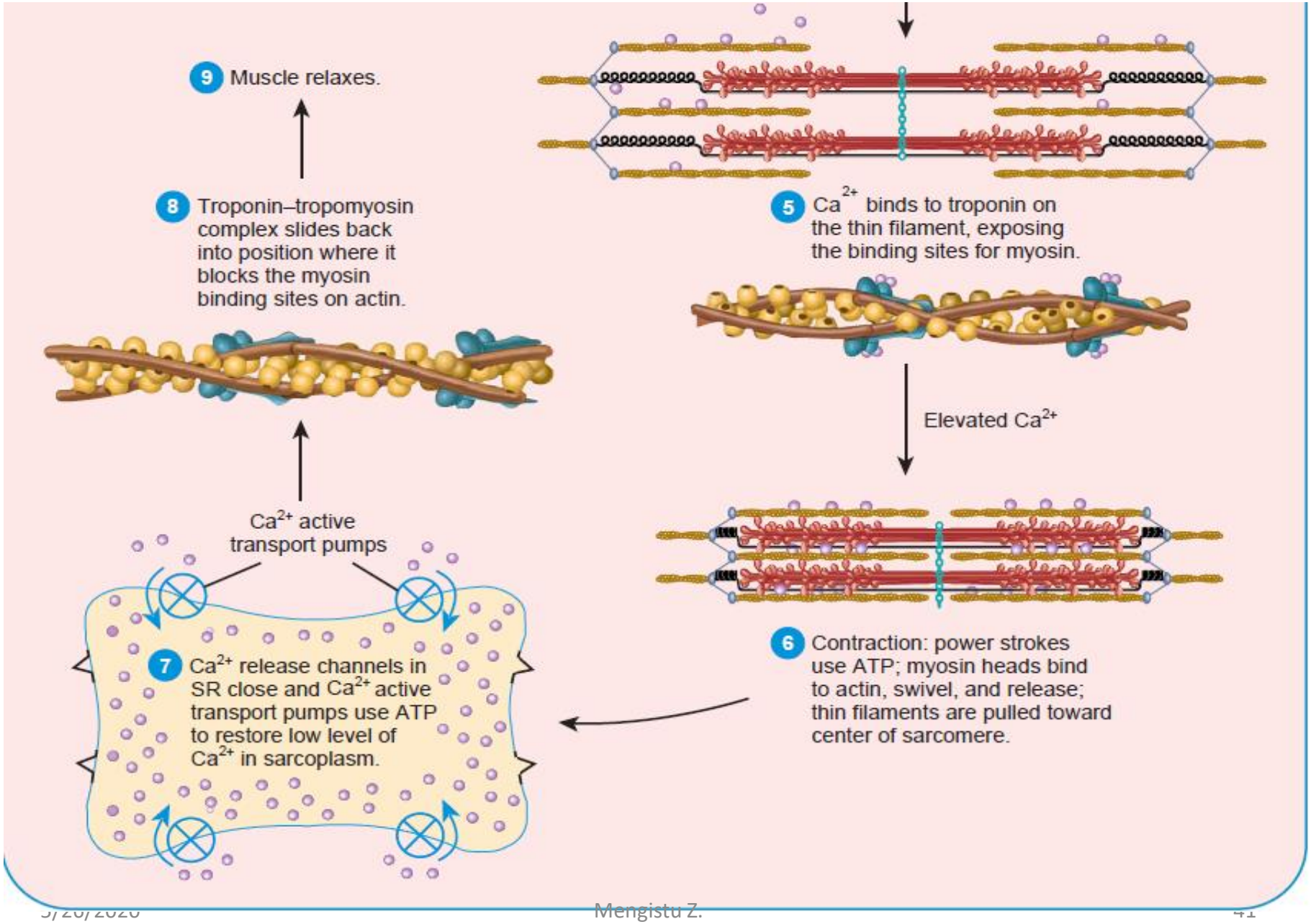
b. Troponin I: inhibits the interaction of myosin with actin.

c. Troponin C: it has the binding site for Ca^{2+} that initiates contraction.

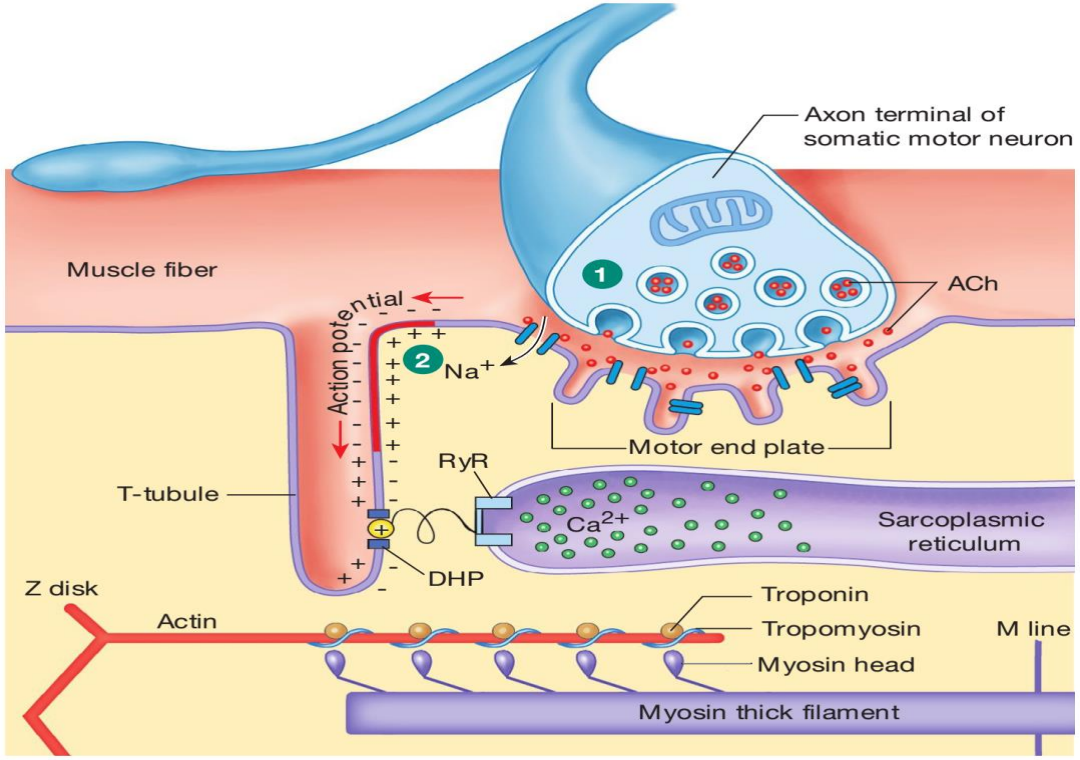

Myofibril
Myofilaments
Tropomyosin
G-actin
Troponin complex
F-actin
Active site
Thin filament

3.1.2. Muscle excitation contraction coupling;NMJ




9 Muscle relaxes.
8 Troponin–tropomyosin complex slides back into position where it blocks the myosin binding sites on actin.
5 Ca^{2+} binds to troponin on the thin filament, exposing the binding sites for myosin.
Elevated Ca^{2+}
Ca^{2+} active transport pumps
7 Ca^{2+} release channels in SR close and Ca^{2+} active transport pumps use ATP to restore low level of Ca^{2+} in sarcoplasm.
6 Contraction: power strokes use ATP; myosin heads bind to actin, swivel, and release; thin filaments are pulled toward center of sarcomere.

Summary, Excitation-Contraction Coupling…



1. Somatic motor neuron releases ACh at neuromuscular junction.
2. Net entry of Na^+ through ACh receptor-channel initiates a muscle action potential.
3. Action potential in t-tubule alters conformation of DHP receptor.
4. DHP receptor opens RyR Ca^{2+} release channels in sarcoplasmic reticulum and Ca^{2+} enters cytoplasm.
5. Ca^{2+} binds to troponin, allowing actin-myosin binding.
6. Myosin heads execute power stroke.
7. Actin filament slides toward center of sarcomere.

KEY
DHP = dihydropyridine L-type calcium channel
RyR = ryanodine receptor-channel

Excitation- contraction; Neuromuscular junction/NMJ/

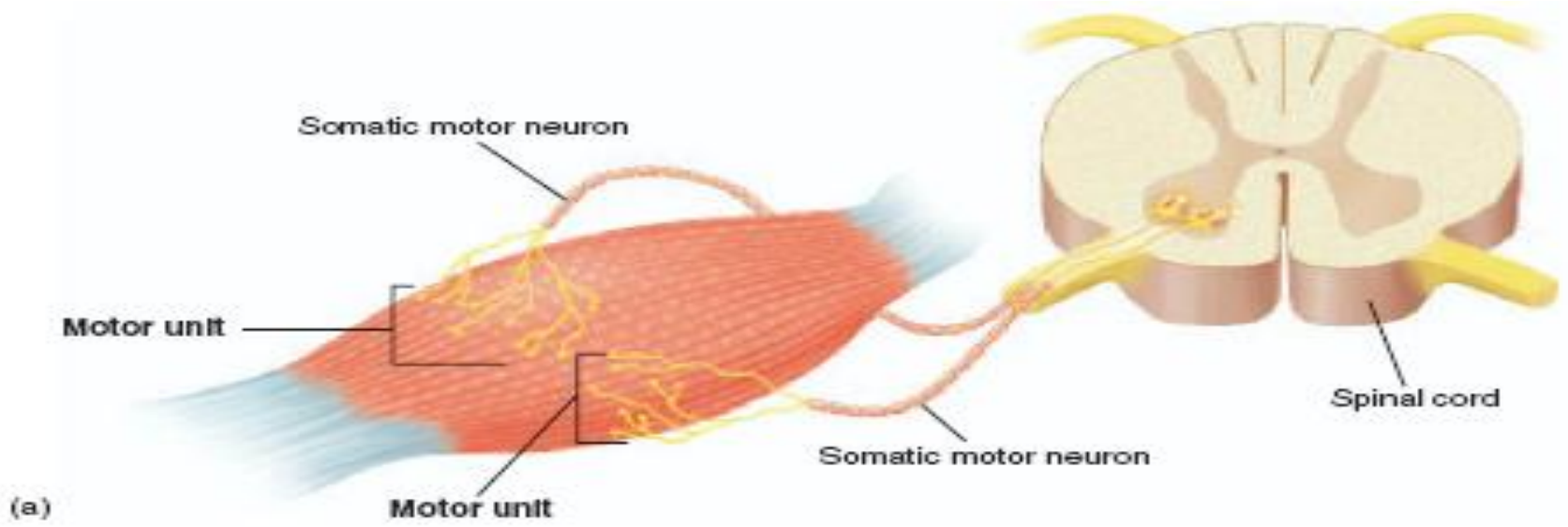
Def.≈ Neuromuscular junction is the junction between terminal branch of the nerve fiber and muscle fiber.

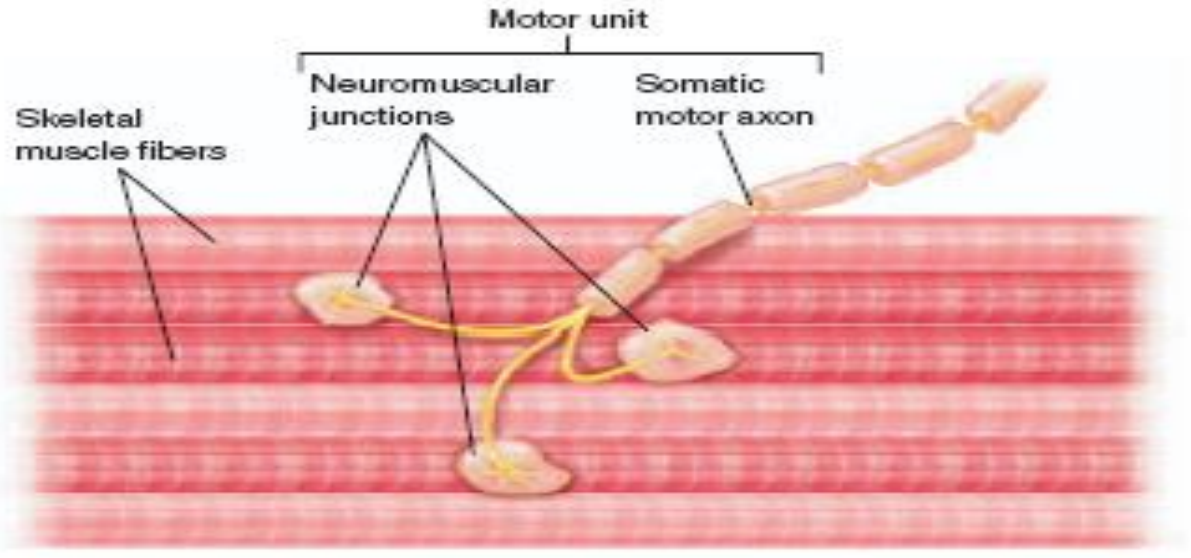
- Neuro muscular junction is ~ a synaptic transmission between an α-motor neuron and skeletal muscle fiber.

- **Motor Unit:** Muscle fibers innervated by a single motor neuron is called a muscle unit, and that together with its motor neuron is called a motor unit.

- Def.~ a synaptic transmission between an α-motor neuron and skeletal muscle fiber is called neuromuscular transmission.

Motor Unit and NMJ





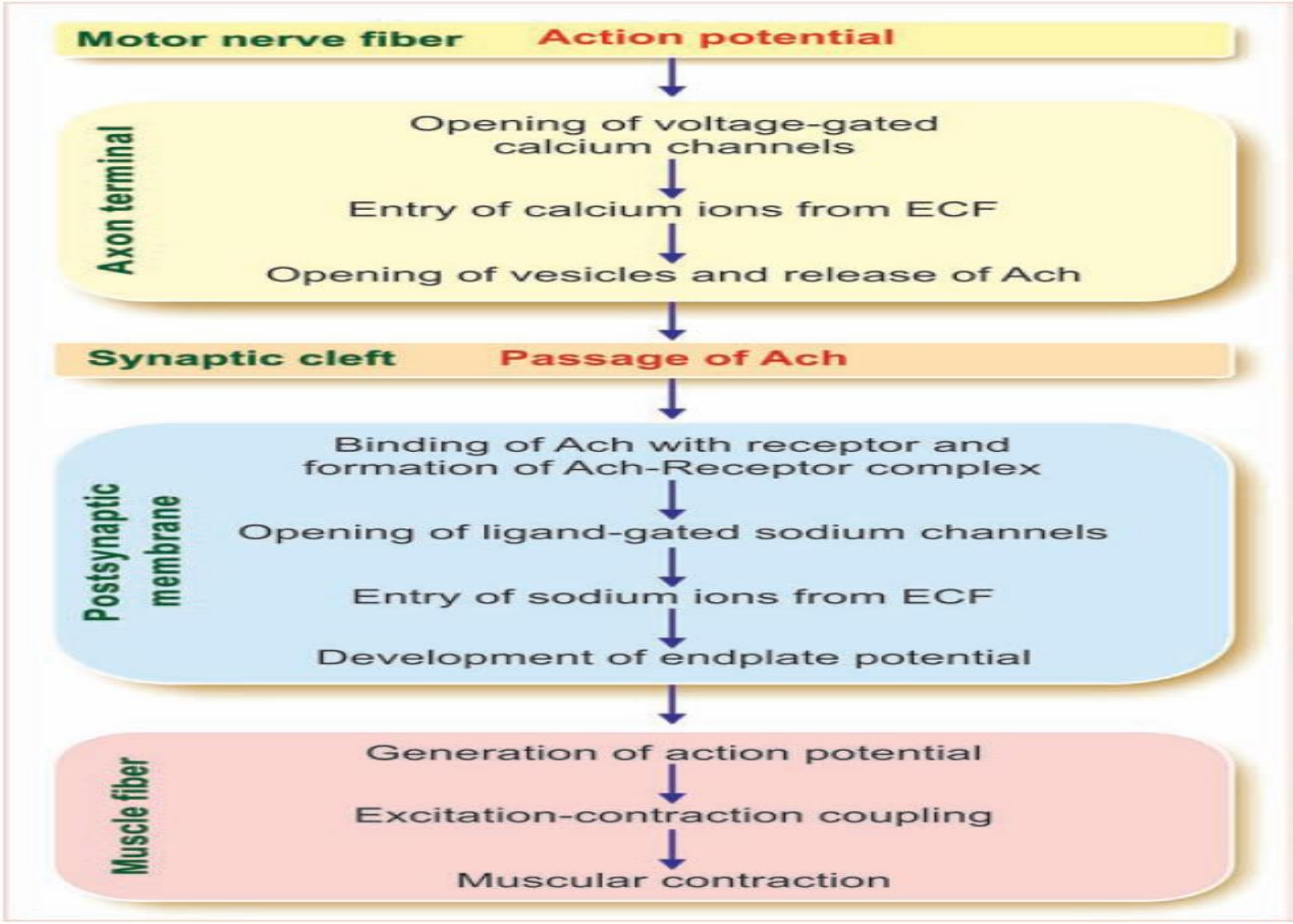
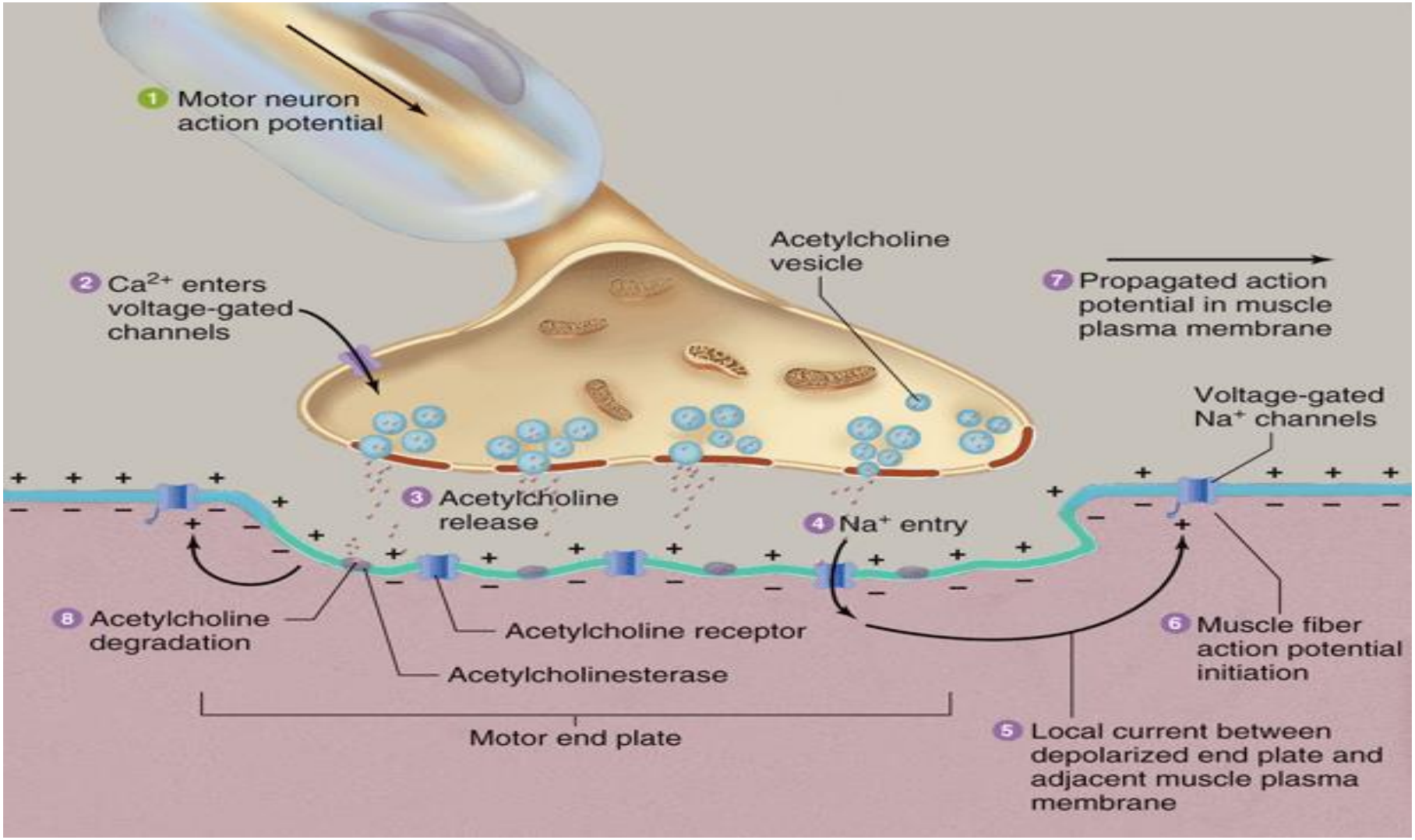
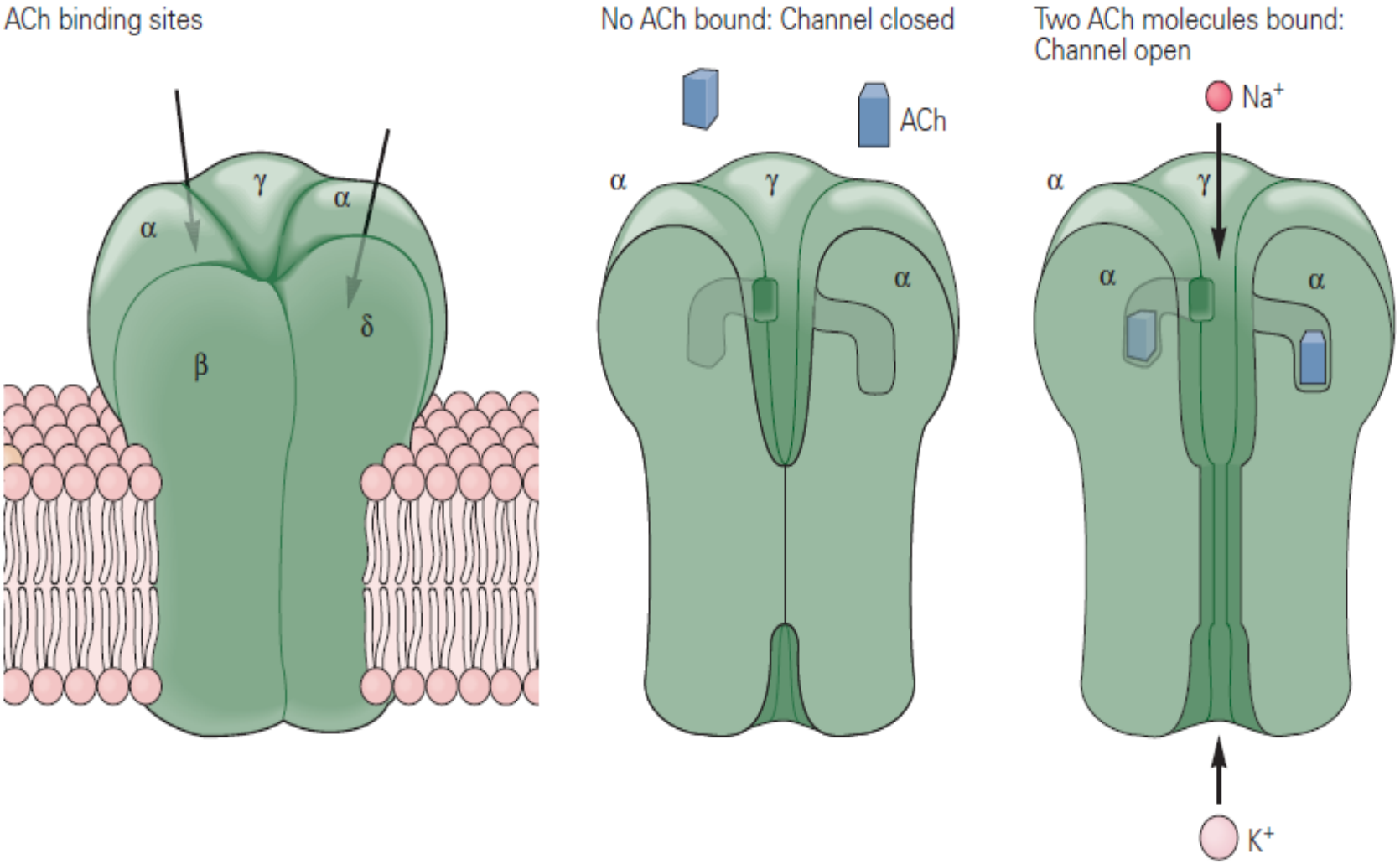


FIGURE 32.3: Sequence of events during neuromuscular transmission. Ach = Acetylcholine, ECF = Extracellular fluid.

Neuromuscular junction/NMJ/




ACh binding sites
γ
α
α
δ
β
No ACh bound: Channel closed
ACh
α
γ
α
Two ACh molecules bound:
Channel open
Na+
α
γ
α
α
K+

*n*AchR

Actions of NMJ

- 2α subunits occupied → conformational change → opening of the gate → permeability to Na^+, K^+.
- Na^+ enters, K^+ leaves the cell → cell depolarizes→ EPP.

- Electrochemical gradient for Na^+ > electrochemical gradient for K^+
- The amount of Na^+ entering the cell > the amount of K^+ leaving the cell.

Endplate Potential/EPP

i. A graded response on the end plate region of the muscle with the magnitude of depolarization proportional to the number of open acetylcholine channels (Ach R).

ii. Is Transient, short lived action; (**b/c** Ach is hydrolyzed to form choline and acetate within short time interval).

iii. Has an Amplitude of **>50mV** (mostly it reaches up to 70mV).

iv. Has no voltage-gated Na^+ and K^+ channels at the endplate region. (VG Na^+, K^+ channels are located on the muscle membrane contiguous to the endplate).

Excitation contraction coupling; NMJ

Discharge of motor neuron

↓

Release of Ach at motor endplate

↓

Binding of Ach to nAchR

↓

↑gNa^+ and gK^+ in endplate membrane

↓

Generation of EPP

↓

Generation of AP in muscle fibers

↓

Inward spread of depolarization along T-tubules

↓

Release of Ca^{2+} from terminal cisterns of SR and diffusion to thick and thin filaments

↓

Binding of Ca^{2+} to troponin C, uncovering myosin-binding sites on actin

↓

Formation of cross-linkages between actin and myosin and sliding of thin on thick filaments, producing movement

Reading

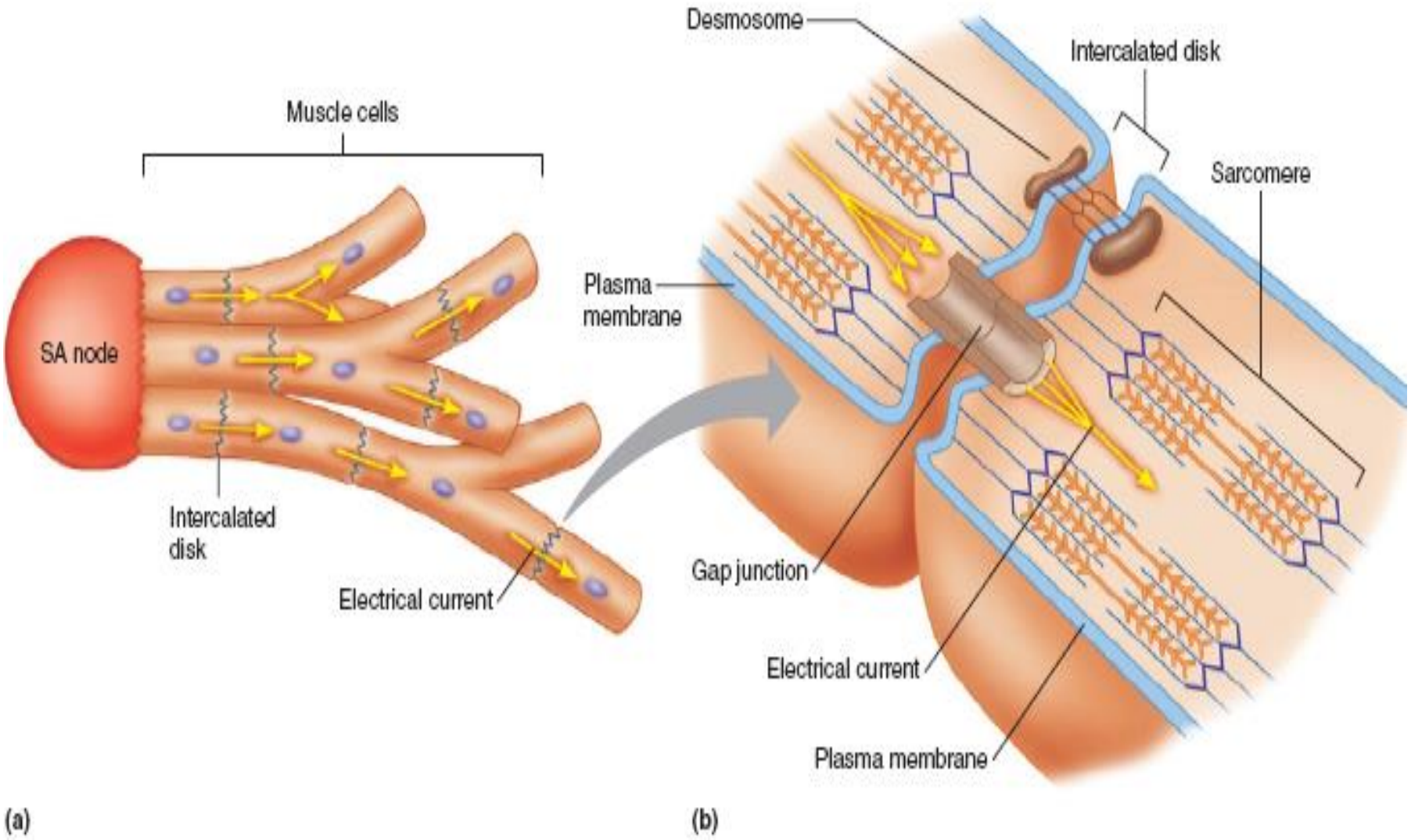
- Muscle energetics
- Muscle contraction kinetics (types of contraction, summation, tetanus and fatigue)
- Types of skeletal muscle fibers

3.2. Cardiac Muscle

- Has cross-striations and functionally syncytial.
- Modulated via the autonomic nervous system, and it can contract rhythmically in the absence of external innervation owing to the presence of pacemaker cells that discharge spontaneously.
- The heart is composed of three major types of cardiac muscle: atrial, ventricular, and specialized excitatory and conductive muscle fibers.

- Cardiac muscle fibers have the same arrangement of;
  - ✓ **Actin and myosin,**
  - ✓ the same band zones and Z discs as skeletal muscle fibers.
- **There is an intercalated discs in** cardiac muscle fibers.
  - ✓ The discs contain desmosomes, which hold the fibers together,
  - ✓ Gap junctions, which allow muscle **AP** to spread from one cardiac muscle fiber to another

Cardiac muscles cont'd



Reading

- **Skeletal muscle vs cardiac muscle vs smooth muscle excitation contraction coupling**

NB: Refer CVS Physiology for more detail in cardiac muscle

3.3. Smooth Muscle

- **Smooth muscles found** in the airways, blood vessels, GIT, and hollow organs (bladder, uterus...).
- Sheets or layers of smooth muscle cells are contained in the walls of various organs and tubes in the body, including the blood vessels, stomach, intestines, bladder, airways, uterus, and the penile and clitoral cavernosal sinuses.

- When made to contract, the smooth muscle cells shorten, thereby propelling the luminal contents of the organ, or the cell shortening varies the diameter of a tube to regulate the flow of its contents.
- There are also bundles of smooth muscle cells attached to the hairs of the skin and to the iris and lens of the eye. When these bundles contract, the hairs become erect and the lens of the eye changes shape to focus light on the retina.

Smooth muscle…

- Smooth muscle cells lack the striated banding pattern found in cardiac and skeletal muscle, and they receive neural innervation from the autonomic nervous system.
- In addition, the contractile state of smooth muscle is controlled by hormones, autocrine/paracrine agents, and other local chemical signals.

- Smooth muscle cells also develop tonic and phasic contractions in response to changes in load or length.
- Regardless of the stimulus, smooth muscle cells use cross-bridge cycling between actin and myosin to develop force, and calcium ions (Ca^{2+}) serve to initiate contraction.

Smooth muscle…

- **Sarcoplasmic Reticulum (SR)** is present, but it is less extensive than in skeletal or cardiac muscle.
- smooth muscles contain few mitochondria and depend, to a large extent, on glycolysis for their metabolic needs.
- As in skeletal and cardiac muscle, Ca 2+ plays a prominent role in the initiation of contraction of smooth muscle.

- ❑ No Troponin in smooth muscle; and so prevents Ca 2+ activation via troponin binding.
- Rather, myosin in smooth muscle must be phosphorylated for activation of the myosin ATPase.

- In smooth muscle, Ca 2+ binds to calmodulin, and the resulting complex activates **calmodulin-dependent myosin light chain kinase.**

- **This enzyme catalyzes the phosphorylation of** the myosin light chain **increasing its ATPase activity.**

Smooth Muscle contractile mechanisms

- THE CONTRACTILE MECHANISM In the intact body, the process of smooth muscle cell contraction is regulated principally by receptor and mechanical (stretch) activation of the contractile proteins myosin and actin.

- A change in membrane potential, brought on by the firing of action potentials or by activation of stretch-dependent ion channels in the plasma membrane, can also trigger contraction.

- For contraction to occur, myosin light chain kinase (MLC kinase) must phosphorylate the 20-kDa light chain of myosin, enabling the molecular interaction of myosin with actin.

Smooth muscle contraction…

- Energy released from ATP by myosin ATPase activity results in the cycling of the myosin cross-bridges with actin for contraction.
- Thus contractile activity in smooth muscle is determined primarily by the phosphorylation state of the light chain of myosin—a highly regulated process.
- In some smooth muscle cells, the phosphorylation of the light chain of myosin is maintained at a low level in the absence of external stimuli (i.e., no receptor or mechanical activation).
- This activity results in what is known as smooth muscle tone and its intensity can be varied.

Smooth muscle contraction..

❑ Ca2+-DEPENDENT CONTRACTION OF SMOOTH MUSCLE

- Contraction of smooth muscle is initiated by a Ca2+mediated change in the thick filaments, whereas in striated muscle Ca2+ mediates contraction by changes in the thin filaments.

- In response to specific stimuli in smooth muscle, the intracellular concentration of Ca2+ increases, and this activator Ca2+ combines with the acidic protein calmodulin.
- This complex activates MLC kinase to phosphorylate the light chain of myosin.

Smooth Muscle contraction…

- Cytosolic Ca2+is increased through Ca2+ release from intracellular stores (sarcoplasmic reticulum) as well as entry from the extracellular space through Ca2+ channels (receptor-operated Ca2+ channels).
- Agonists (norepinephrine, angiotensin II, endothelin, etc.) binding to serpentine receptors, coupled to a heterotrimeric G protein, stimulate phospholipase C activity.
- This enzyme is specific for the membrane lipid phosphatidylinositol 4,5-bisphosphate to catalyze the formation of two potent second messengers: inositol trisphosphate (IP3) and diacylglycerol (DG).

- The binding of IP3 to receptors on the sarcoplasmic reticulum results in the release of Ca2+ into the cytosol.
- DG, along with Ca2+, activates protein kinase C (PKC), which phosphorylates specific target proteins.
- There are several isozymes of PKC in smooth muscle, and each has a tissue-specific role (e.g., vascular, uterine, intestinal, etc.)

Smooth Muscle contraction….

- In many cases PKC has contraction-promoting effects such as phosphorylation of L-type Ca2+ channels or other proteins that regulate cross-bridge cycling.

- Phorbol esters, a group of synthetic compounds known to activate PKC, mimic the action of DG and cause contraction of smooth muscle.

- Finally, L-type Ca2+ channels (voltage-operated Ca2+ channels) in the membrane also open in response to membrane depolarization brought on by stretch of the smooth muscle cell.

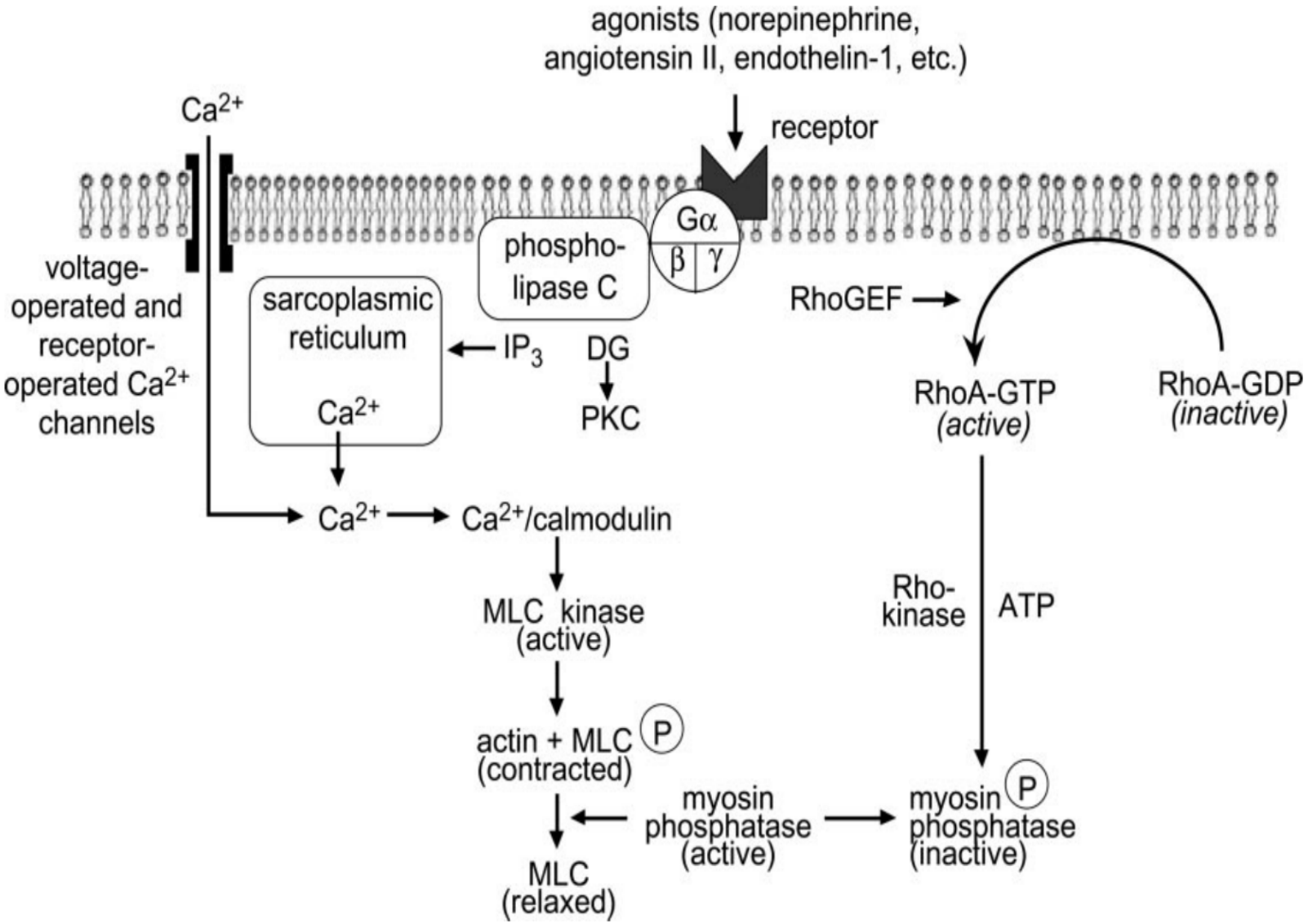
❑ Ca2+ SENSITIZATION MECHANISM AND CONTRACTION OF SMOOTH MUSCLE

- In addition to the Ca2-dependent activation of MLC kinase, the state of myosin light chain phosphorylation is further regulated by MLC phosphatase [aka myosin phosphatase (1, 4, 9, 11–16)], which removes the high-energy phosphate from the light chain of myosin to promote smooth muscle relaxation (Fig. 1).

- There are three subunits of MLC phosphatase: a 37- kDa catalytic subunit, a 20-kDa variable subunit, and a 110- to 130-kDa myosin-binding subunit.
- The myosinbinding subunit, when phosphorylated, inhibits the enzymatic activity of MLC phosphatase, allowing the light chain of myosin to remain phosphorylated, thereby promoting contraction.
- The small G protein RhoA and its downstream target Rho kinase play an important role in the regulation of MLC phosphatase activity. Rho kinase, a serine/threonine kinase, phosphorylates the myosin-binding subunit of MLC phosphatase, inhibiting its activity and thus promoting the phosphorylated state of the myosin light chain

- (Fig. 1). Pharmacological inhibitors of Rho kinase, such as fasudil and Y-27632, block its activity by competing with the ATP-binding site on the enzyme. Rho kinase inhibition induces relaxation of isolated segments of smooth muscle contracted to many different agonists. In the intact animal, the pharmacological inhibitors of Rho kinase have been shown to cause relaxation of smooth muscle in arteries, resulting in a blood pressure-lowering effect

Smooth muscle contraction…



Smooth Muscle…..

- Contraction starts more slowly and lasts much longer than striated muscles.
- Shorten and stretch to a greater extent than the other muscle types.

- Ca2+ increases in the cytosol initiates contraction, like striated muscle.
- SR found in small amounts in smooth muscle.

- ❑ No T- tubules, so takes longer for Ca2+ to reach the filaments in the center of the fiber and trigger the contractile process.
- ➢ **This accounts for the slow onset of contraction of smooth muscle.**

SMOOTH MUSCLE RELAXATION

- Smooth muscle relaxation occurs either as a result of removal of the contractile stimulus or by the direct action of a substance that stimulates inhibition of the contractile mechanism (e.g., atrial natriuretic factor is a vasodilator).
- Regardless, the process of relaxation requires a decreased intracellular Ca2+concentration and increased MLC phosphatase activity (Fig. 2) (10, 16).
- The mechanisms that sequester or remove intracellular Ca2+ and/or increase MLC phosphatase activity may become altered, contributing to abnormal smooth muscle responsiveness.

- A decrease in the intracellular concentration of activator Ca2+ elicits smooth muscle cell relaxation. Several mechanisms are implicated in the removal of cytosolic Ca2+ and involve the sarcoplasmic reticulum and the plasma membrane.
- Ca2+uptake into the sarcoplasmic reticulum is dependent on ATP hydrolysis.

- This sarcoplasmic reticular Ca,Mg-ATPase, when phosphorylated, binds two Ca2+ions, which are then translocated to the luminal side of the sarcoplasmic reticulum and released.
- Mg2+ is necessary for the activity of the enzyme; it binds to the catalytic site of the ATPase to mediate the reaction

Relaxation of smooth muscle….

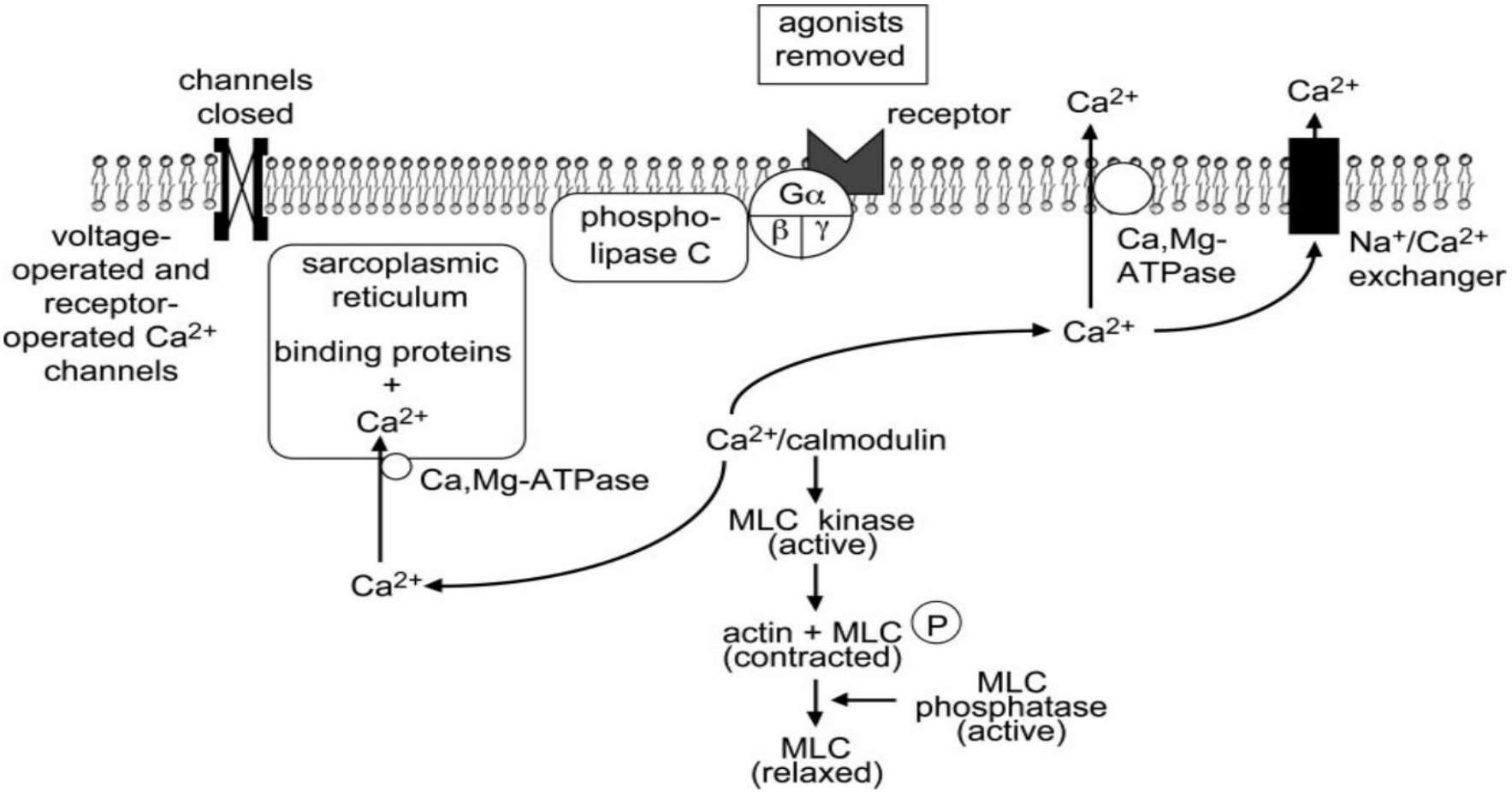


FIG. 2.

Relaxation of smooth muscle. Smooth muscle relaxation occurs either as a result of removal of the contractile stimulus or by the direct action of a substance that stimulates inhibition of the contractile mechanism. Regardless, the process of relaxation requires a decreased intracellular Ca^{2+} concentration and increased MLC phosphatase activity. The sarcoplasmic reticulum and the plasma membrane contain Ca,Mg-ATPases that remove Ca^{2+} from the cytosol. Na^+/Ca^{2+} exchangers are also located on the plasma membrane and aid in decreasing intracellular Ca^{2+}. During relaxation, receptor- and voltage-operated Ca^{2+} channels in the plasma membrane close resulting in a reduced Ca^{2+} entry into the cell.

Smooth Muscle…

- **ABNORMAL CONTRACTILE REGULATION OF SMOOTH MUSCLE**
- Alterations in the regulatory processes maintaining intracellular Ca2+ and MLC phosphorylation have been proposed as possible sites contributing to the abnormal contractile events in smooth muscle cells of various organs and tissues (2, 5, 8, 9).

- In addition, alterations in upstream targets that impact Ca2+ and MLC phosphorylation have also been implicated.

- For example, changes in the affinity, number, or subtype o f alpha-adrenergic receptors leading to enhanced vasoconstriction have been characterized in arterial smooth muscle cells in some types of hypertension.
- Increases in the activity of RhoA/Rho kinase signaling lead to increased contractile responses that may contribute to erectile dysfunction in the penis and clitoris.
- Increased activity of the RhoA/Rho kinase-signal ing pathway may also contribute to augmented contraction or spastic behavior of smooth muscle in disease states such as asthma or atherosclerosis.

Summary, smooth muscle abnormality…

- Impaired function may occur as the result of a change in the direct action of a substance that stimulates inhibition of the contractile mechanism.
- For example, decreased relaxation responses can be due to a reduction in cyclic nucleotide-dependent signaling pathways coupled with reductions in receptor activation appha-adrenergic receptors and cyclic AMP) or agonist bioavailability (endothelium dysfunction, reduced nitric oxide and cyclic GMP).
- Importantly, it is the complexity and redundancy of these cell signaling athways regulating intracellular Ca2 and MLC phosphorylation in smooth muscle that provide therapeutic potential for dysfunction.

Smooth Muscle Cont'd

Two types of smooth muscles

a. Single unit smooth muscle (Visceral smooth muscle)

i. Large sheets of mononucleated small cells.

ii. Have low resistance bridge of gap junctions; **AP can spread**.

iii. Show synchronous excitation and contractions (functional syncytium); like cardiac muscle.

iv. Found in gut, ureter, small blood vessels and uterus.

- **Single unit; because all the smooth muscle cells in the organ behave as one unit.**

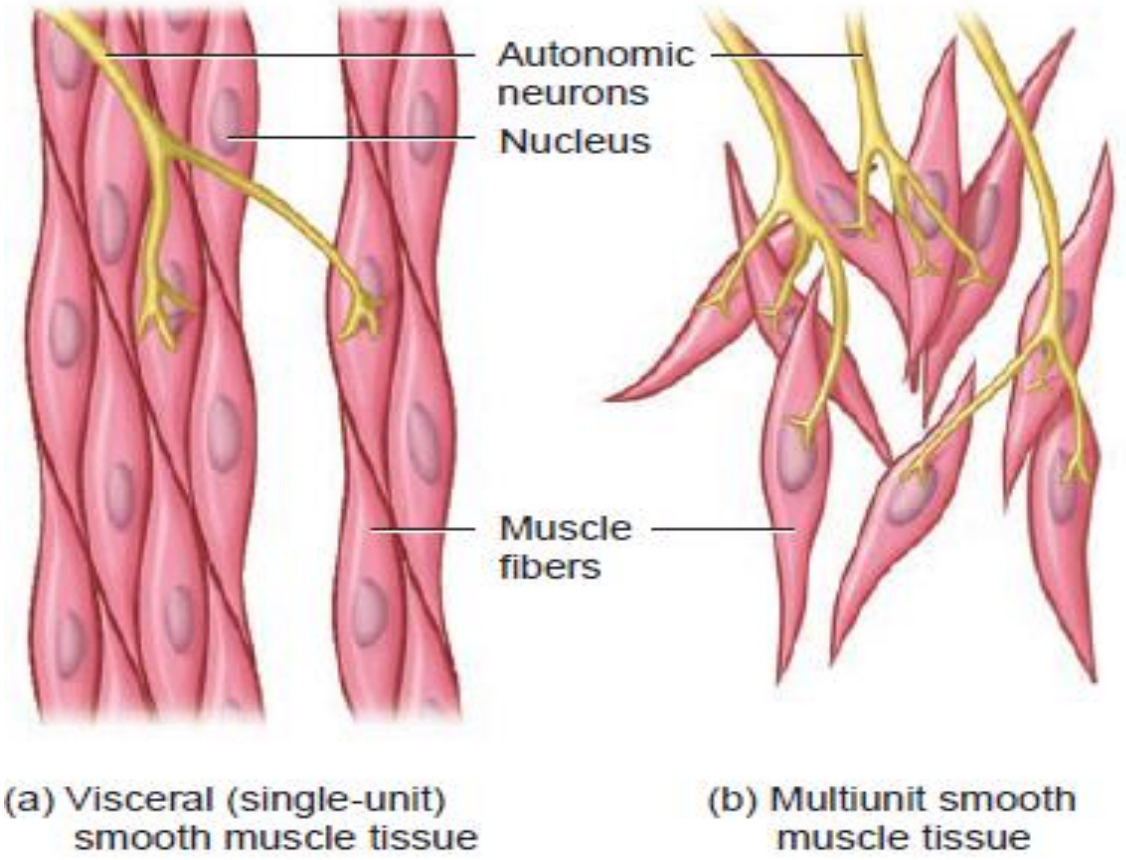
b. Multiunit smooth muscles

i. Found in iris, lungs, hair roots and large arteries.

ii. Have no **gap junctions** but each cell receive ANS nerve terminal.

Smooth Muscle cont'd

a. One motor neuron synapses with several **single unit fibers** & AP spread to neighboring fibers through **gap junctions.**



b. Three motor neurons synapse with individual **multiunit** fibers. Stimulation of one multiunit fiber causes contraction of that fiber only.

Features	Skeletal muscle	Cardiac muscle	Smooth muscle
Location	In association with bones	In the heart	In the visceral organs
Shape	Cylindrical and unbranched	Branched	Spindle-shaped, unbranched
Length	1 cm to 4 cm	80 µ to 100 µ	50 µ to 200 µ
Diameter	10 µ to 100 µ	15 µ to 20 µ	2 µ to 5 µ
Number of nucleus	More than one	One	One
Cross-striations	Present	Present	Absent
Myofibrils	Present	Present	Absent
Sarcomere	Present	Present	Absent
Troponin	Present	Present	Absent
Sarcotubular system	Well developed	Well developed	Poorly developed
'T' tubules	Long and thin	Short and broad	Absent
Depolarization	Upon stimulation	Spontaneous	Spontaneous
Fatigue	Possible	Not possible	Not possible
Summation	Possible	Not possible	Possible
Tetanus	Possible	Not possible	Possible
Resting membrane potential	Stable	Stable	Unstable
For trigger of contraction, calcium binds with	Troponin	Troponin	Calmodulin
Source of calcium	Sarcoplasmic reticulum	Sarcoplasmic reticulum	Extracellular
Speed of contraction	Fast	Intermediate	Slow
Neuromuscular junction	Well defined	Not well defined	Not well defined
Action	Voluntary action	Involuntary action	Involuntary action
Control	Only neurogenic	Myogenic	Neurogenic and myogenic
Nerve supply	Somatic nerves	Autonomic nerves	Autonomic nerves

Muscle comparison…

Comparative Physiology
of
Skeletal, Smooth & Cardiac Muscle Fibers

Ziser, 2001

Striated Muscle Cells	Smooth Muscle Cells	Cardiac Muscle Cells
Voluntary	Involuntary	Involuntary
Attached to bones or skin	Line walls of most internal organs	Found only in the Heart
Very long, cylindrical, multnucleate, cells	Single, tapering, cells with a single nucleus	Branching chains of cells connected by porous intercalated discs, with single nucleus and striations
Striated: packed with orderly arrangement of myofibrils	Not Striated: Fewer myofibrils of varying lengths	Striated: many myofibrils in orderly arrangement
Not self stimulating: each fiber innervated by branch of somatic motor neuron as part of *motor unit*	Self stimulating: not individually innervated, impulse spreads from cell to cell	Self stimulating: impulse spreads from cell to cell
Under control of nervous system	Under control of nervous and endocrine systems and various chemicals and stretching	Under control of nervous and endocrine systems and various chemicals
High energy requirement: lots of mitochondria, creatine phosphate, myoglobin	Lower energy requirement: fewer mitochondria, etc.	Intermediate energy requirement
Fast Contracting	Slower contracting and rhythmic in some organs producing peristaltic waves along organ	Intermediate speed of contraction yet contraction spreads quickly through tissue due to intercalated discs
No rhythmic contractions	Rhythmic contractions	Rhythmic contractions
Strength increases with stretching	Stress - Relaxation Response	Strength increases with stretchiing
Fatigues Easily	Doesn't fatigue	Doesn't fatigue

Clinical scenario

1. Tetanus

- Tetany is a pathologic condition accompanying hypocalcemia (low extracellular Ca+2), associated with hyperexcitability of nerve and muscle cells.
- Low Ca+2 tends to reduce chemical transmitter release
- Lowering the Ca+2 concentration tends to reduce the threshold for initiating AP.
- The combined effect of low Ca+2 is to make the membrane of the muscle cell easier to depolarize and thus better able to initiate AP, despite the decreased chemical transmitter release.

✓ Found in skeletal muscle cells.

✓ Occurs due to over or continuous stimulation by external or internal factors.

✓ Not found in cardiac cells because of long refractory period due to slow calcium channels.

Physiology of muscle….

2. Myasthenia gravis

- Myasthenia gravis is a neuromuscular disease associated with weakness and fatigability of skeletal muscle.
- The condition is aggravated by exercise.
- The fatigability associated with myasthenia gravis is explained by the tendency for transmitter release to depress with repeated activation of a motor neuron.
- Such depression may be due to depletion of the pool of synaptic vesicles in the presynaptic terminal.
- There is no known cure for myasthenia gravis.
- A common treatment, however, is the use of neostigmine by blocking the actions of AChE, makes more ACh available to bind with post-junctional ACh receptors and thus partially compensates for the reduced number of receptors in the myasthenic patient.

- **Myasthenia ,** defined as abnormal muscle weakness or disease, can also be related to loss of ion channel function in the muscle.

❖ In **congenital myasthenia ,** the patient has an inheritable disorder of one of a group of ion channels necessary for the transmission of neuronal signaling to muscle response.

- Mutations in Ca2+ channels that allow for neuronal transmitter release or in the Ach receptor nonspecific cation channels, important in recognition of neuronal transmitters, have both been shown to cause congenital myasthenia.

❖ Alterations of channel functions can also occur via autoimmune disease, such as that observed in **myasthenia gravis .**

- In this disease, antibodies to the nicotinic acetylcholine receptor can reduce its functional presence at the muscle membrane by up to 80%, and thus limit muscle response to neuronal transmitter release.

Clinical…..

3. Rigor Mortis

- It is a state of prolonged muscle contracture, i.e., contraction produced without AP and not followed by relaxation.
- It is a contracture which occurs in the muscles after death.
- It starts in small muscles (2-3hrs) after death and involves all muscles in 12 hrs.
- The rigidity is due to depletion of ATP from the muscle.
- Ca+2 diffuses out of SR & can't be recollected by the Ca+2 pump".
- Ca+2 initiates muscle contraction using the remaining ATP molecules; relaxation does not occur because calcium is not recollected back into the SR, and no ATP is available to disconnect the myosin heads from actin.
- It disappears when muscle fibers are autolysed by lysosomal enzymes released after death.
- It starts to disappear 14hrs after death and completed in 24hrs.
- High env'tal To accelerates the disappearance of rigor mortis.

4: The Integumentary System

- **Integumentary system includes**; Skin and its accessory organs, such as hair, nails, sweet glands and sensory receptors.
- **The integumentary system contributes to homeostasis by;**
  - ✓ to maintain a constant body temperature,
  - ✓ protects the body, and
  - ✓ provides sensory information about the surrounding env't

- Dermatology is the study of integumentary system & its disorders.
- The **skin is the largest organ in the body which covers** the external surface.

- From all the body's organs, none is more easily exposed to infection, disease, and injury than the skin.

➢ Despite these, the skin's protective features ward off such damage

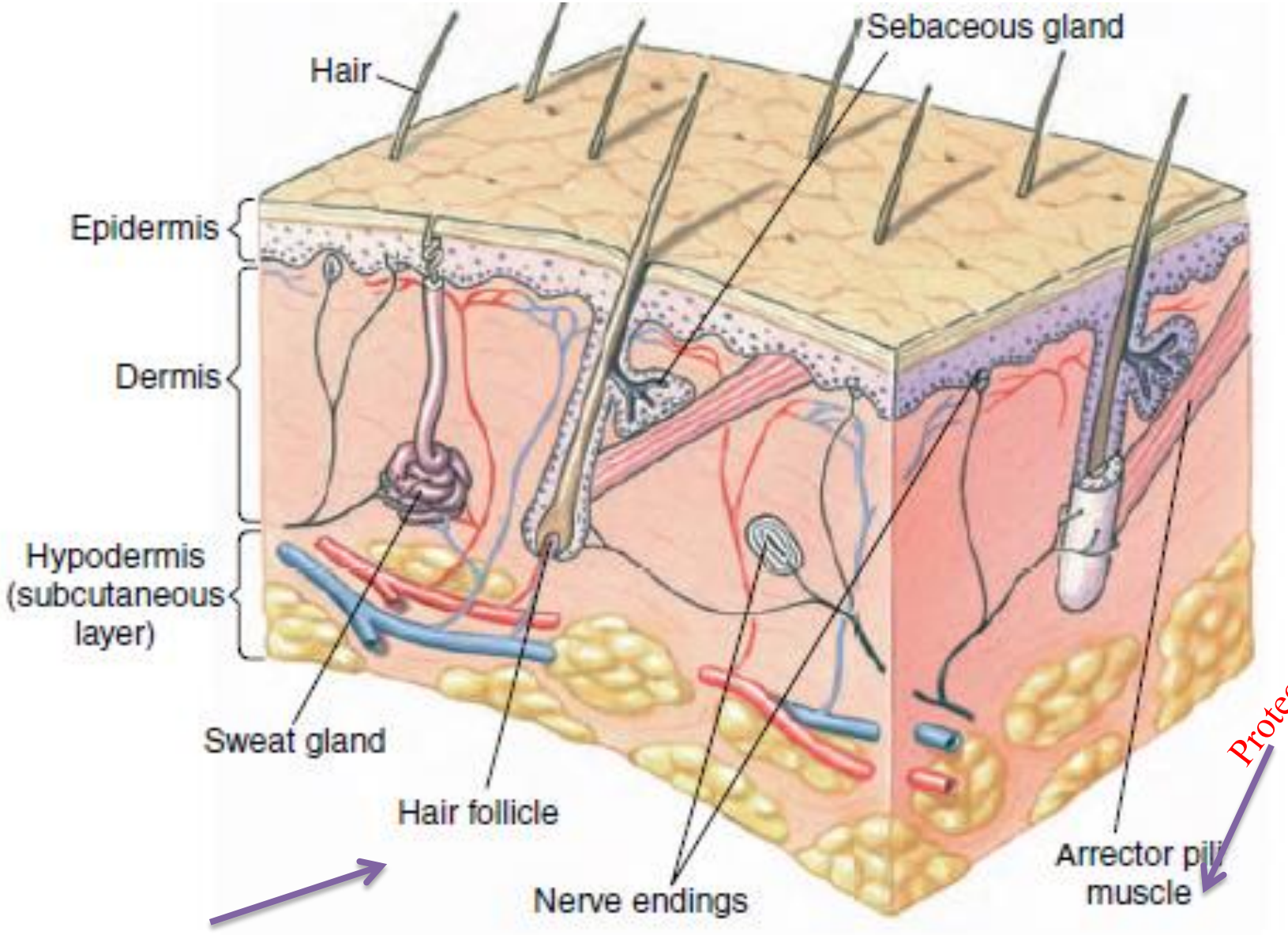
Skin cont'd

❑ Functions of the Skin

- ✓ **Protection** the internal structures of the body from physical damage, chemical, UV.
- ✓ **First line of defense** against bacteria, viruses and other microbes.
- ✓ prevents **dehydration**.

- ➢ **Sensations** – for sensing touch, pressure, heat, cold, pain …
- ➢ **Storage of chemical compounds** (fats)
- ➢ **Excretion of wastes –** sweat glands release (water, salts, $NH_{3)}$
- ➢ **Synthesis of compounds (**vitamins and hormones)

Skin cont'd



Protecting the hair

Small connective tissue, surround Hair root

Skin cont'd

Different components of the skin

- **papillary region**
  - ✓ 1/5th of the thickness of dermis.
  - ✓ Provide nutrition for the epidermis
  - ✓ The superficial portion of the dermis.
  - ✓ Consists connective tissue with thin collagen fibers.

- **Reticular region**
  - ✓ $4/5^{th}$ of the thickness of dermis.
  - ✓ The deeper portion of the dermis
  - ✓ Consists of dense irregular connective tissue with thick collagen fibers.

- **Dermal papillae**
  - ✓ Consist of blood vessels and nourishes all the hair follicles

Skin cont'd

- **Meissner corpuscles**
  - ✓ Nerve endings initiate signals & give rise to sensations of warmth, coolness, pain, tickling and itching.

- **Hair Follicles;** Surrounds the root of hair.
- **Hair root;** Found below the surface of the skin.

- **Arrector pili muscle**
  - ✓ Contraction of the muscle causes the hair to stand; protecting hair.
  - ✓ Small muscle attached to hair follicles

- **Capillary root;** site for transport of O2 and other nutrients.

Skin cont'd

- Skin has two main parts/layers/; Epidermis, Dermis.
- The third layer is not the part of skin, important for the survival of the two layers of the skin.

1. **Epidermis**
   - ✓ thin, outermost stratified epithelial layer, give rise hair, feathers.
   - ✓ a vascular structure receives nourishment from dermis.

- **It contains four principal types of cells**

A. Keratinocytes

- ✓ Constitutes 90% of epidermal cells.
- ✓ produces keratin protein (a tough, fibrous protein).
- ✓ Keratin used to protect the skin from heat, microbes & chemicals.

Skin cont'd

B. Melanocytes

- The second most numerous cell & constitute 8% of epidermis.
- Produce the pigment **melanin** to protect the skin from UV radiation& sun burn.

C. Langerhans cells

- ✓ Arise from red bone marrow and make up over 1% of epidermis.
- ✓ Detect and fight pathogens that attempt to enter the body.

D. Merkel(Tactile) cells

- ✓ 1% of all epidermal cells
- ✓ Important for **sensing touch**.
- ✓ Form a disk along the deepest edge of the epidermis.

Skin cont'd

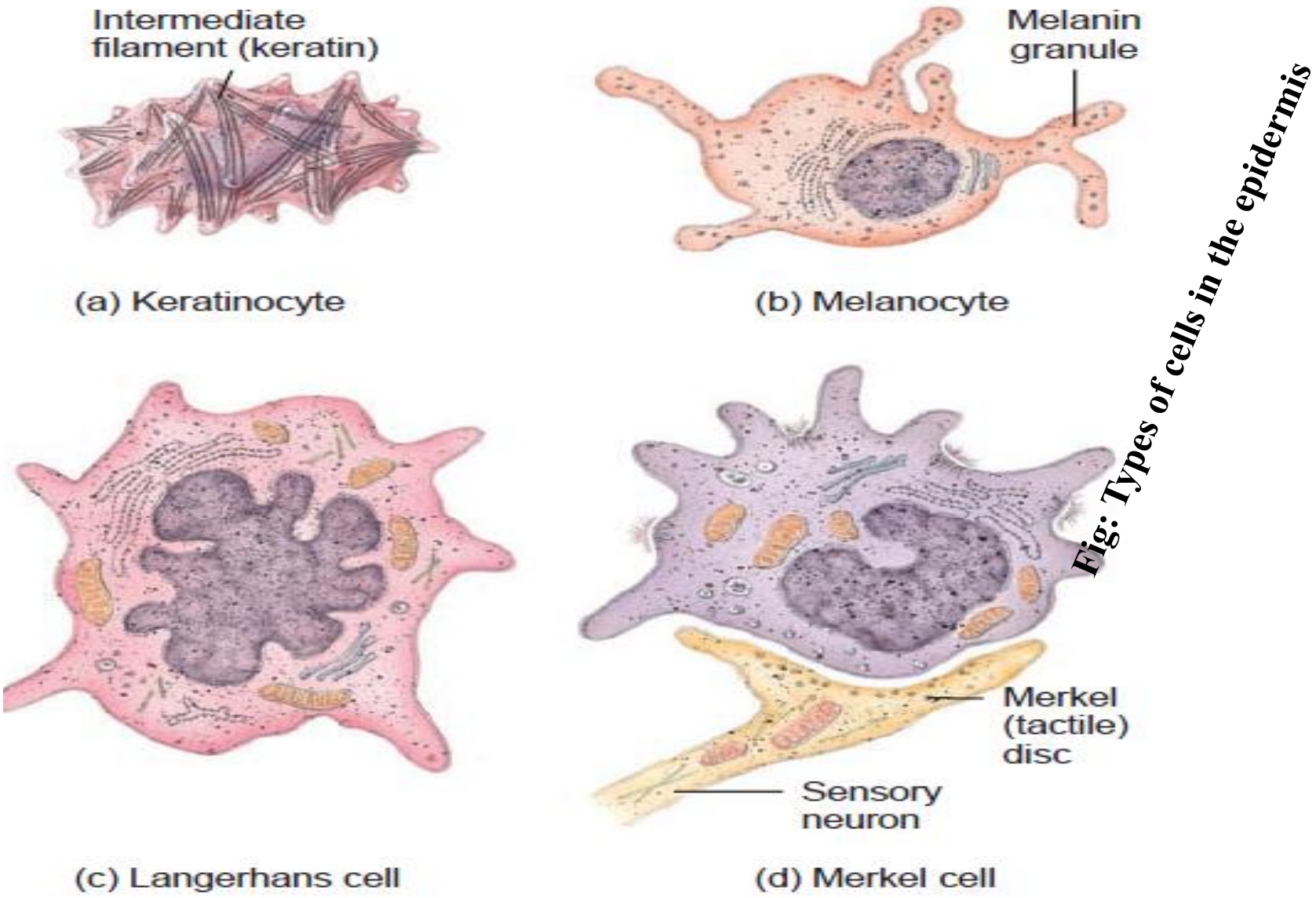


Fig: Types of cells in the epidermis

Skin cont'd

❖ **Pigments;** there are three pigments in the body.

a. Melanin

- Produced by melanocytes.
- Skin color varies b/c of the amount of melanin.
- Melanin protect skin from UV rays.

- **Albinism:** inherited inability of an individual to produce melanin.
  - ✓Resulting in white hair and pink eyes in mammals.

Skin cont'd

b. Hemoglobin

- ✓ Oxygen-carrying pigment in red blood cells.
- ✓ Skin color ranges from pink to red depending on the oxygen content of the blood moving through capillaries in the dermis.

- The red color is due to **hemoglobin.**

c. Carotene

- ✓ Any of several orang/red crystalline hydrocarbon pigments.
- ✓ precursor of vitamin A(to synthesize pigments needed for vision).

Skin cont'd

2. Dermis

- The second, deeper part of the skin,
- composed of a strong connective tissue; collagen fibers,
- Thickest layer of skin,
- Lies beneath and supports the epidermis,
- Gives skin its **strength**

- Rich in nerves, receptors, blood vessels and lymph vessels
- Hair follicles and sweat glands extend into it
- The dermis is essential to the **survival of the epidermis**.

Skin cont'd

❑ Subcutaneous Layer(hypodermis)

- ✓ Not a part of skin
- ✓ Found bellow the skin.
- ✓ Helps to insulate the body.
- ✓ Loose connective tissue.
- ✓ Packed with adipose **cells/tissue/** subcutaneous fat.
- ✓ Stabilizes position of skin.

NB: Mainly infants and elderly have less Hypodermis than adults and are therefore more sensitive to cold.

Accessory structures of the skin

- Includes hair, skin glands & nails.

1. Hair

- ✓ Covers entire body except palms, soles, lips.
- ✓ Genetic and hormonal influences determine the thickness & distribution.

- ✓ Among the fastest growing tissues.
- ✓ On the head guards the **scalp** from: **injury & the sun's rays, decreases heat loss from the scalp.**

- ✓ Eyebrows and eyelashes protect the eyes from foreign particles.
- ✓ Hair root plexuses function in **sensing** light touch.

Hair cont'd

- The rate of growth and the replacement cycle may be altered by
  - illness, radiation therapy, chemotherapy, age, genetics, gender & severe emotional stress.
  - Rapid weight-loss diets severely restrict calories or protein increase hair loss.
  - The rate of shedding also increases for 3 to 4 months **after childbirth.**

- **Alopecia**
  - the partial or complete lack of hair
  - may result from genetic factors, aging, endocrine disorders, chemotherapy, or skin disease.

Hair cont'd

- **Hair color**
  - Depend on the amount and type of **melanin**.
  - **Dark-colored** hair contains **eumelanin**; red hair contain variants of pheomelanin.
  - Hair becomes gray B/c of a progressive decline in melanin production.
  - White hair results from the lack of melanin.

- **Hair texture**
  - ✓ straight hair is round
  - ✓ wavy hair is oval
  - ✓ tightly curly hair is relatively flat.

Skin cont'd.

Skin Glands

- ✓ All glands of the body are classified as either endocrine or exocrine.
- ✓ Glands are epithelial cells that secrete a substance.
- ✓ Several kinds of exocrine glands are associated with the skin:
  - ✓Sebaceous(oil) glands, sudoriferous (sweat) glands AND…
- ✓ Mammary glands, specialized sudoriferous glands that secrete milk.

1. Sebaceous Glands

- ➢ keeps hair soft and pliable.
- ➢ on face and scalp, not on palms or soles
- ➢ reduces heat loss(B/c of **lipids** are poor heat conductors)
- ➢ helps prevent water evaporation
- ➢ secrete **sebum (**a waxy, oily substance)

Hair cont'd

2. Sudoriferous(Sweet) Glands

- ✓ Small tubular structures
- ✓ A type of **exocrine gland**, produce and secrete substances onto an epithelial surface by way of a duct.
- ✓ Three to four million **sweat glands.**
- ✓ Release sweat into hair follicles or onto the skin surface through pores.

- Divided into **eccrine and apocrine**;
  - ✓ based on their structure, location and type of secretion.

a. Eccrine (merocrine) sweet glands

- ✓ Major sweet glands and distributed almost all over the body.
- ✓ Simple, coiled tubular glands much more common than **apocrine**.
- ✓ Distributed throughout the skin of most regions of the body.
- ✓ In the margins of the lips, glans penis, glans clitoris & labia minora.
- ✓ The secretory portion is located mostly in the **deep dermis**.

Glands cont'd

b. Apocrine glands

- ✓ Composed of a coiled secretory portion located at the junction of the dermis and subcutaneous fat.
- ✓ Associated with hair follicles
- ✓ Are mostly limited to the armpits and perianal areas in humans.
- ✓ They are not significant for cooling in humans, but
- ✓ Are the sole effective sweat glands in animals; camels, donkeys, horses

Glands Cont'd

Comparison of Eccrine and Apocrine Sweat Glands

FEATURE	ECCRINE SWEAT GLANDS	APOCRINE SWEAT GLANDS
Distribution	Throughout skin of most regions of the body, especially in skin of forehead, palms, and soles.	Skin of the axilla, groin, areolae, bearded regions of the face, clitoris, and labia minora.
Location of secretory portion	Mostly in deep dermis.	Mostly in subcutaneous layer.
Termination of excretory duct	Surface of epidermis.	Hair follicle.
Secretion	Less viscous; consists of water, ions (Na^+, Cl^-), urea, uric acid, ammonia, amino acids, glucose, and lactic acid.	More viscous; consists of the same components as eccrine sweat glands plus lipids and proteins.
Functions	Regulation of body temperature, waste removal, and stimulated during emotional stress.	Stimulated during emotional stress and sexual excitement.
Onset of function	Soon after birth.	Puberty.

Accessory cont'd

3. Nails; Reading assignment!

- Scale-like modification of the epidermis
- Very thin, dead, scaly cells, densely packed.
  - More fleshy and sensitive fingertips
  - Can be used for digging and picking apart food, etc
- **Features:**
- **Nail matrix:** growth zone beneath proximal skin nail.
- **Nail plate:** visible portion of nail
- Finger nails grow ~1 mm/week; toe nails more slowly.
- APPERANCE: Spoon like, flat, concave e.tc.

Accessory cont'd

- Primate feature; Grasping

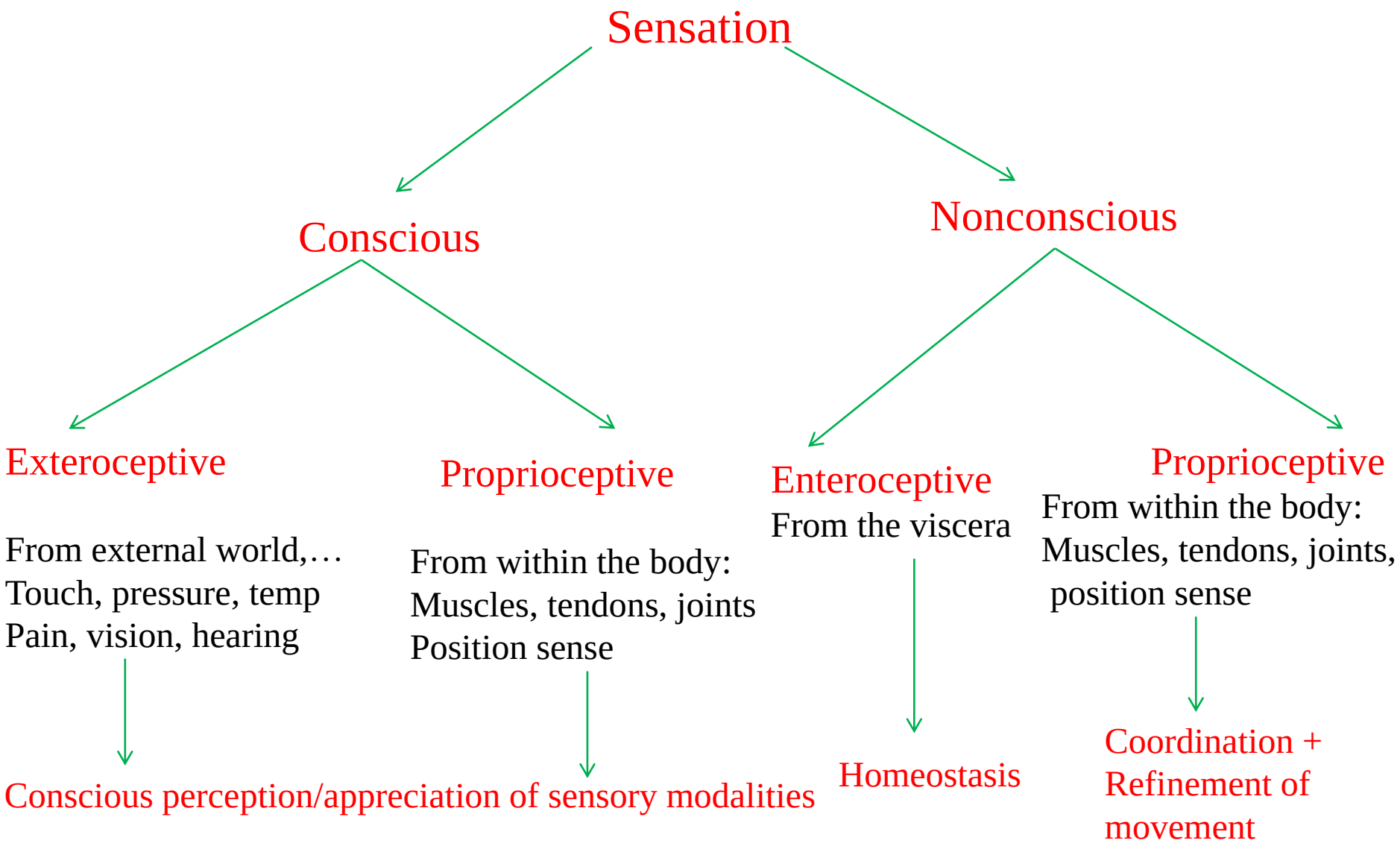
Skin… Receptors

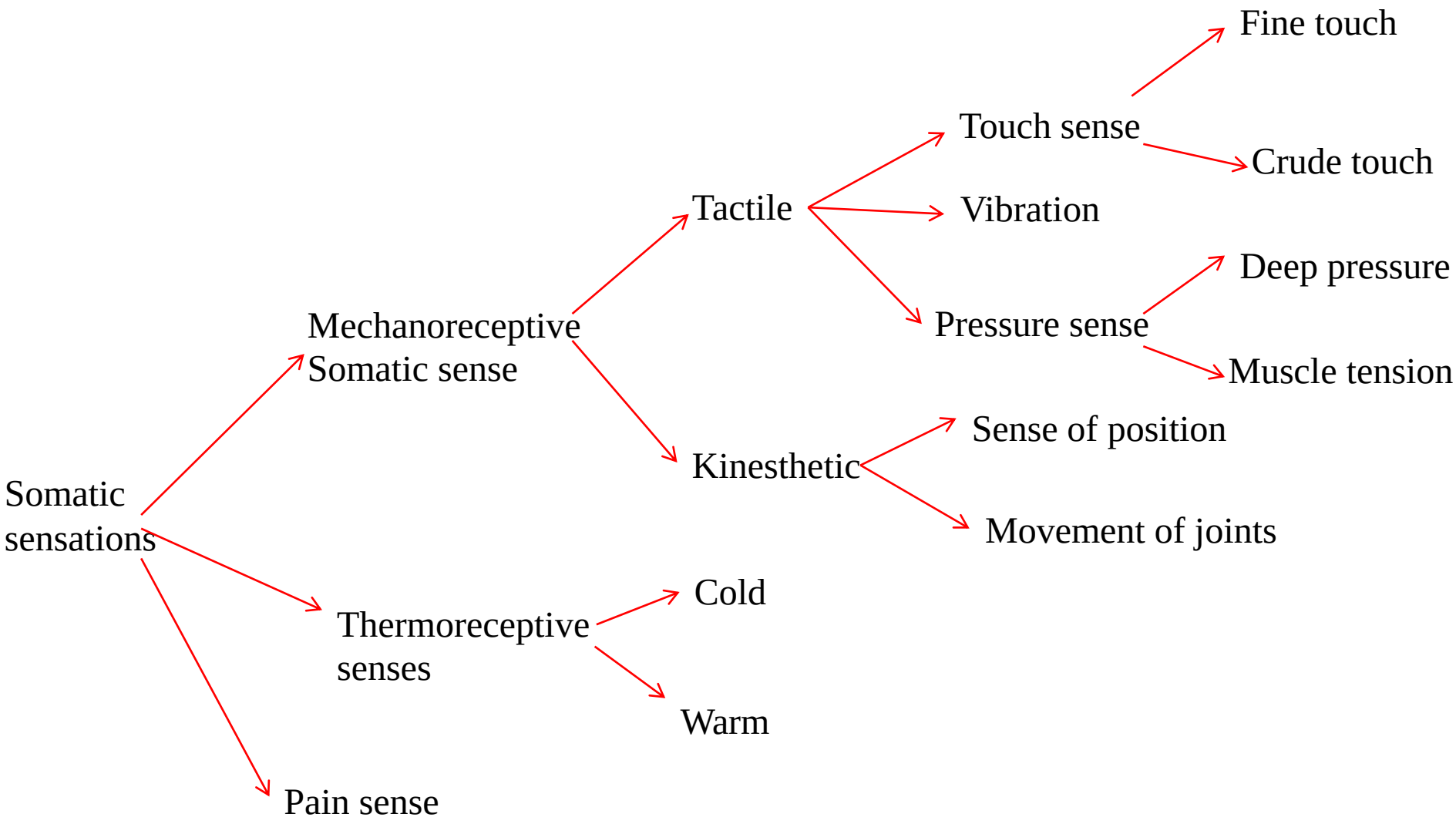
Significance:

- ➢ Proprioception…
- ➢ Exteroception…
- ➢ Interoception…

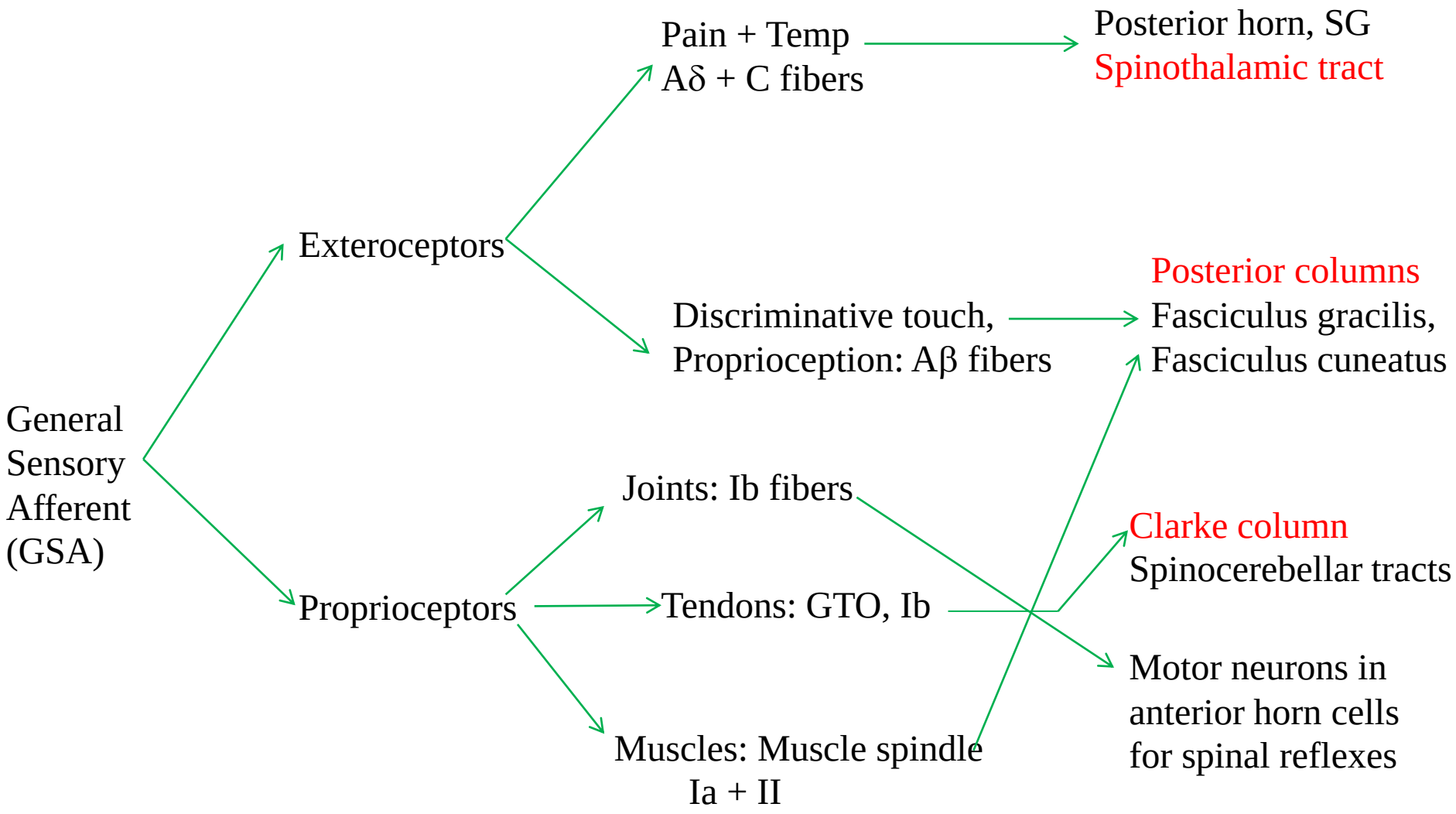
- A diverse sensory system that provides information to the CNS about the state of the body and its contact with the world.

- *Sensation*: is the awareness of sensory stimuli in the brain.
- *Perception*: meaningful interpretation or conscious understanding of sensory data


Sensation
Conscious
Nonconscious
Exteroceptive
From external world,…
Touch, pressure, temp
Pain, vision, hearing
Conscious perception/appreciation of sensory modalities
Proprioceptive
From within the body:
Muscles, tendons, joints
Position sense
Enteroceptive
From the viscera
Homeostasis
Proprioceptive
From within the body:
Muscles, tendons, joints,
position sense
Coordination +
Refinement of
movement



- Each sensation is associated with a specific receptor type.


General Sensory Afferent (GSA)
Exteroceptors
Proprioceptors
Pain + Temp
Aδ + C fibers
Posterior horn, SG
Spinothalamic tract
Discriminative touch,
Proprioception: Aβ fibers
Posterior columns
Fasciculus gracilis,
Fasciculus cuneatus
Joints: Ib fibers
Tendons: GTO, Ib
Muscles: Muscle spindle
Ia + II
Clarke column
Spinocerebellar tracts
Motor neurons in anterior horn cells for spinal reflexes

Classes of receptors

- Mechanoreceptors (movement + pressure)
- Proprioceptors (joints, muscles, tendons)
- Thermoreceptors…
- Nociceptors…
- …

Receptor types active in somatic sensation…

Receptor type	Fiber group	Fiber name	Modality
Cutaneous and subcutaneous mechanoreceptors 8			Touch
Meissner corpuscle	Aα,β	RA1	Stroking, flutter
Merkel disk receptor	Aα,β	SA1	Pressure, texture
Pacinian corpuscle	Aα,β	RA2	Vibration
Ruffini ending	Aα,β	SA2	Skin stretch
Hair-tylotrich, hair-guard	Aα,β	G1, G2	Stroking, fluttering
Hair-down	Aδ	D	Light stroking
Field	Aα,β	F	Skin stretch
C mechanoreceptor	C		Stroking, erotic touch
Thermal receptors 4			Temperature
Cool receptors	Aδ	III	Skin cooling (<25°C [77°F])
Warm receptors	C	IV	Skin warming (>35°C [95°F])
Heat nociceptors	Aδ	III	Hot temperature (>45°C [113°F])
Cold nociceptors	C	IV	Cold temperature (<5°C [41°F])

Mechanoreceptors

- Respond to physical deformation, tactile stimuli, sound, vibrations, pressure…mechanical distension, pressure on skin, stretch of muscles…
- Skin receptors…Meissner's corpuscle, Pacinian corpuscle, hair cells … (epidermis and dermis…)
- Size, shape and texture of objects and their movements across the skin…
- Produce receptor potentials…APs…
- Can be phasic or tonic receptors.
- Membrane receptor proteins respond to mechanical deformation → opening of stretch sensitive ion channels→ ΔE_m → depolarization → RPs….→ APs…brain → interprets as sensation…

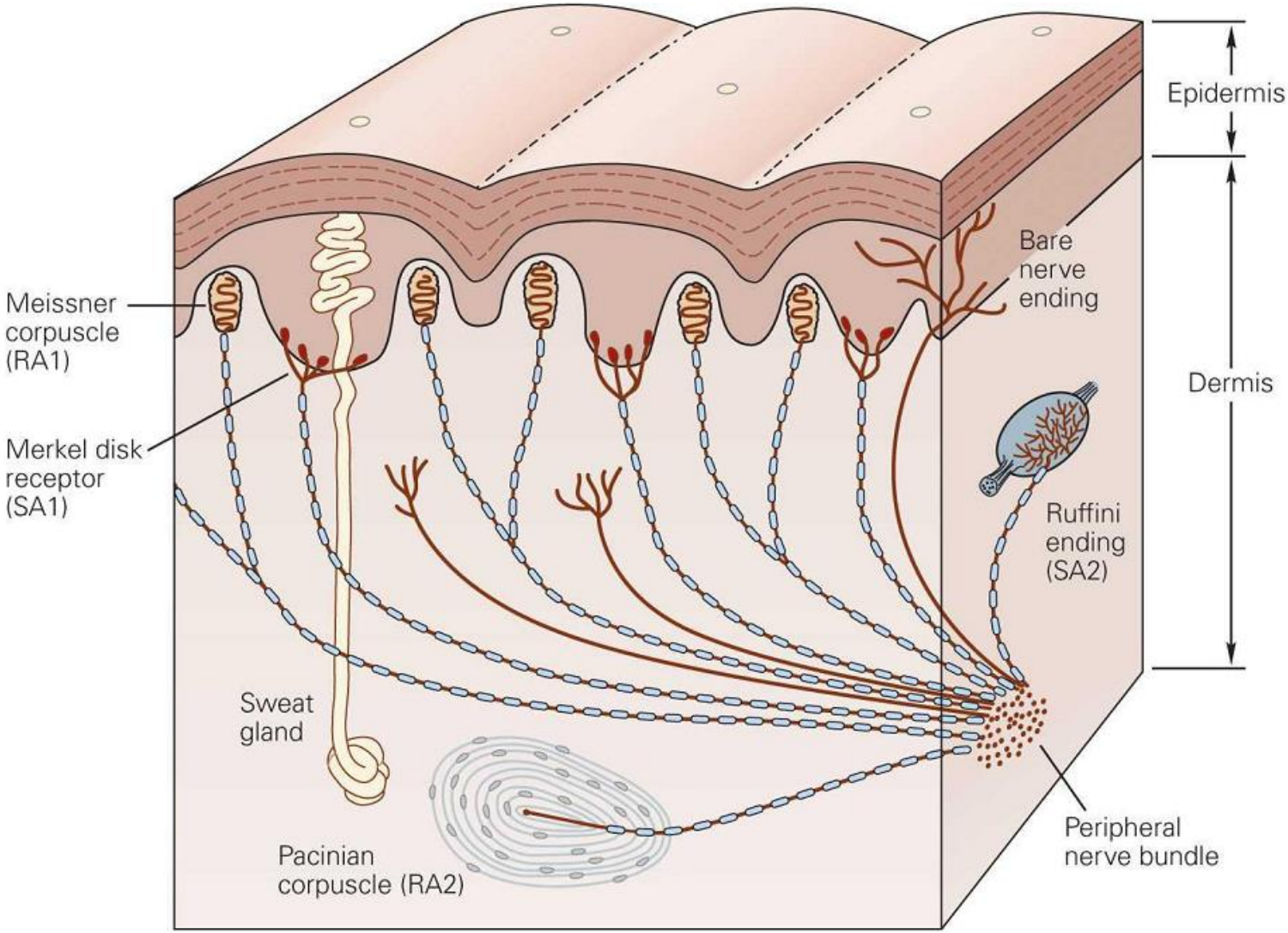
Mechanoreceptors in the skin

- Touch and proprioception…
- Type of stimulation (mechanoreceptors…).
- Size of receptive field (large/small).
- Rate of adaptation (fast/slow).

Tactile receptors…

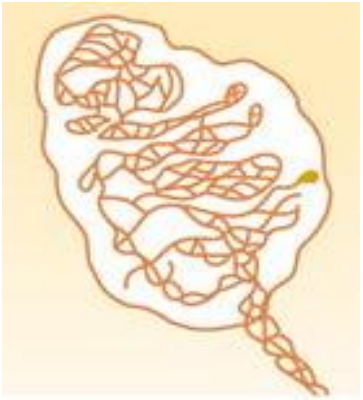
Receptor type	Sensitivity
*Meissner's corpuscle	Light touch
*Merkel's disk	Light pressure/texture
*Pacinian corpuscle	Firm pressure
*Ruffini endings	Skin stretch
Free nerve endings	Movement of hair; pain

*Low-threshold (high-sensitivity) mechanoreceptors; innervated by Aβ myelinated axons.



Four mechanoreceptors are responsible for the sense of touch…

Meissner's corpuscles



- Located at epidermis-dermis junction
- Fingers, palms, lips, nipples, and soles / glabrous skin
- Fingertips (50/mm^2), 40% afferent innervation
- Fast adapting…
- Small receptive field/two-point discrimination/precise location
- Low frequency vibrations (30-50Hz initial contact of the hand with objects, slippage of objects held in hand, motion of the hand over textured objects…)
- Innervated by RA1 fibers
- Every Meissner's corpuscle has at least two RA axons, and every RA axon innervates between 20 and 50 separate corpuscles

Merkel's disk

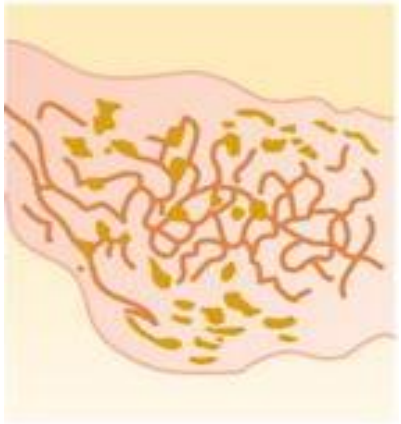
- Located at epidermis-dermis junction.
- 25% of mechanoreceptors of the hand.
- Dense in fingertips, lips and external genitalia.
- Slow adapting, small receptive field…
- Fine spatial detail, static discrimination of shapes/form, edges/object curvature/corners + rough texture, points (Braille), amount of pressure/ steady pressure…
- Innervated by SA1 fibers.

Pacinian corpuscle

- Located at subcutaneous tissue.
- 10-15% of cutaneous receptors in hand.
- Fast adapting (dynamic qualities).
- Large receptive field…

- High frequency *vibrations* (250-350Hz)/filters out low frequency mechanical stimuli, sustained pressure…fluid-filled capsule around…closure of cation channel…Onset and Offset & a changing stimulus).
- Discrimination of fine surface textures or other moving stimuli, vibrations of tools, objects…
- Innervated by RA2 fibers.
- Pacinian corpuscle > Meissner's corpuscles (degree of adaptation).

Ruffini endings

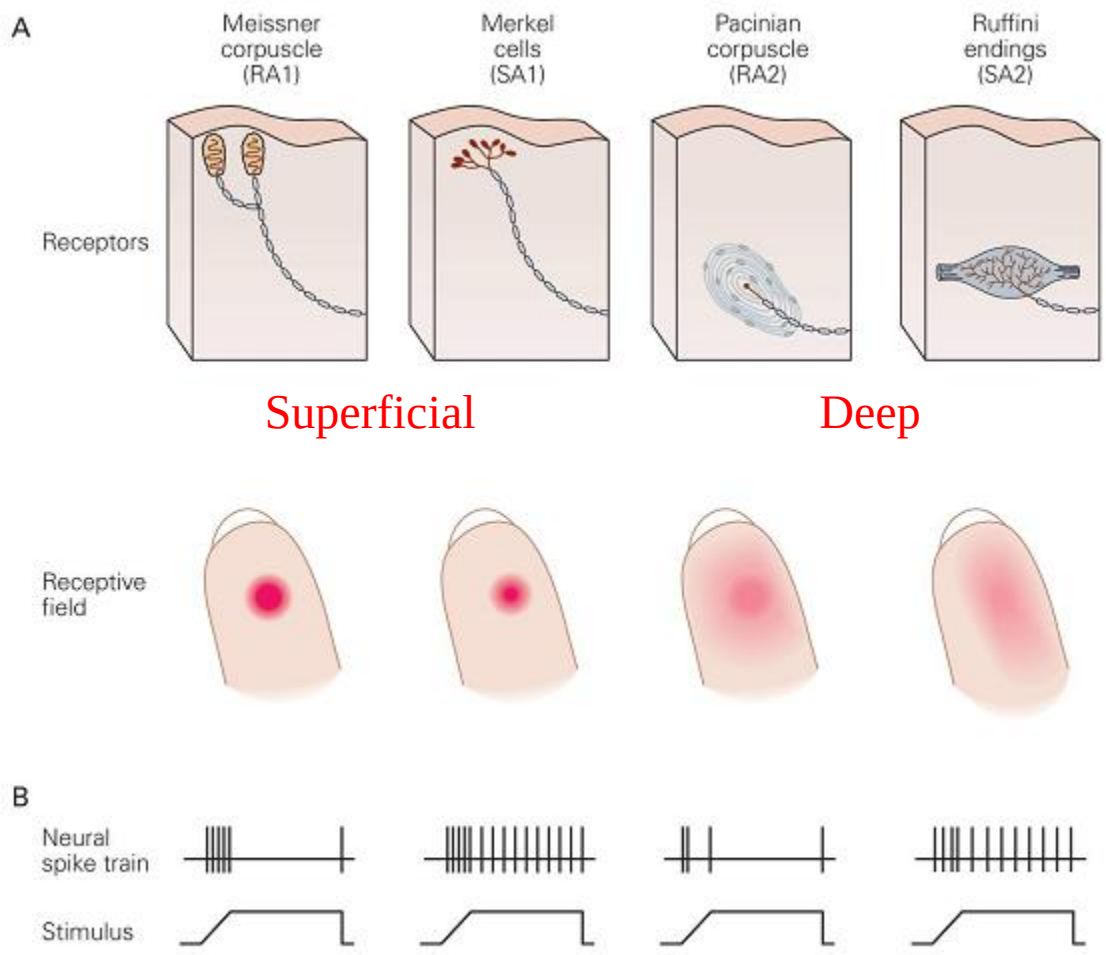


Ruffini's endings

- Located in dermis, joints, ligaments and tendons.
- 20% of receptors of the human hand.
- Slowly adapting, large receptive field.
- Sustained downward pressure, stretch, grasp.
- Sensitive to shapes of large objects in the hand.
- Movements of fingers and other joints…
- Innervated by SA2 fibers

Mechanism of transmission of tactile signals

- Touch → deformation of receptors (Meissner's corpuscles + Iggo dome receptors + hair receptors + Ruffini's endings…) → opening of pressure sensitive Na^+ ion channels in the axon membrane (Aβ & Aδ fibers +) → influx of Na^+ → RP → APs…

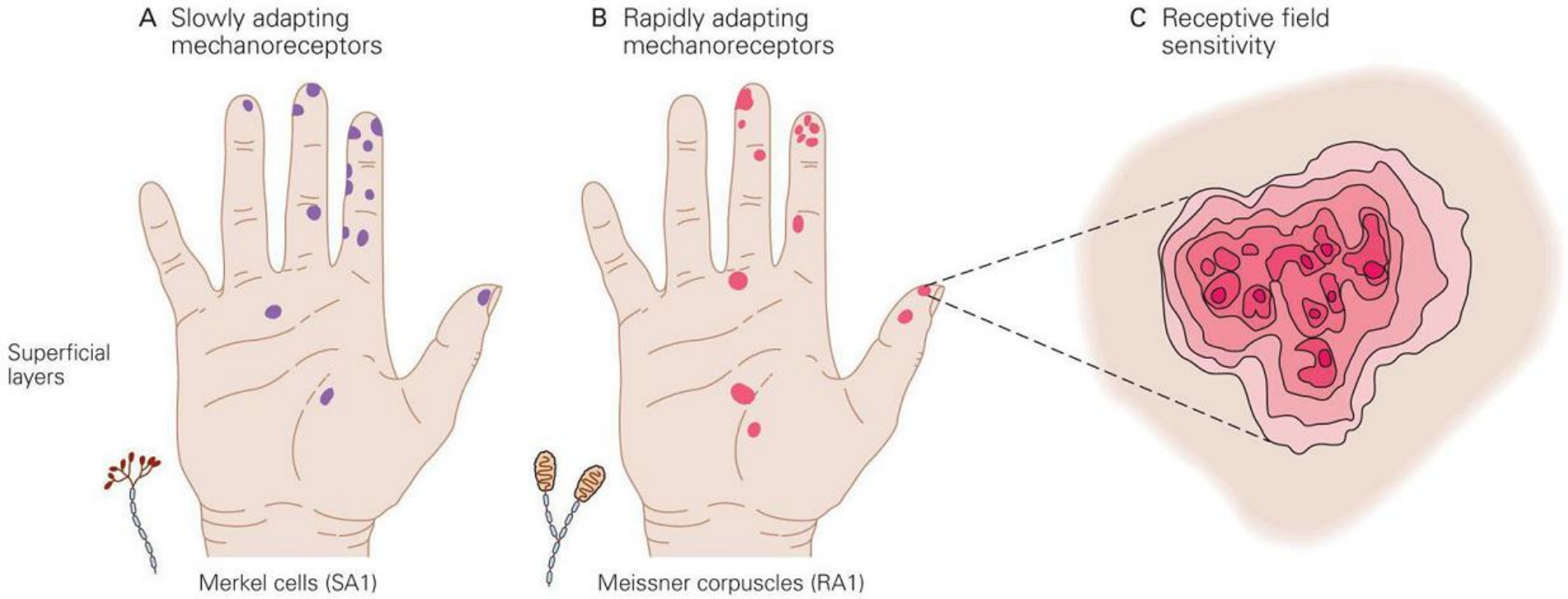


- Morphology of the receptors
- Innervation patterns
- Location in the skin
- Receptive field size
- Physiological responses to touch

➢ RF reflects location & distrib^{n} of its terminals in the skin.

➢ Receptors in superficial layers of the skin have smaller RFs than those in the deep layers.

Touch is mediated by four types of mechanoreceptors in the human hand

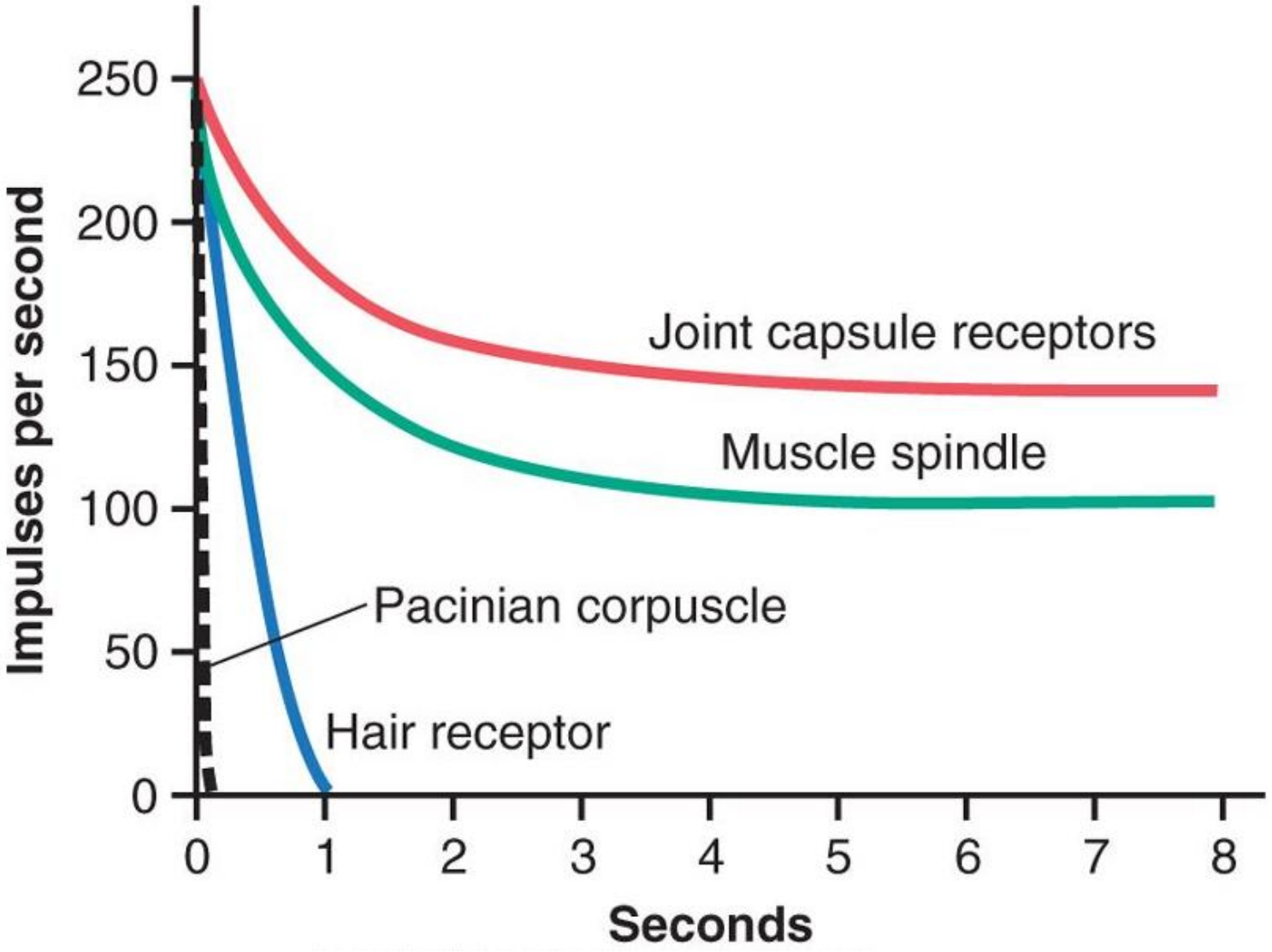


Locations of mechanoreceptors in the human hand…

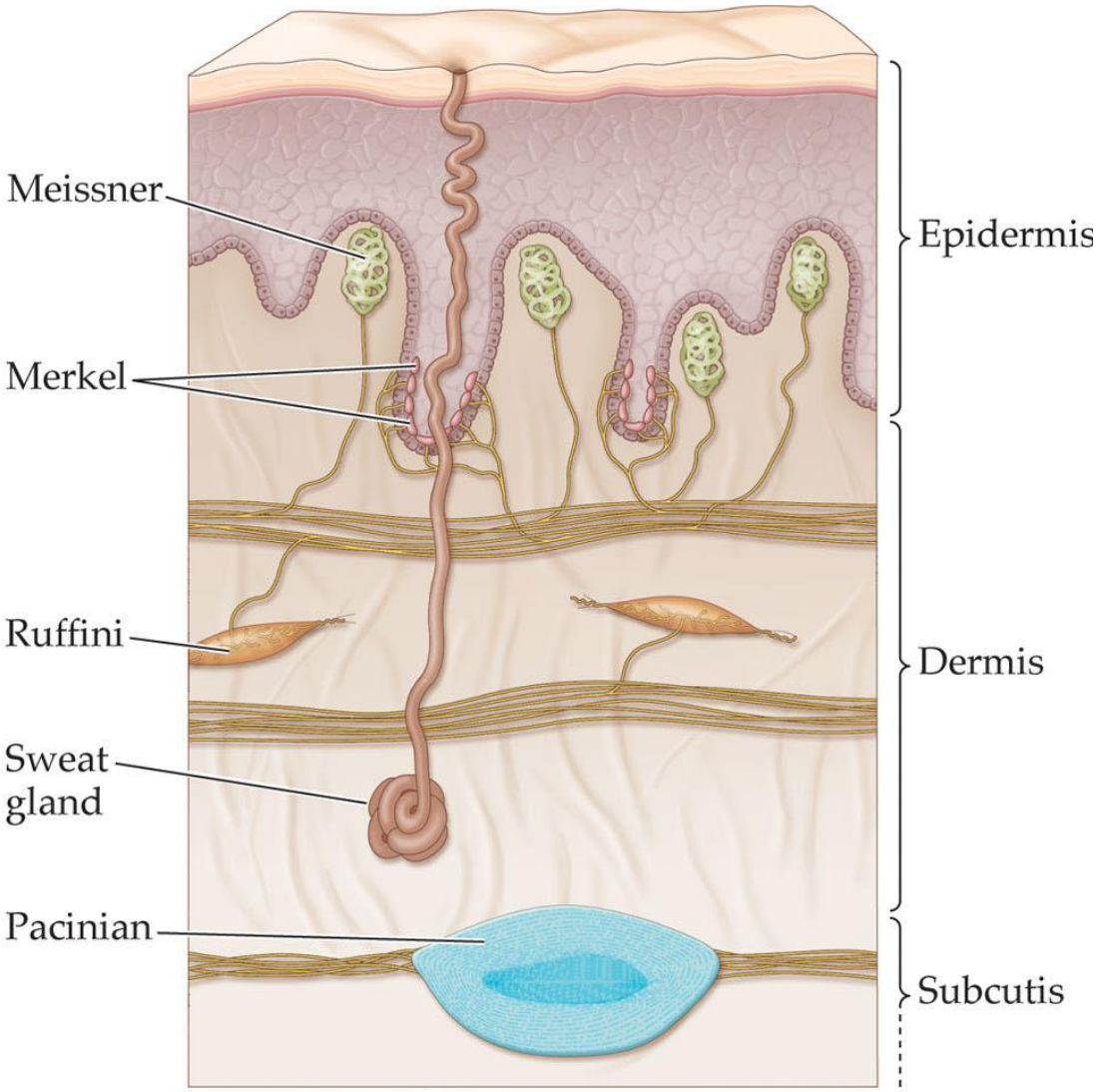
Cutaneous Mechanoreceptor Systems

	Type 1		Type 2	
	SA1	**RA1**[1]	**SA2**	**RA2**[2]
Receptor	Merkel cell	Meissner corpuscle	Ruffini ending	Pacinian corpuscle
Location	Tip of epidermal sweat ridges	Dermal papillae (close to skin surface)	Dermis	Dermis (deep tissue)
Axon diameter (μm)	7–11	6–12	6–12	6–12
Conduction velocity (ms)	40–65	35–70	35–70	35–70
Best stimulus	Edges, points	Lateral motion	Skin stretch	Vibration
Response to sustained indentation	Sustained with slow adaptation	None	Sustained with slow adaptation	None
Frequency range (Hz)	0–100	1–300		5–1,000
Best frequency (Hz)	5	50		200
Threshold for rapid indentation or vibration (best) (μm)	8	2	40	0.01

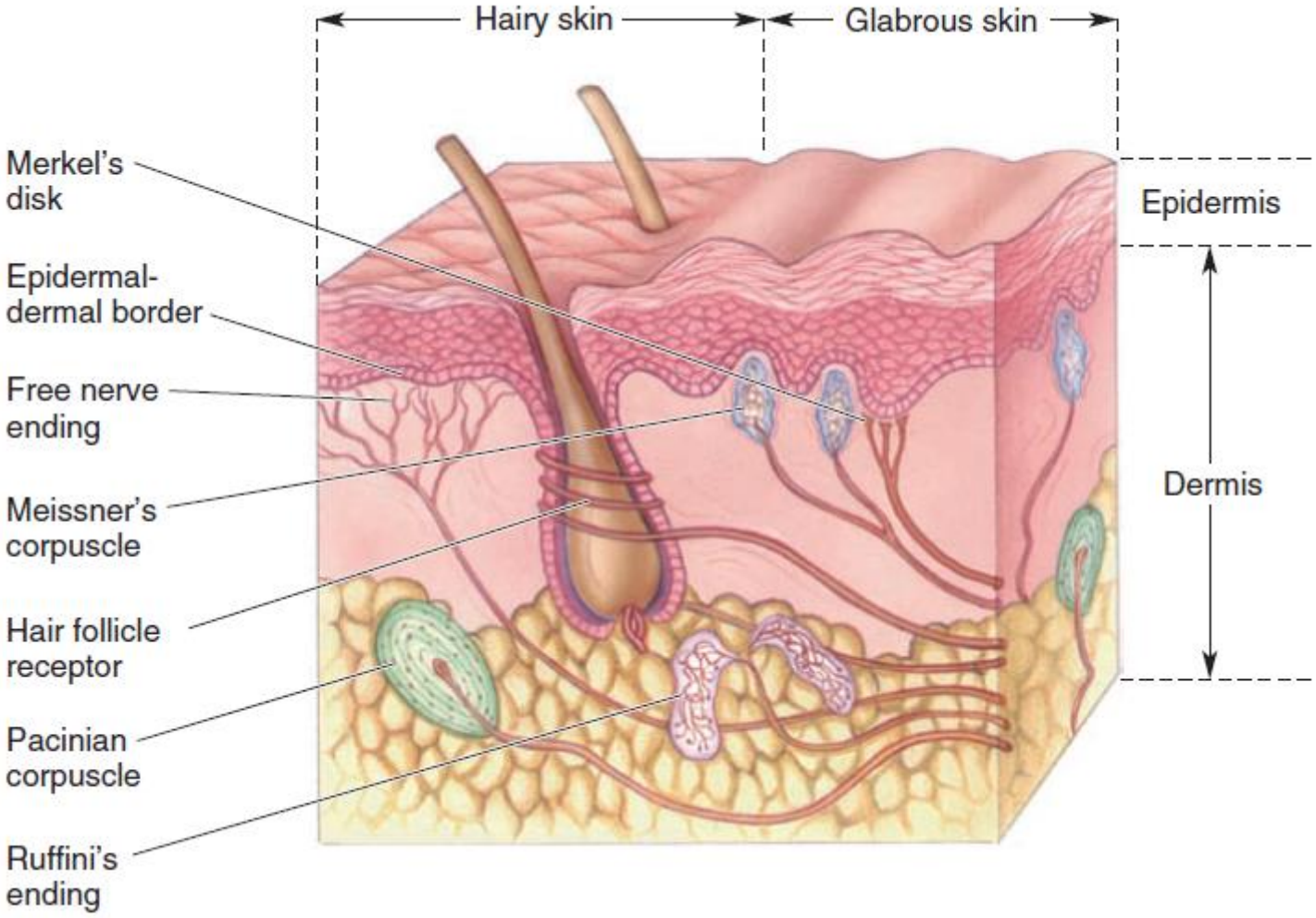
Rate of adaptation of different types of receptors



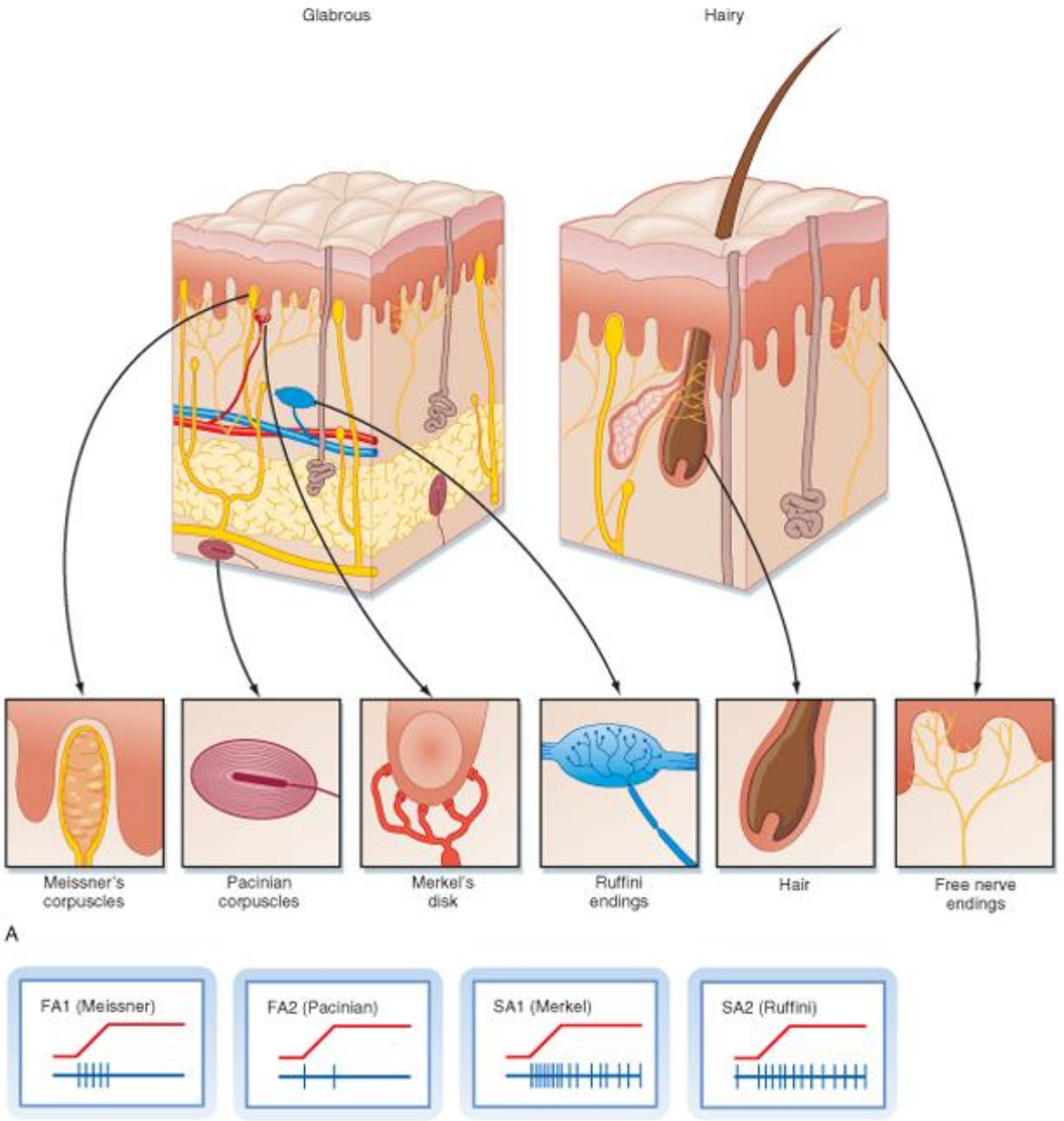
Mechanoreceptors of skin



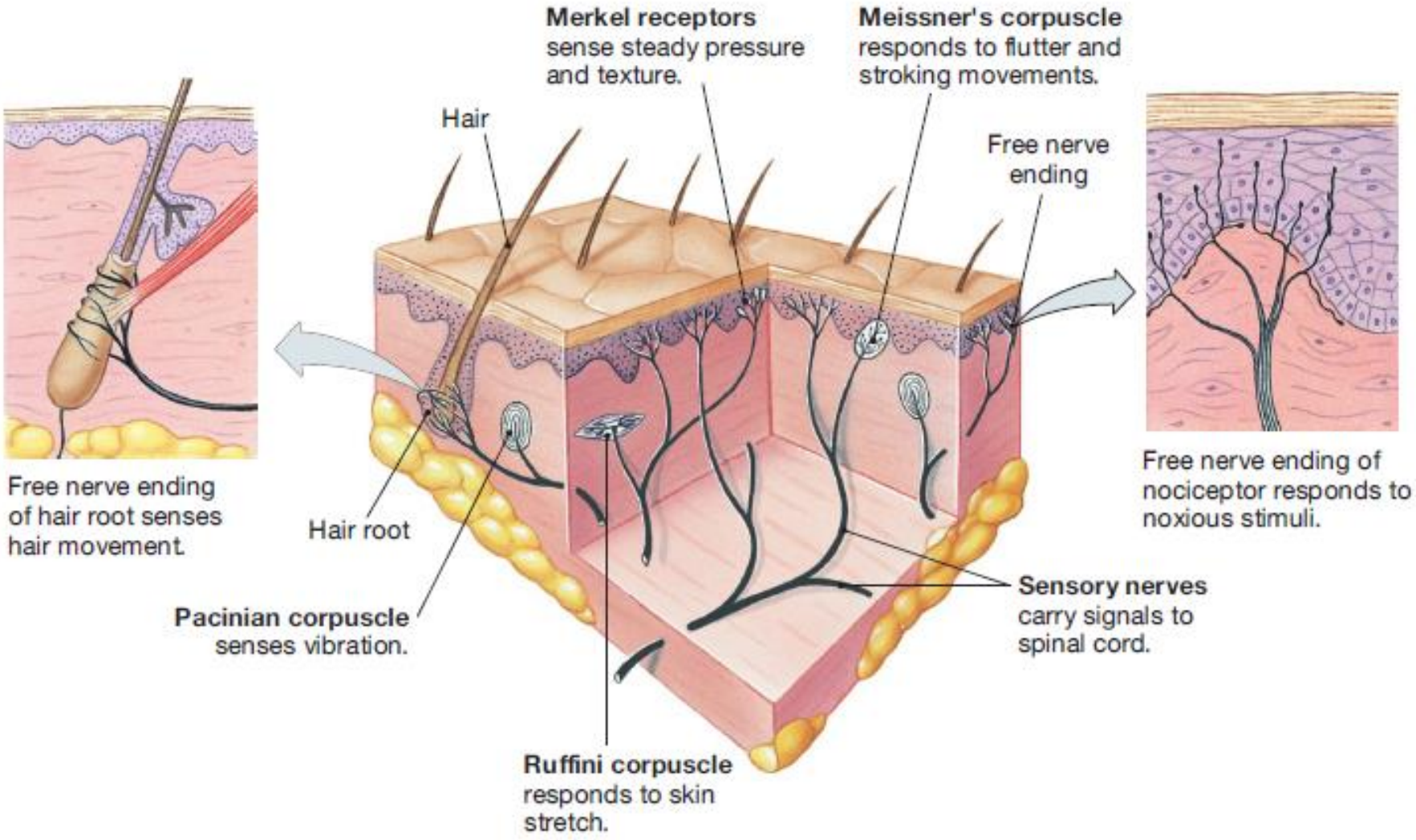
Mechanoreceptors of skin



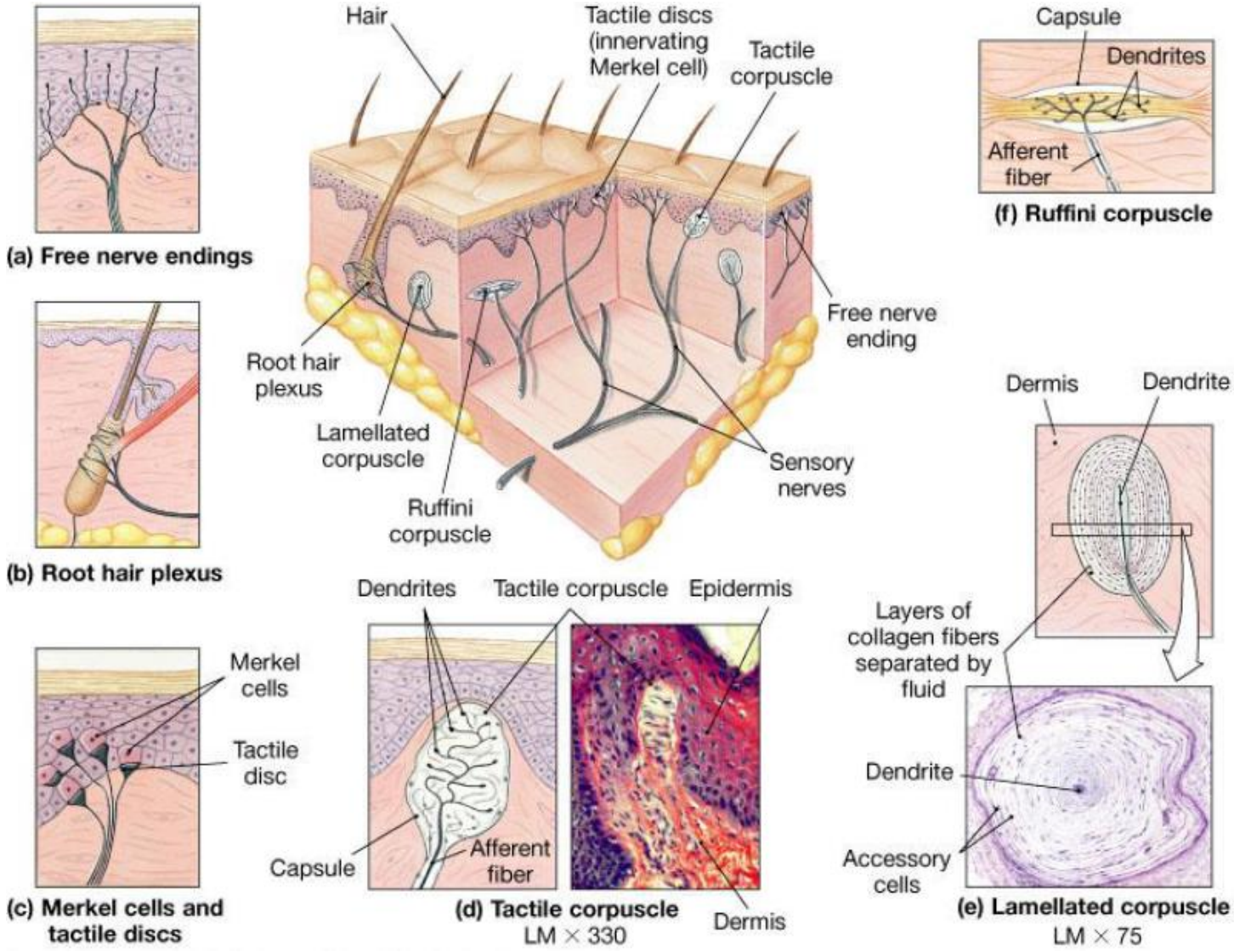
Mechanoreceptors of skin

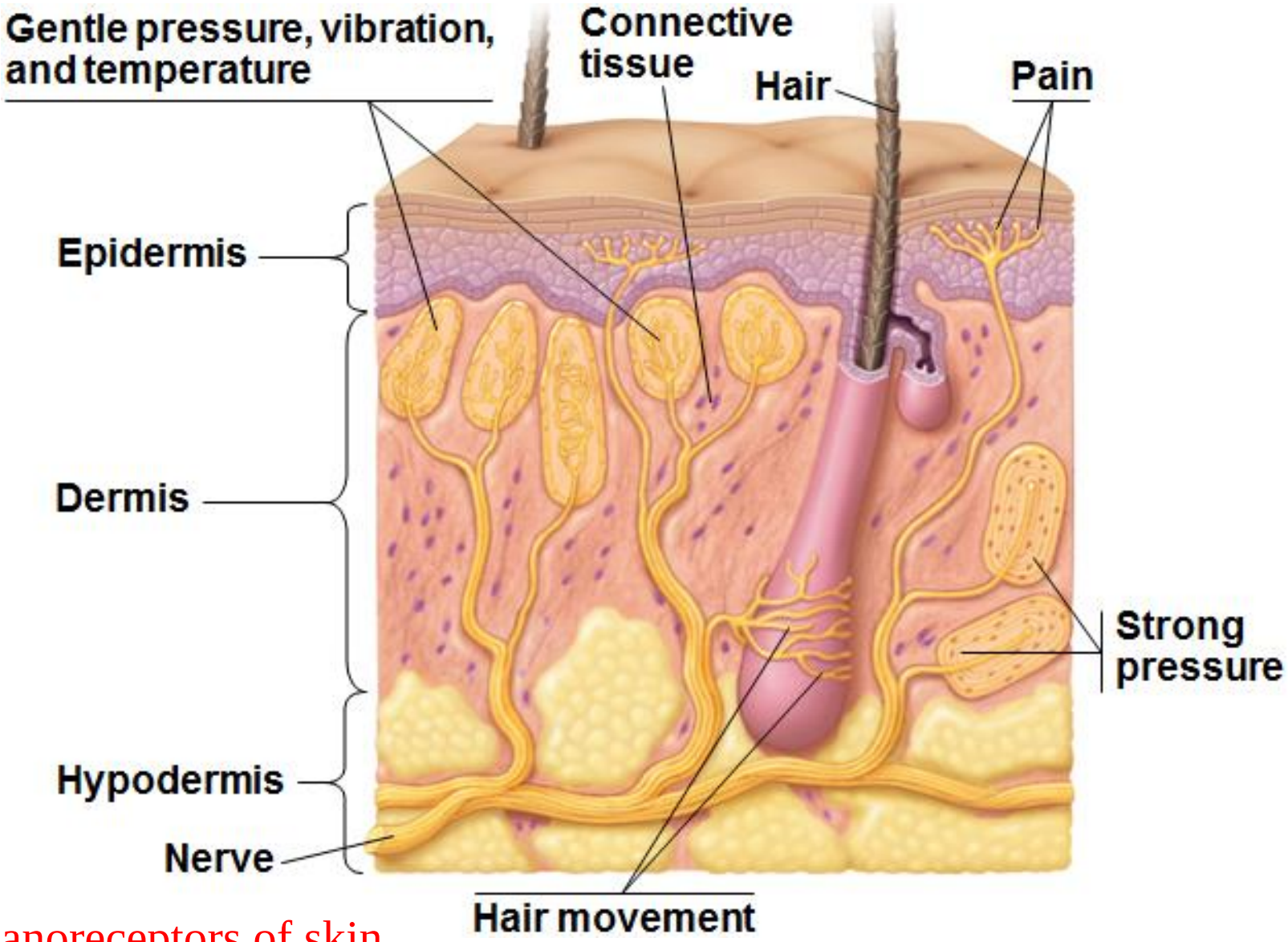


Mechanoreceptors of skin



Mechanoreceptors of skin





Mechanoreceptors of skin

Hair follicle afferents

- Hairy skin is innervated by a separate receptor, called the D-hair receptor/hair follicle afferent (HFA).
- It is the most sensitive receptor in hairy skin (- Meissner corpuscles)
- HFAs innervate 10-30 hairs spread over an area of 1-2cm^2 (sensitive to hair movement but not to static pressure).
- HFAs conduct action potentials in the Aδ range (velocity of 20–25 m/s).
- Functions are similar to Meissner corpuscle/+ velocity and direction of movement…

Field Receptors…

C mechanoreceptors… C-fibers…slow stroking of the skin…erotic touch…

Thermoreceptors

- Respond to heat or cold.
- Humans recognize four distinct types of thermal sensation: cold, cool, warm, and hot (Δs between the external temperature of the air or of objects contacting the body and the normal skin temperature of approximately 32°C).
- Help regulate body temperature by signaling both surface + body core temperature.
- A number of kinds of thermoreceptors, each specific for a particular temperature range…
- Membrane receptor proteins respond to temperature $\rightarrow \Delta E_m \rightarrow$ RPs $\rightarrow$ APs to the brain…$\rightarrow$ interprets as sensation…warm and cold…
- Skin receptors… free nerve endings… + hypothalamic thermostat …

Nociceptors

- Pain receptors…
- Free nerve endings (tissue damage, chemical irritation…)
- Respond selectively to stimuli that can damage tissue.
- Respond directly to mechanical and thermal stimuli.
- Respond indirectly to other stimuli by means of chemicals released from cells in the traumatized tissue…
- Signal impending tissue injury and provide a constant reminder of tissues that are already injured and must be protected.

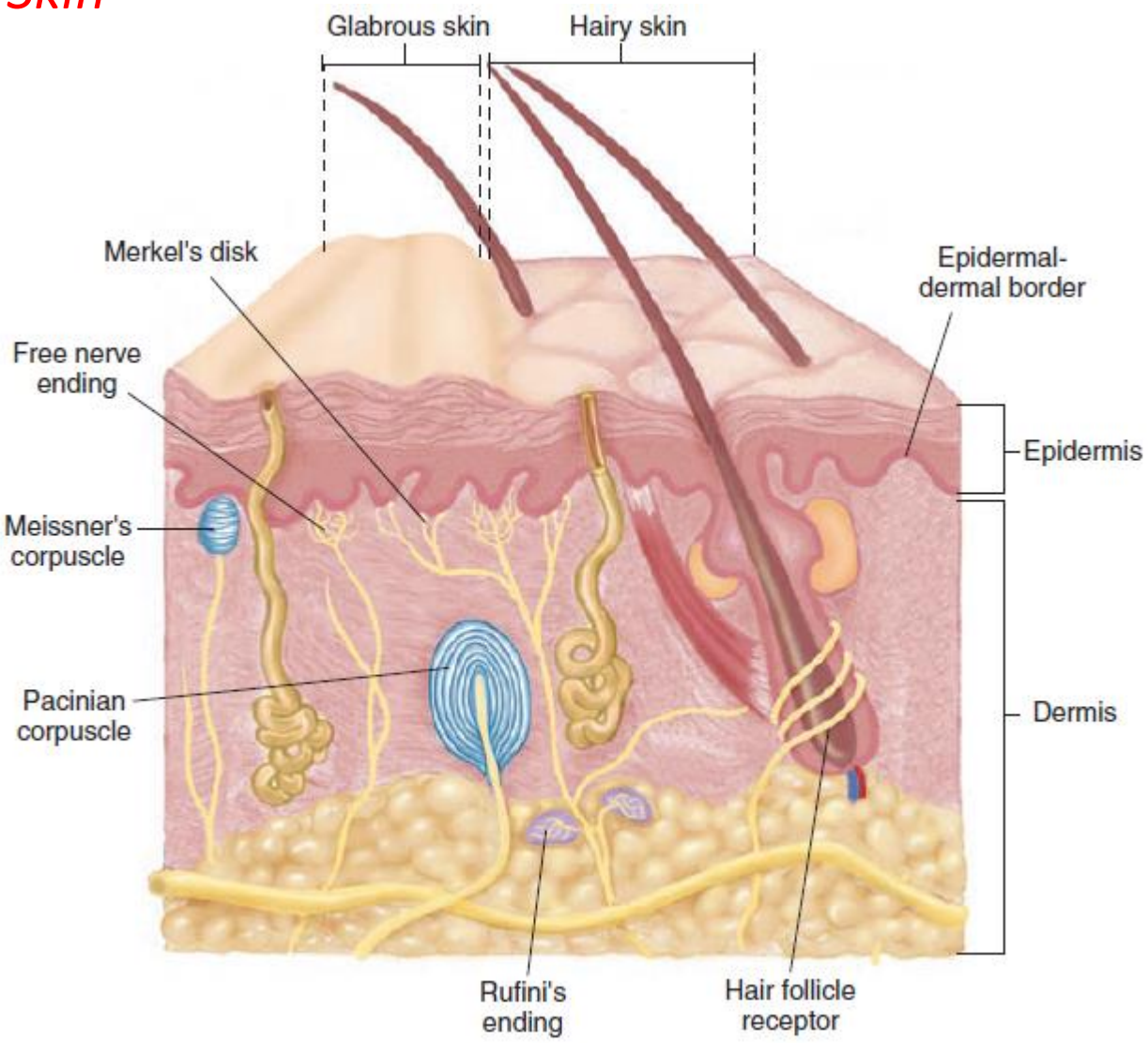
- Two classes of afferent fibers (Aδ + C fibers).
- Aδ fibers: short-latency, sharp and pricking…
- Mechanical nociceptors: sharp objects that penetrate, squeeze or pinch of the skin, noxious heat…
- C-fibers: dull burning pain, diffusely localized and poorly tolerated…
- Polymodal nociceptors
  - Noxious, mechanical, thermal + chemical stimuli… (such as pinch or puncture, noxious heat and cold, and irritant chemicals applied to the skin..).
- Viscera nociceptors
  - Activated by distension or swelling…

Proprioceptors

- Provide information about mechanical forces arising from within the body (musculoskeletal system, muscle and tendon receptors).
- Provide detailed and consistent information about the position of the limbs in space (posture + movement).
- Three proprioceptors:
  - *Muscle spindle*
    - ✓ In skeletal muscle (EOM, intrinsic muscles of the hand + neck).
    - ✓ Signal changes in muscle length (Ia and II, *parallel*).
  - *GTO*
    - ✓ Distributed among collagen fibers that form the tendons (*series*).
    - ✓ Inform CNS about changes in muscle tension.
  - *Joint capsule receptors*
    - ✓ Located in and around joints.
    - ✓ Gathers information about limb position and joint movement.

Skin….Touch

Skin



- Skin: the largest sense organ…
- Glabrous skin + hairy skin.
- 0.006 mm x 0.04mm
- *Functions*: …

Fine Touch…

- Accurately localized (*Topognosis)* + number of stimuli identifiable.
- Receptors: Meissner's corpuscles + Merkel's discs…

- Accurate in the fingertips and lips than in other areas.
  (Rich in receptors + afferent neurons + widely represented in S1).
- Nerve fibers: Aβ fibers (θ = 8-15μm, ν = 30-60m/s).
- Tract: spinal cord → gracile and cuneate tracts → sensory area of cerebral cortex.

NB: Crude touch vs fine touch?

Receptor field…

- The region within which a tactile stimulus evokes a sensory response in the cell or its axon (define the zone of tactile sensitivity…)
- *RF:* a limited area of the skin where individual mechanoreceptor fibers convey information/microneurography.
- RF of a mechanosensitive neuron varies:
  - Tip of fingers: 1-2mm (∵more encapsulated mechanoreceptors).
  - Palms: 5-10mm
- Type 1 fibers have small, highly localized receptive fields with multiple spots of high sensitivity that reflect the branching patterns of their axons in the skin.

Receptive field…

- RFs on the fingertips are the smallest on the body.
  - SA1: 11mm^2
  - RA1: 25mm^2.
- Lower density of mechanoreceptors → RFs become progressively larger on the proximal phalanges and the palm.

Tactile acuity…

- Tactile acuity is determined by:
  - How close the mechanoreceptors are to each other…
  - Size of the receptive field…
- Slightly greater in women than in men and varies between fingers. (not between hands)
- Distal pad of the index finger has the keenest sensitivity.
- Spatial acuity declines progressively from the index to the little finger and declines rapidly at locations proximal to the distal finger pads…
- Tactile spatial resolution is 50% poorer at the distal pad of the little finger and six to eight times coarser on the palm.
- Tactile acuity on proximal parts of the body decreases in parallel with the growing size of RFs of SA1 and RA1 fibers.

Two-point discrimination/Tactile discrimination

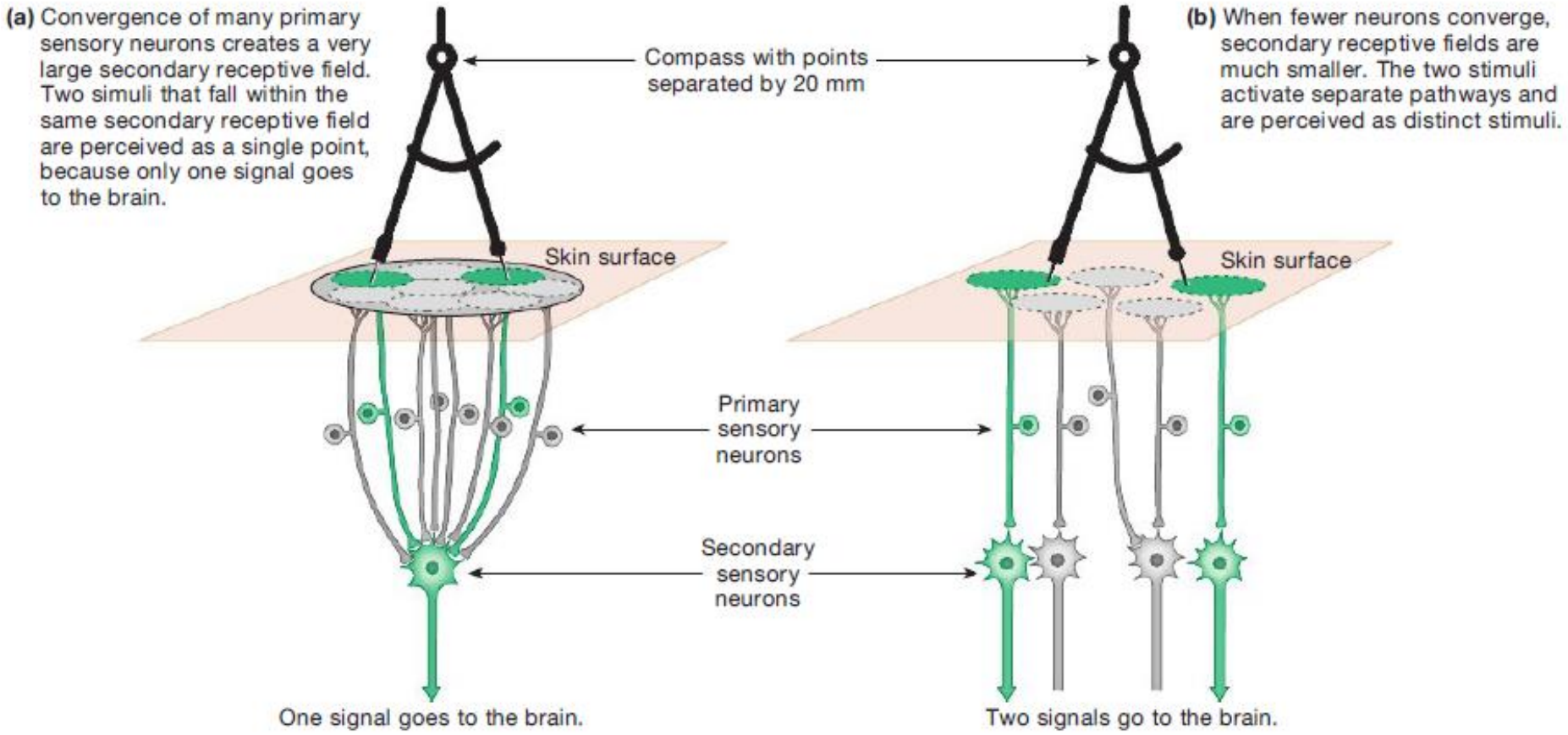
- It is the minimal distance at which the two stimuli are felt as two separate points of contact (Two-point threshold measures the minimum distance at which two stimuli are resolved as distinct).
- The two points of touch should stimulate 2 separate receptors → resulting impulses should be transmitted along 2 separate afferent fibers to 2 separate neurons in the sensory area of the cerebral cortex.
- T.D. is more acute in the tongue (1mm) and finger tips (2-3mm) than in the back (15-20mm) or the shoulder and thigh (about 70mm).
- Threshold for spatial acuity on the fingertips:
    - Young adults: ≈ 1mm
    - Elderly: ≈ 2 mm.

- Two-point threshold varies for different body regions…
  - Finger tips = 2mm, palm = 5-10mm, arm = 40mm
- *Reasons*:
  - Greater number of receptors…
  - Size of the sensory receptive fields (RF $\propto \frac{1}{\text{Density of receptors}}$)
  - Innervation density (greater number of afferents) of mechano-receptors in the superficial layers of skin + variety of receptors…
  - Less convergence (+ more area of cortical representation).

- The two-point threshold for any part of the body is determined by the size of the RFs and the extent of overlap.
  (↓ Overlap →↑discrimination).
- Blind individuals use the fine spatial sensitivity of SA1 and RA1 fibers to read Braille…(1.0mm x 2.5mm)

NB

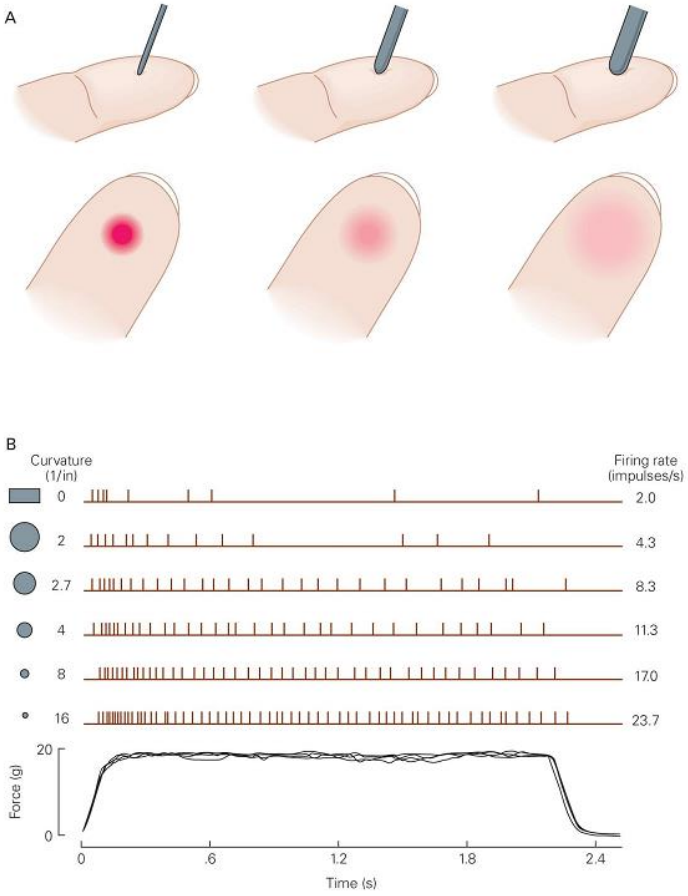
- Discrimination is most developed in the eyes, where the **fovea centralis** of the retina can discriminate very near points of light.



- If two points stimulate two different receptors, you will feel two points. If two points stimulate only one receptor, you will feel only one.

Slowly adapting fibers detect object pressure and form

- SA1 + SA2 signal skin deformation & pressure.
- SA1 receptor is sensitive to edges, corners, points, & curvature provides information about object shape, size, surface texture, and compliance/we perceive an object as hard or rigid if it indents the skin, and soft if the skin surface instead deforms the object.
- As an object's diameter increases, the responses of individual SA1 fibers become weaker & the sensation less distinct…
- …tip of a pencil pressed 1mm into the skin feels sharp, unpleasant, and highly localized at the contact point, whereas a 1mm indentation by the eraser feels blunt & broad…



- The area of contact on the skin determines the firing rate + total number of SA1 fibers stimulated.
- Firing rate of an individual SA1 fiber is determined by the probe diameter.
- Sensitivity of SA1 receptors to local stretch of the skin enables them to detect edges, the places where an object's curvature changes abruptly.
- SA1 firing rates are many times greater when a finger touches an edge than when it touches a flat surface…
- A small-diameter, sharply pointed probe activates a small population of SA1 receptors.
- Activated fibers fire intensely because all of the force is concentrated in a small area.

- The intensity of color is proportional to the firing rates of the stimulated receptors.

- Why these objects evoke different sensations???

Slowly adapting type 1/SA1 fibers encode the shape & size of objects touching the hand.

- The indentation force of a flat or gently curved surface is distributed symmetrically within the central contact zone, whereas the force applied by an object boundary displaces the skin asymmetrically, beyond the edge as well as at the edge…
- This asymmetric distribution of force produces enhanced responses from RFs located along the edges of an object….As edges are often perceived as sharp, we tend to grasp objects on flat or gently curved surfaces rather than by their edges…
- During steady pressure the firing rate is proportional to the curvature of each probe. The highest firing rates are evoked by the smallest probe, while the weakest responses are produced by flat surfaces and gently rounded /large diameter probes. The tip's curvature is expressed as the inverse of its spherical radius…

- SA1 receptors at both the center + surrounding "hillsides" of skin are stimulated, firing spike trains proportional to the degree of local stretch/*tensile strain…*
- As more probes are added within the RF, the response intensity of each fiber becomes progressively weaker because the displacement forces on the skin are distributed across the entire contact zone/*less is more*…
- Individual SA1 fibers respond more vigorously to a small object than to a large one because the force needed to indent the skin is concentrated at a small contact point/each SA1 fiber integrates the local skin indentation profile within its RF...

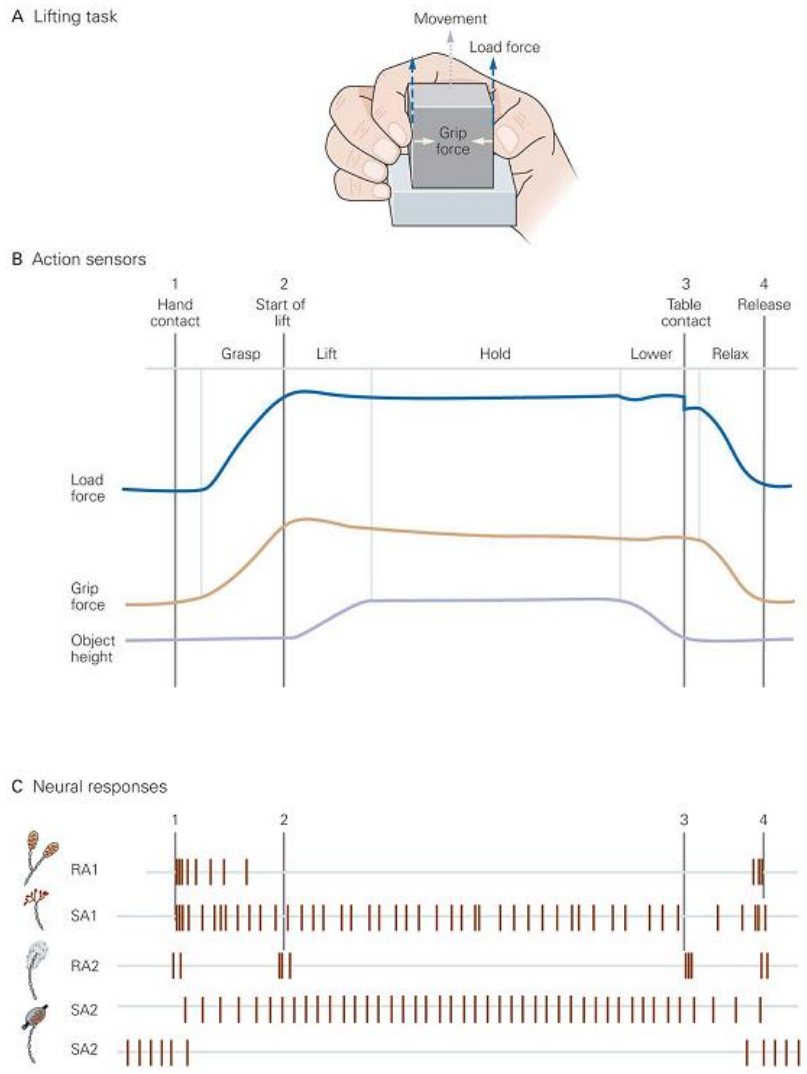
- SA2 fibers that innervate Ruffini endings respond more vigorously to stretch of the skin than to indentation because the receptors are located along the palmar folds or at the finger joints…
- SA2 fibers provide information about the shape of large objects grasped with the entire hand, the "power grasp" in which all five fingers press an object against the palm…
- Provide information about hand shape + finger movements when the hand is empty. If the fingers are fully extended and abducted we feel the stretch in the palm & proximal phalanges as the glabrous skin is flattened…
- If the fingers are fully flexed, forming a fist, we feel the stretch of the skin on the back of the hand, particularly over the metacarpal-phalangeal and proximal interphalangeal joints…

- SA2 system play a central role in *stereognosis*...
- SA2 innervation in the hairy skin…perception of hand shape & finger position…
- SA2 fibers aid the perception of finger joint angle by detecting skin stretch around the knuckles…
- Ruffini endings near these joints are aligned such that different groups of receptors are stimulated as the fingers move in specific directions/the SA2 system provides a neural representation of skin stretch over the entire hand, a proprioceptive rather than exteroceptive function…

Rapidly adapting fibers detect motion and vibration

- RA1 receptor organ/Meissner corpuscle, detects events that produce low-frequency, low-amplitude skin motion…
- Hand motion over the surface of objects, the detection of microscopic surface features, and low-frequency vibration…
- RA1 fibers contribute to detection of *Braille* patterns because they sense the change in skin indentation as individual dots pass over their receptive fields…
- Can detect irregularities & bumps as small as 10μm.

- RA2 receptor/Pacinian corpuscle, is the most sensitive mechanoreceptor in the somatosensory system…
- Exquisitely responsive to high-frequency (30–500Hz) vibratory stimuli, and can detect vibration of 250Hz in the nanometer range…
- The buzzing sensation experienced when a tuning fork is pressed against the skin in a neurological examination is mediated by the synchronized firing of RA2 units…
- It is a useful measurement of dynamic sensitivity to touch, particularly in cases of localized nerve damage…



- The grip force is adapted to the surface texture + weight of the object.
- All four mechanoreceptors detect hand contact with the object but each monitors a different aspect of the action as the task progresses...
- SA1 fibers encode the grip force + SA2 fibers the hand posture…
- RA1 fibers encode the rate of force application & movement of the hand on the object.
- RA2 fibers sense vibrations in the object with each movement: at hand contact, lift-off, table contact, and release of grasp.

Sensory information from the hand during grasping and lifting

Mechanism of transmission of tactile signals

- Touch → deformation of receptors (Meissner's corpuscles + Iggo dome receptors + hair receptors + Ruffini's endings…) → opening of pressure sensitive Na^+ ion channels in the axon membrane (Aβ & Aδ fibers +) → influx of Na^+ → RP → APs…

Crude Touch

- Not sharply localized; or number of stimuli not accurately distinct.
- Receptors: Hair end organs (basket hair endings).
  Free nerve endings.
- Nerve fibers: Aδ fibers (θ = 1-5μm, ν = 5-15m/s).
- Tract: spinal cord → ventral spinothalamic tract → somatosensory cortex.

Tickle

- A sensation produced by mild tactile stimulation of certain superficial areas of skin → reflex involuntary laughter.
- Basket hair nerve endings/+ type C fibers.

Itch

- Skin + ocular conjunctiva and the mucosa.
- Skin irritation that leads to the desire for scratching of the skin (scratch reflex).
- Moving tactile stimulus (e.g., a moving flea).
- Substances released in skin (bradykinin, histamine+ histamine receptors).
- Receptors: free naked nerve endings (superficial layer skin).
- Conducted by unmyelinated C fibers (0.5m/s).
- Scratching relieves itch by removing the irritating stimulus +++ (∵scratching activates large fast conducting afferents…+ Lateral presynaptic inhibition of itch-conducting fibers…).

Vibration Sense

- A flickering or repetitive sensation.
- All tactile receptors are involved in detection of vibration.
- Two types of receptors:
  - Meissner's corpuscles: respond to vibration frequencies from 2 up to 80 Hz.
  - Pacinian corpuscles: respond to frequencies from 30 to 800 Hz.
- Aβ fibers (1000 impulses/sec).
- Tract: gracile and cuneate tracts to cerebral cortex.
  (the *dorsal column-lemniscal system*).

Pressure Sense…

- A sensation produced by a strong, blunt, static mechanical stimulus.
- Depending on the intensity of the mechanical stimulus:
  - Light pressure: cutaneous receptors
  - Deep pressure: deeper receptors (fasciae + connective tissues).
- Receptors:
  - Ruffini's endings (slowly adapting)
  - Pacinian corpuscles (rapidly adapting).

Types of pressure sensation:

- Crude pressure sensation:
  - Low ability to discriminate two different weights. (*Ventral spinothalamic tract*).
- Fine pressure sensation
  - High ability to discriminate different weights. (*gracile and cuneate tracts*).

Stereognosis

- The ability to recognize objects from its shape, size, weight, etc., by handling them without seeing them.
- Touch + pressure sensations + cortical somatic association areas of the parietal lobe.
- Conducted by the gracile and cuneate pathway.

Proprioception sense (*Kinesthetic sensations*)

- Conscious perception of:
  - Orientation of different parts of the body with respect to each other and the position of the body in space.
  - Rate of movement of different parts of the body.
- Two categories:

a. Sense of position (Static proprioception)

  - Sense of the position of different parts of the body relative to each other.
  - Receptors: muscle spindle + Golgi tendon organs.

b. Dynamic proprioception/Sense of movement

- Sense of movements of joints.
- Receptors: Pacinian corpuscles + GTO in ligaments + synovial membranes of joints.
- Neural tracts: gracile and cuneate tracts.

Touch Vs Pressure Vs Vibration senses

- Touch sense: stimulation of tactile receptors in the skin/beneath the skin.
- Pressure: stimulation of deeper tissues.
- Vibration : rapidly repetitive sensory signals.

5. Skeletal System; Bone

- The entire framework of bones and their cartilages, along with ligaments and tendons, constitutes the **skeletal system.**

- **Bone** is a connective tissue which continuously undergoing;
  - ✓ growing, remodeling and repairing

- Bone contributes to the homeostasis of the body!

❖ 18% of the weight of the human body is bone tissue.

Bone cont'd

Functions of Bone Tissue

1. **Supports** soft tissue and provides attachment for skeletal muscles.

2. **Protection of vital organs;** one of the important function.
   - ✓ Brain, Heart, Urogenital system, spinal cord are protected by different bones.

3. **Assists in movement** along with skeletal muscles.

4. **Stores and releases minerals**;
   - ➢ **Ca and P;** deposited and withdrawn as needed.

5. **Contains red bone marrow;** produces blood cells.

6. **Contains yellow bone marrow;** stores triglycerides.

Bone cont'd

❑ **Components of bone**

- **Bones** consist of living cells embedded in a mineralized organic matrix.

❖ This matrix consists of organic **components**, mainly type I collagen

- Inorganic **components**, primarily salts of calcium and phosphate.

❑ **Cartilages, Tendons and ligaments**

– Support different structures– nose, external ears, ribs and trachea

- **Cartilage**
  - It is more flexible than bone
  - Are model for bone growth
- **Tendons and ligaments form attachments**
  - Ligaments used to attach bone to bones or bone to joints
  - Tendon used to attach muscle to bone

Bone Cont'd

- Bone is not completely solid but has many small spaces between its cells and extracellular matrix.
  - ✓ Some spaces serve as **channels for blood vessels;**
  - ✓ **O**ther spaces act as **storage areas for red bone.**
- Depending on the size and distribution of the spaces, the regions of a bone are

1. Spongy bone; 80%

- **C**omposed of **spicules** to form a porous network.
- ✓ The space are usually filled with **marrow**.
- ✓ the medullary cavity of the diaphysis contains yellow bone marrow; adults

2. Compact bone; 20%

- The hard layer constitutes the exterior of most bones and forms almost the entire shaft of long bones.

Bone's role in calcium homeostasis

- Bone is the body's major calcium reservoir

✓ storing 99% of total body calcium.

- To maintain the level of Ca in the blood:

✓ control the rates of Ca resorption from bone into blood and Ca deposition from blood into bone are important determinants.

- Both nerve and muscle cells depend on a stable level of Ca+2
- Blood clotting also requires Ca+2.

NB: Hemostasis vs Homeostasis?

Bone Cont'd

- Ca2 exchange is regulated by hormones.
- The most important is **PTH secreted by** the parathyroid gland.

- PTH also acts on the kidneys to decrease loss of Ca2 in the urine, so more is retained in the blood.

- PTH stimulates formation of **calcitriol (the active form of vitamin D),**

✓ a hormone promotes absorption of Ca2+ from foods in the GIT into the blood.

- **Both of these actions help elevate blood Ca2 level.**

- This is the end

- Read related text books (e. g: Guyton and Hall Medical Physiology Text book, Essentials of Medical Physiology, Silverton…..

- Hopefully we will meet after the some time!

- Stay safe!!!