NERVES & MUSCLES PHYSIOLOGY

Lecture 7

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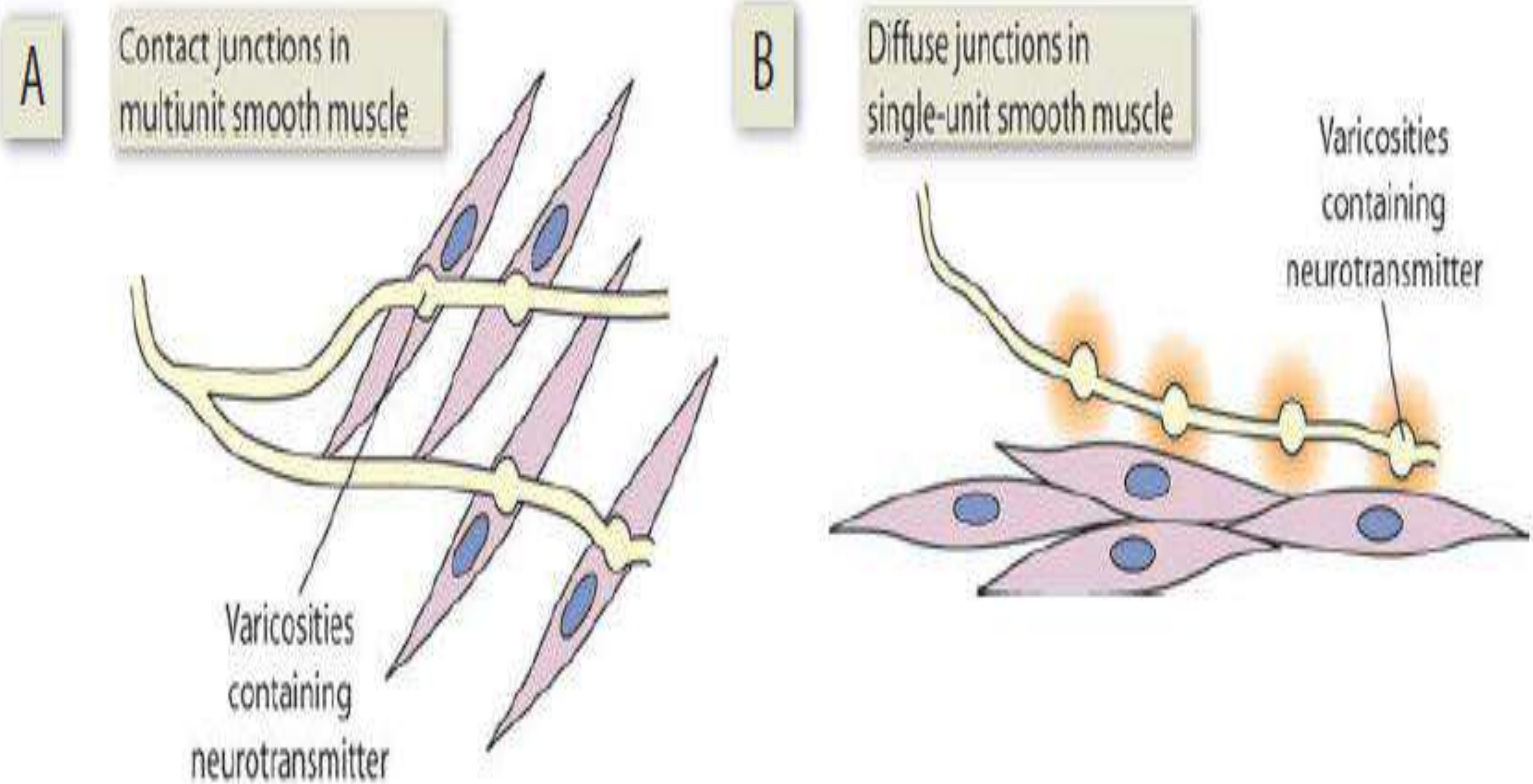
Objectives for this lecture

- Describe the types of smooth muscles, and the mechanism of smooth muscle contraction and relaxation.
- Explain the difference between smooth, skeletal, and cardiac muscles.

Smooth muscle can generally be divided into two major types, the **multi-unit** and the **single unit** smooth muscle :
Single-unit smooth muscle cells can be found in the gut and blood vessels. Because these cells are linked together by gap junctions, they are able to contract as a syncytium.
Single-unit smooth muscle cells contract myogenically, which can be modulated by the autonomic nervous system.

The multi-unit smooth muscle cells are non-rhythmical and found in the muscle of the eye and in the base of hair follicles.
Multi-unit smooth muscle cells contract by being separately stimulated by nerves of the autonomic nervous system.
As such, they allow for fine control and gradual responses, much like motor unit recruitment in skeletal muscle.


A
Contact junctions in
multiunit smooth muscle
Varicosities
containing
neurotransmitter
B
Diffuse junctions in
single-unit smooth muscle
Varicosities
containing
neurotransmitter

The junction between the nerve terminals and smooth muscles are either **contact junction** (morphologically more like skeletal muscle neuromuscular junction) as in multiunit smooth muscles or **diffuse junction** as in single unit smooth muscles.

In these junctions, the nerve fiber of **autonomic nervous system** branch diffusely on top of a sheet of muscle fiber without making an actual direct contact with single unit smooth muscle fibers as in diffuse junction or making a direct contact with multi-unit smooth muscle fibers as in contact junction.

The multiple branches of the nerve fibers are beaded with enlargements (called **varicosities)** from which neurotransmitter substance is released from the nerve fiber which is then diffused into the interstitial fluid and then to the smooth muscle fiber.

Modes of stimulation of smooth muscle: Smooth muscles can contract or relax as a consequence of the following factors:

[1]. Action potential factor: Smooth muscle action potentials arise from membrane can be due to:

- **The rhythmicity**.
- **Stretching the smooth muscles**.
- **Generation of excitatory junctional potential** (EJP).

Depolarization of the plasma membrane opens voltage-gated Ca^{2+} channels.

Calcium ions diffuse through the Ca^{2+} channels from ECF to ICF. EJP results from the interaction between neurotransmitters from autonomic nervous system and excitatory receptors at the multiunit smooth muscle membrane lead to generation of discrete partial depolarization that look like small end-plate potentials and called excitatory junctional potentials (EJPs). The action potential does not develop.

This type of depolarization is called local depolarization or excitatory junctional potential (EJP). This local depolarization travels throughout the entire multiunit smooth muscle fiber and causes contraction. Local depolarization is developed because the multiunit smooth muscle fibers are too small to develop action potential.

Smooth muscle relaxation can be result of the generation of **inhibitory junctional potentials** (IJPs) if interaction between a neurotransmitter and inhibitory receptors occurs with consequent hyperpolarization of the membrane.

[2] Non action potential factors: Smooth muscle contraction can be initiated without the generation of an action potential as a result of **local tissue factors** or **humeral factors**. Chemical substances (Humeral factors through activation of G protein) (norepinephrine, epinephrine, acetylcholine, angiotensin, vasopressin, oxytocin, serotonin, and histamine) can initiate smooth muscle contraction.

cause smooth muscle contraction by **increase the intracellular Ca^{2+} concentration** .

Activated excitatory receptors of **G protein** can activate **G protein-gated Ca^{2+} channels** at the smooth muscle cell membrane or membrane **phospholipase C** ➔ Release of IP3 ➔ Activates IP3-gated Ca channels at the membrane of endoplasmic reticulum :

Local tissue factors:

The smooth muscles of the **arterioles**, **metarterioles**, and **precapillary sphincters** have little or no nervous supply. Yet, the smooth muscle is highly contractile, responding rapidly to change in local condition in the surrounding interstitial fluid (local tissue factors).

Some of the specific control factors are: **↓oxygen, ↓Ca^{++}, ↓body temperature, ↑CO_2, ↑[H^+], ↑Lactic acid**, **↑[K^+]**, **↑adenosine & phosphate compounds,** in the local tissues all cause smooth muscle relaxation and therefore ➔ **vasodilatation**.

The mechanisms by which the local tissue factors excite or inhibit the smooth contraction not clear. It is possible that these factors cause change in the cell membrane potential, changes in the permeability of the membrane to Ca^{2+} ions, and/or changes in the intracellular contractile process.

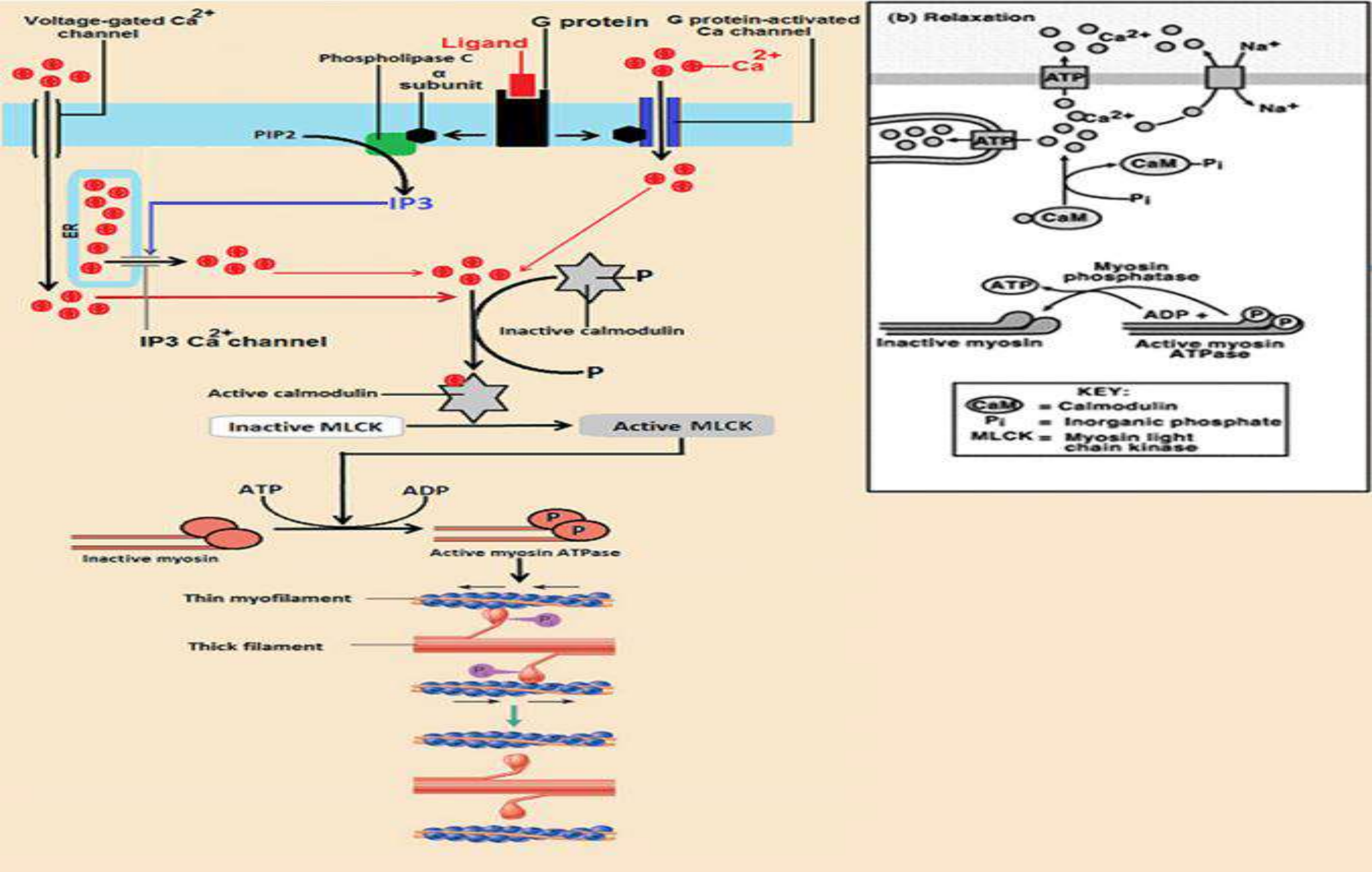
Mechanism of smooth muscle contraction:

As the ICF Ca^{2+} concentration increases, it binds with a regulatory protein called **calmodulin** (instead of troponin that present in skeletal muscle). This calmodulin-Ca^{2+} complex activate a phosphorylating enzyme called **myosin light chain kinase** (MLCK), which leads to phosphorylation of myosin head. This phosphorylation of the head of the cross-bridge will bring about the interaction between the head of myosin with the actin filament and preceding the same as occurs for skeletal muscle, thus causing muscle contraction.

When the Ca^{2+} ion concentration falls below a critical level, all aforementioned processes reverse and the presence of an enzyme **myosin phosphatase** is required to dephosphorylate the head of the cross-bridge and consequently disengagement of the head from the actin filament (relaxation) .

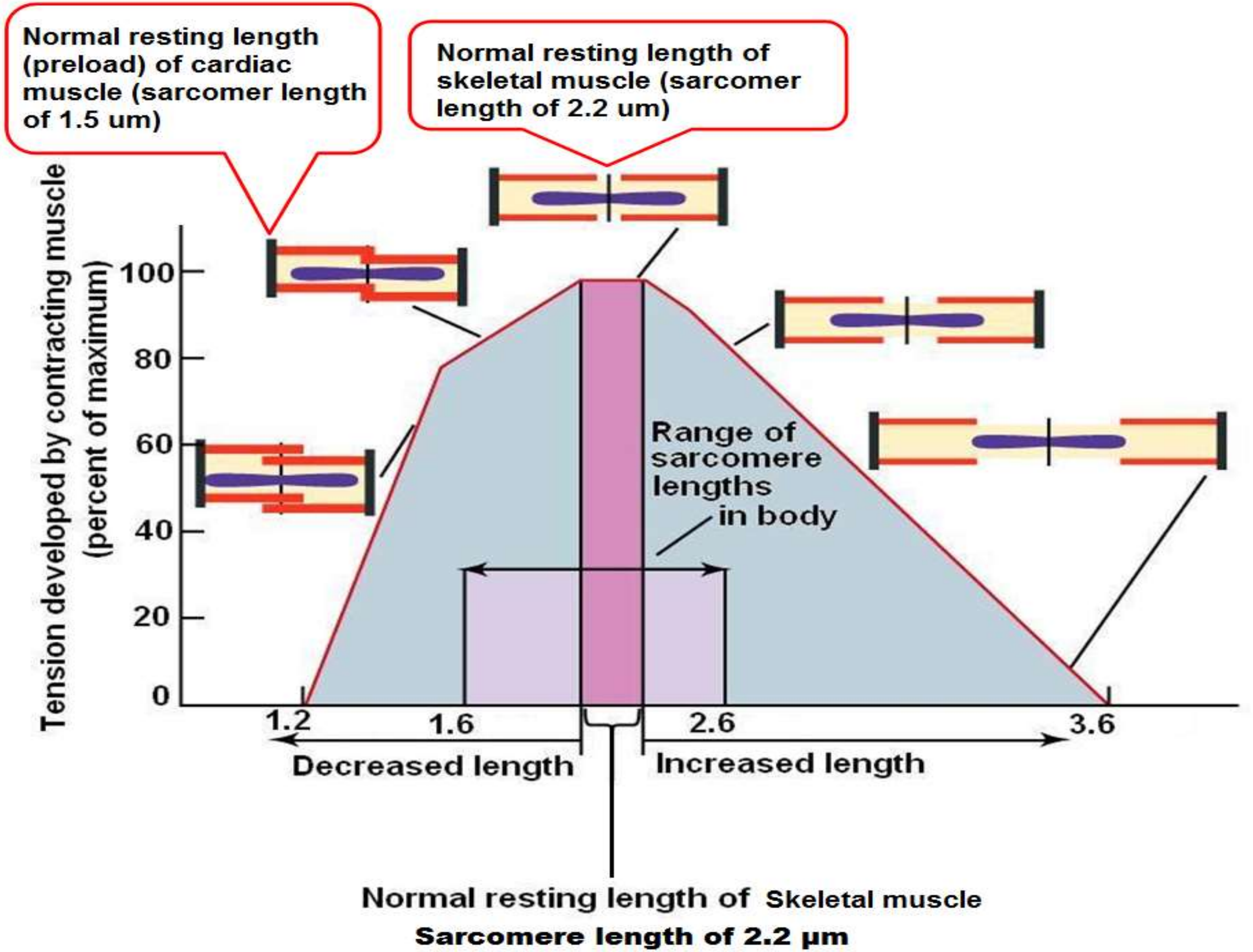
However, myosin dephosphorylation does not necessarily lead to immediate smooth muscle relaxation due to the presence of latch bridge mechanism by which the dephosphorylated myosin cross-bridges remain attached to actin for some time after the cytoplasmic Ca^{2+} ion concentration falls.

This produce sustained contraction with little expenditure of energy.



Mechanism of smooth muscle excitation and relaxation.

Drugs such as nifedipine and related newer compounds are calcium channel blockers. These drugs block Ca^{2+} channels in the membrane of smooth muscle cells within the walls of blood vessels, causing the muscles to relax and the vessels to dilate.
This effect, called vasodilation, may be helpful in treating some cases of hypertension (high blood pressure).
Calcium-channel-blocking drugs are also used when spasm of the coronary arteries (vasospasm) produces angina pectoris, which is pain caused by insufficient blood flow to the heart.



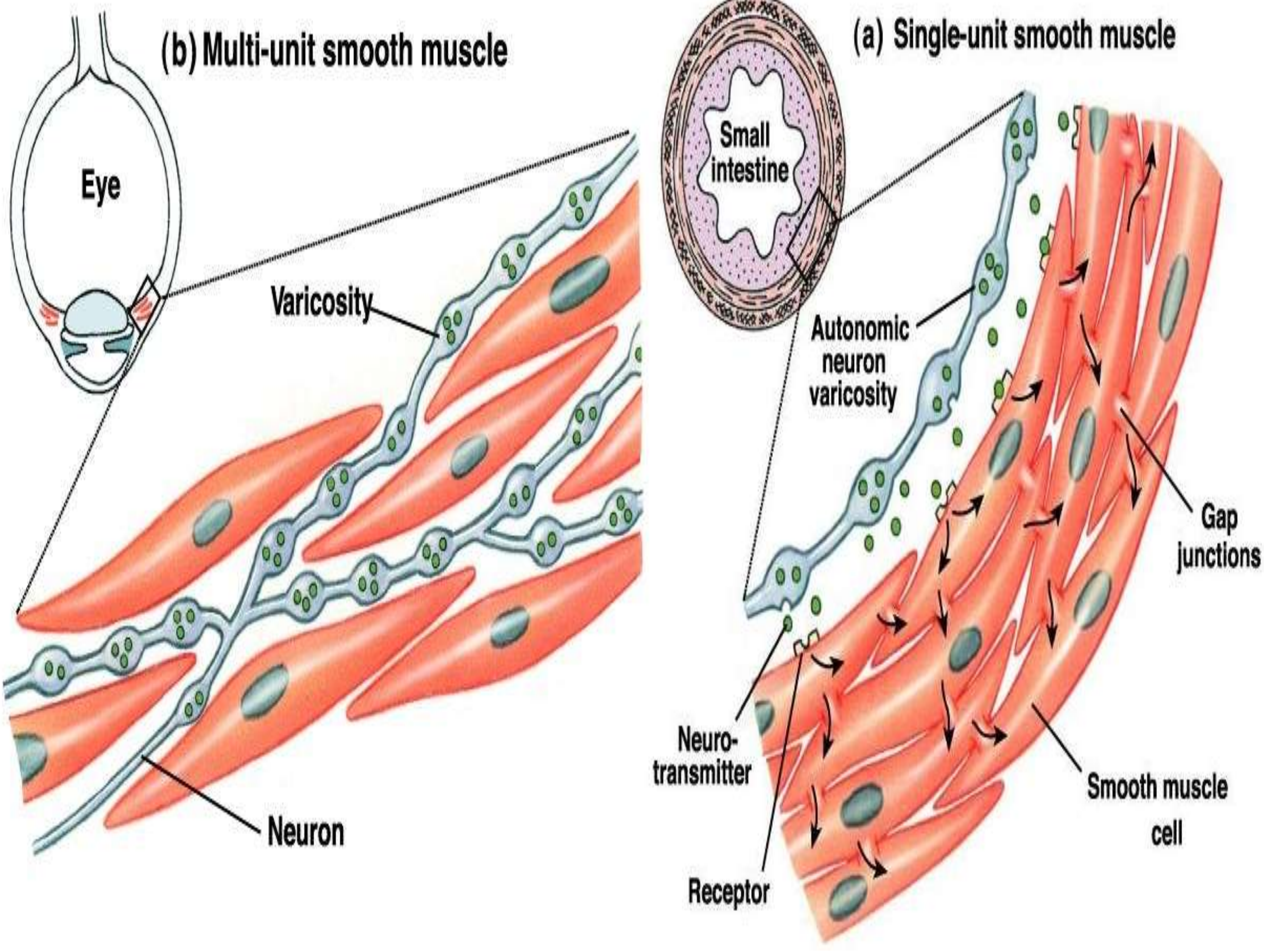
Normal resting length (preload) of cardiac muscle (sarcomer length of 1.5 um)
Normal resting length of skeletal muscle (sarcomer length of 2.2 um)
Tension developed by contracting muscle (percent of maximum)
100
80
60
40
20
0
Range of sarcomere lengths in body
1.2
1.6
2.6
3.6
Decreased length
Increased length
Normal resting length of Skeletal muscle
Sarcomere length of 2.2 µm

At sarcomere length 2.2 μ there is optimum overlap of thick and thin filament -----maximum numbers of cross bridges --- **maximum force**.

At sarcomere length >2.2 μ the overlap between thick and thin filament is decreased ---- **decrease force**.

At sarcomere length <2.2 μ: ends of 2 actine filaments overlap --- decreased numbers of the cross bridge ---- **decrease force.**

Table 4.4: Comparison between red and pale muscles.	
Red (slow twitch) muscles Example: Back muscles and gastrocnemius muscles	**Pale (fast twitch) muscle** Examples: Hand muscles and ocular muscles
Type I fibers are more ➔ Twitch contraction is long ➔ designed for sustained contraction	Type II fibers are more ➔ Twitch contraction is short ➔ designed for short contraction
More Myoglobin content, so it is red, **More** blood vessels, **More** mitochondria ➔ aerobic glycolysis for ATP production ➔ less liable to fatigue.	**Less** myoglobin content, so it is pale, **Less** blood vessels, **Less** mitochondria ➔ anaerobic glycolysis for ATP production ➔ more liable to fatigue.
Sarcoplasmic reticulum is less extensive ➔ Contraction is less powerful	Sarcoplasmic reticulum is more extensive ➔ Contraction is more powerful
Response is slow with long latent period	Response is rapid with short latent period


(b) Multi-unit smooth muscle
Eye
Varicosity
Neuron
(a) Single-unit smooth muscle
Small intestine
Autonomic neuron varicosity
Gap junctions
Neuro-transmitter
Receptor
Smooth muscle cell

Smooth Muscle Contraction & Relaxation

Smooth muscles can contract or relax as a consequence of the increase or decrease the **intracellular Ca^{2+} concentration**. This is achieved by the following factors:

- Action potential-induced contraction ➔ open of the membrane voltage-gated Ca^{2+} channels ➔ Influx of Ca^{2+} ➔ Muscle contraction.
  - **Rhythmicity**
  - **Stretching**
  - **Excitatory junctional potential (EJP)**

Action Potential Generation

Smooth Muscle Contraction & Relaxation

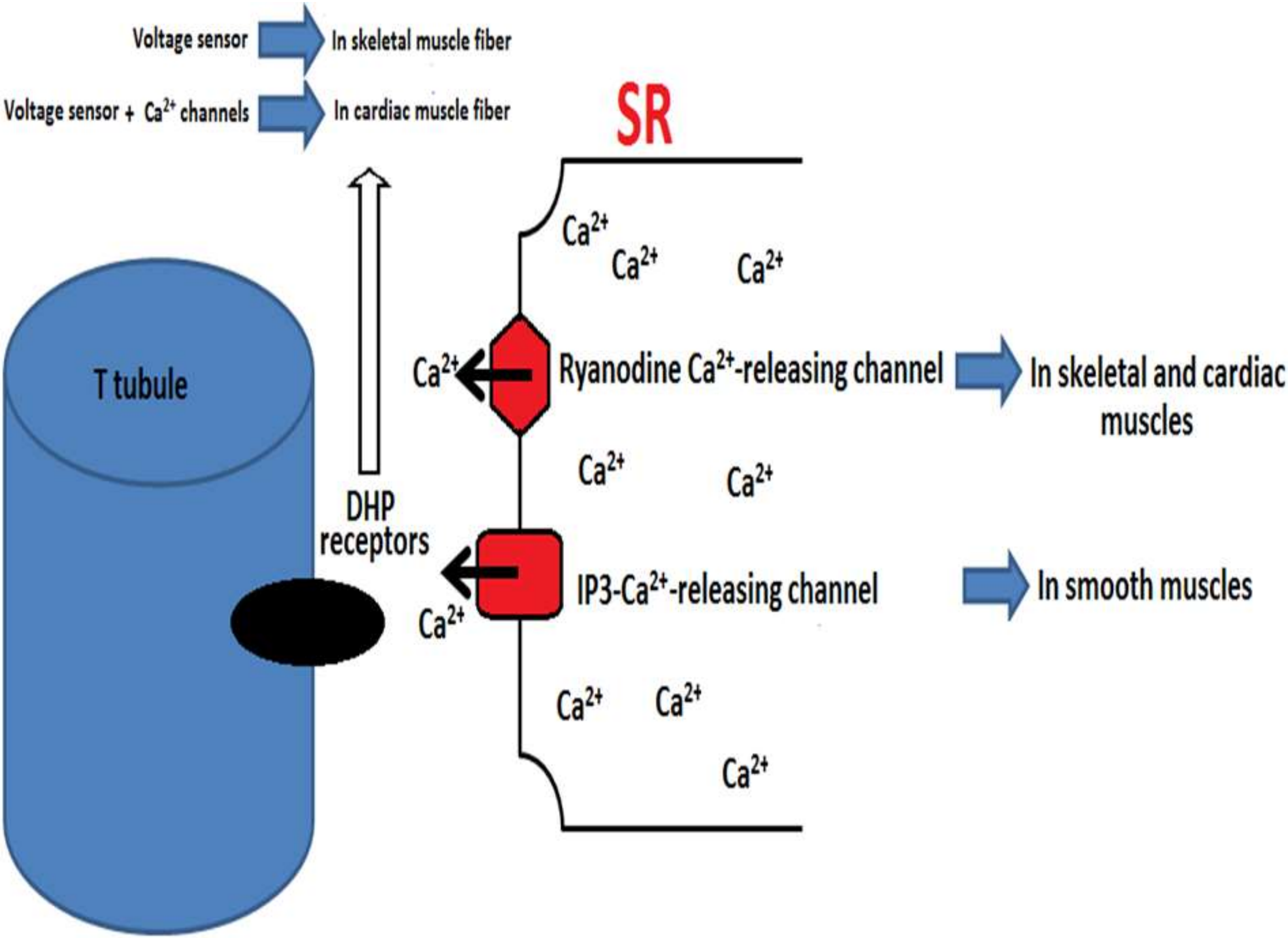
Smooth muscles can contract or relax as a consequence of the increase or decrease the **intracellular Ca^{2+} concentration**. This is achieved by the following factors:

➢ Non-action potential-induced contraction

- **Humoral factors ➔** Increase intracellular Ca^{2+} concentration through activation of G protein, which in turn activates:
- G protein-gated Ca^{2+} channels at the smooth muscle cell membrane or
- Membrane phospholipase C ➔ Release of IP3 ➔ Activates IP3-gated Ca^{2+} channels at the membrane of endoplasmic reticulum➔ Ca^{2+} release from endoplasmic reticulum to cytosol.

(Norepinephrine, Epinephrine, Acetylcholine, Angiotensin, Vasopressin, Oxytocin, Serotonin, and Histamine)

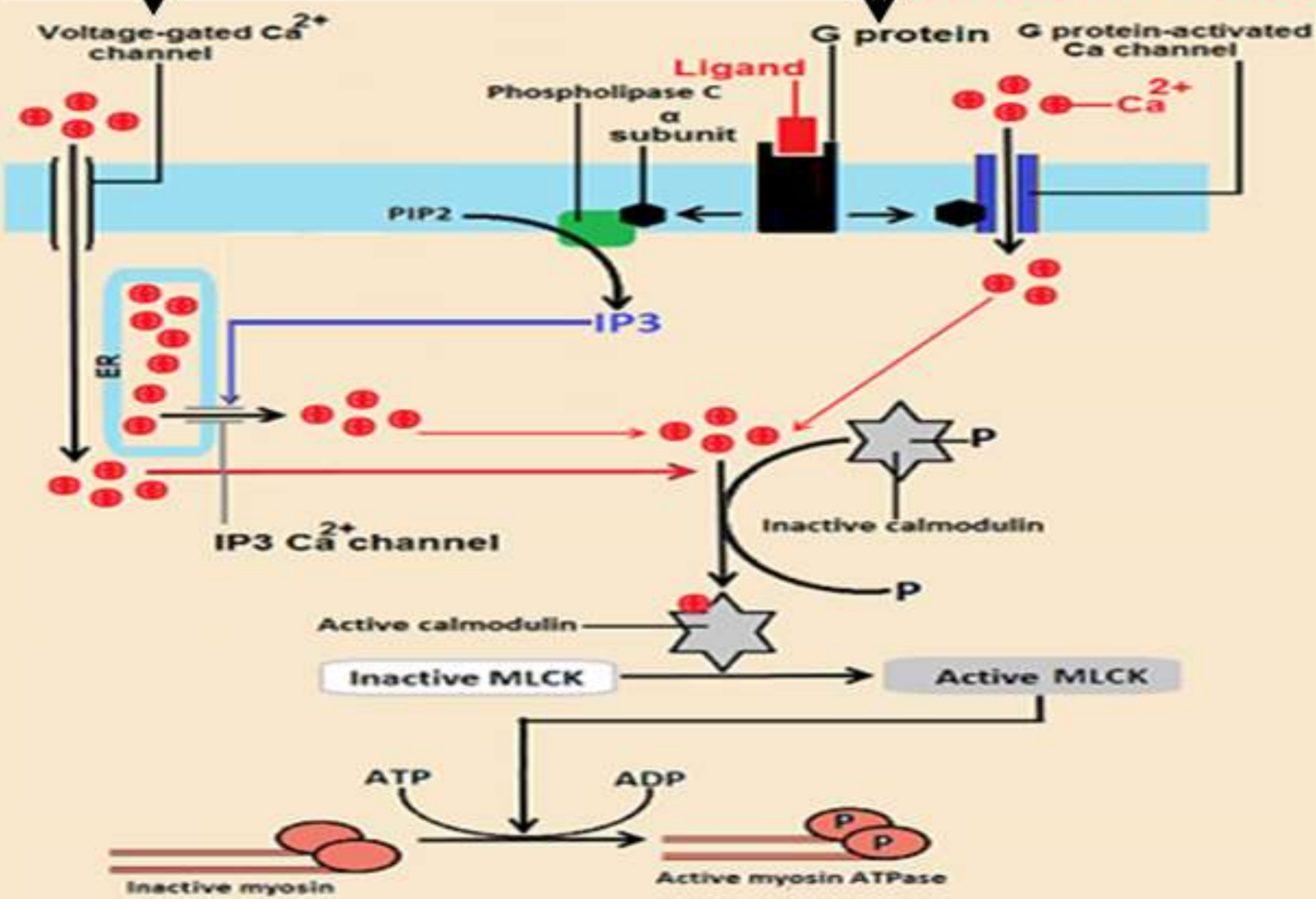
- **Local tissue factors ➔ affect precapillary sphincter & arteriole smooth muscles ➔ Relaxation ➔ Vasodilatation.** **Examples: oxygen, Ca^{++}, body temperature, CO_2, $[H^+]$, Lactic acid, [K], adenosine & phosphate compounds.**

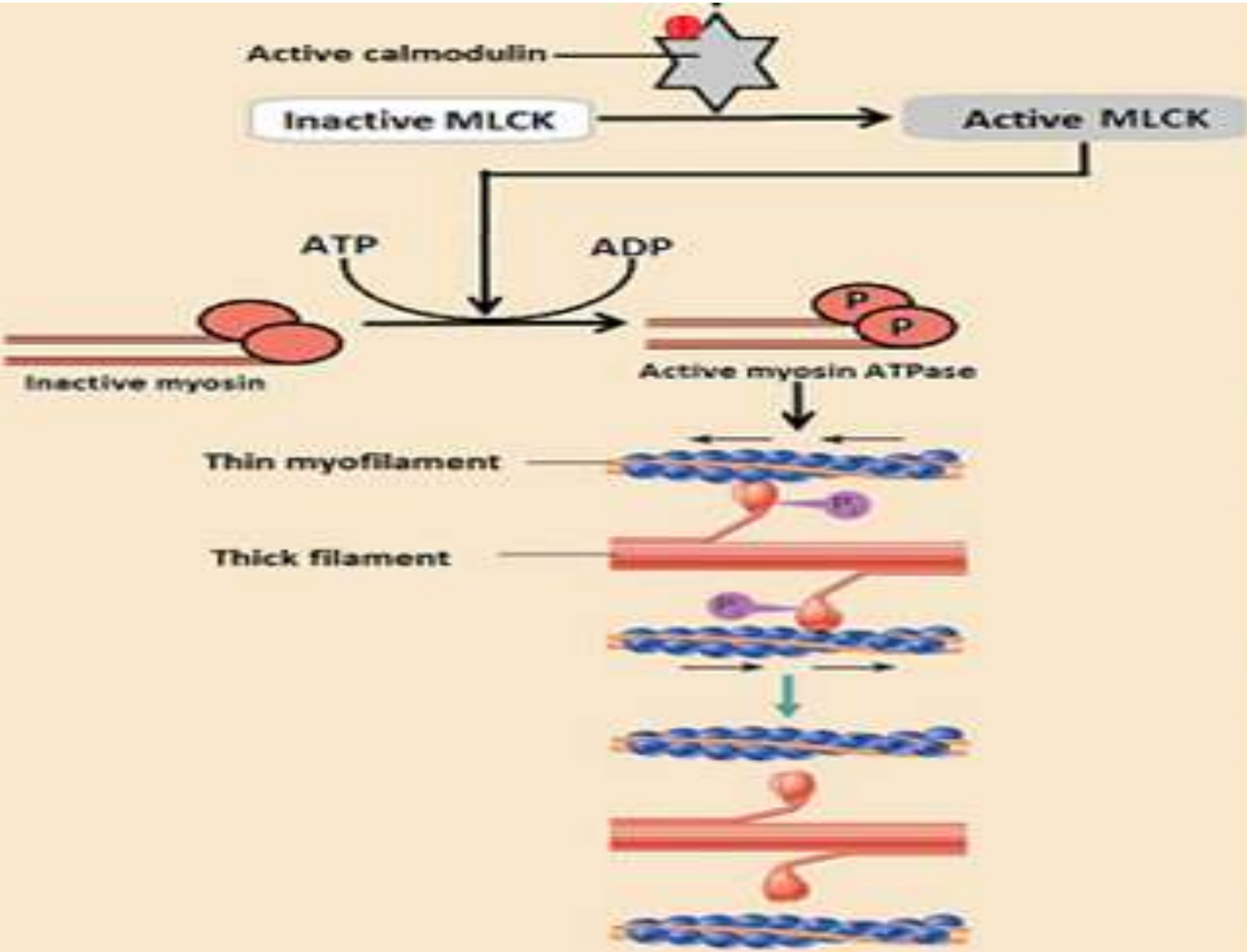

Voltage sensor
In skeletal muscle fiber
Voltage sensor + Ca2+ channels
In cardiac muscle fiber
SR
Ca2+
Ca2+
Ca2+
T tubule
Ca2+
Ryanodine Ca2+-releasing channel
In skeletal and cardiac muscles
Ca2+
Ca2+
DHP receptors
IP3-Ca2+-releasing channel
In smooth muscles
Ca2+
Ca2+
Ca2+
Ca2+

Action potential induced by:

The rhythmicity,
Stretching the smooth muscles, or
generation of Excitatory junctional potential (EJP).

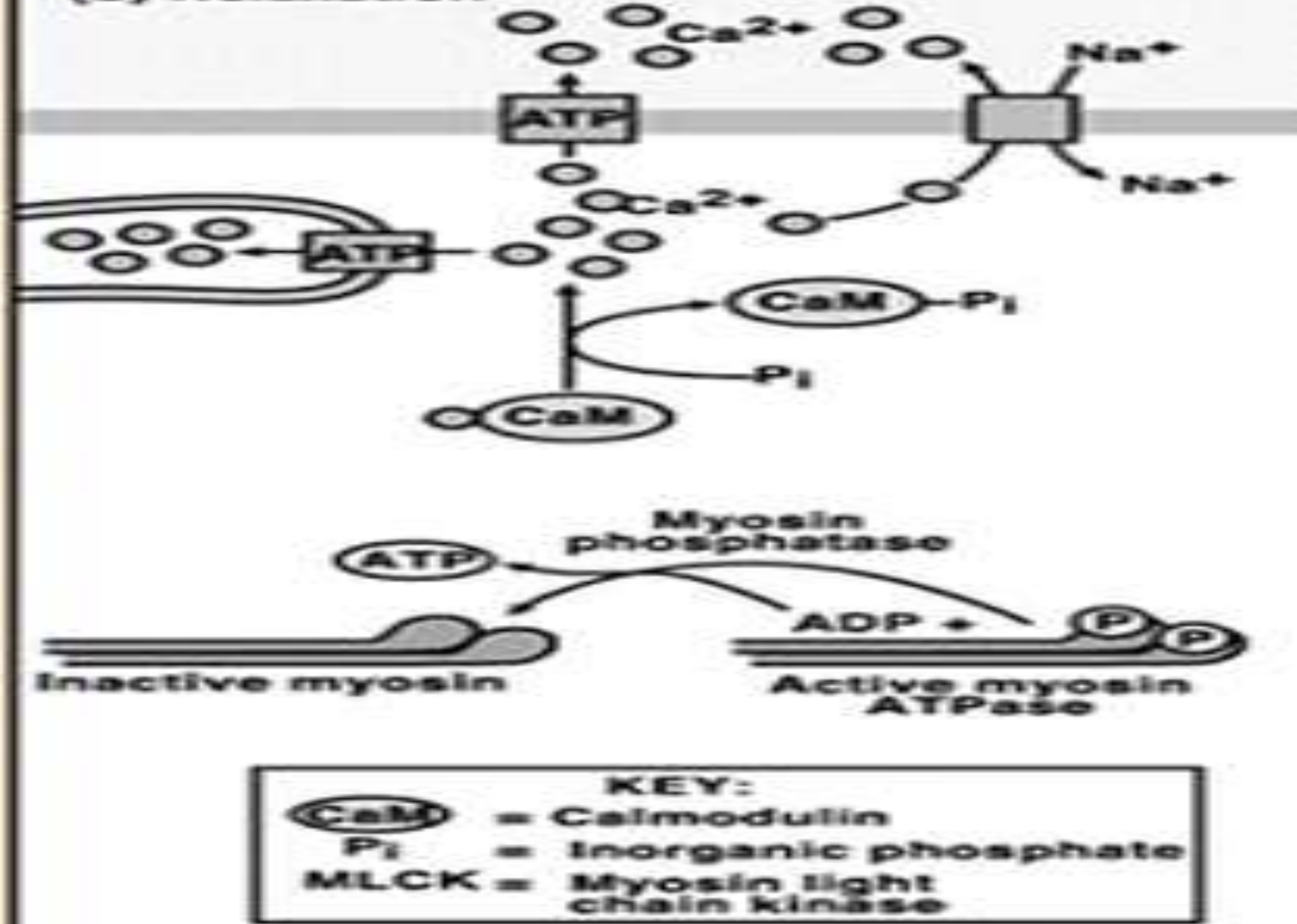
Non-action potential smooth muscle contraction





Active calmodulin
Inactive MLCK
Active MLCK
ATP
ADP
Inactive myosin
P
P
Active myosin ATPase
Thin myofilament
Thick filament

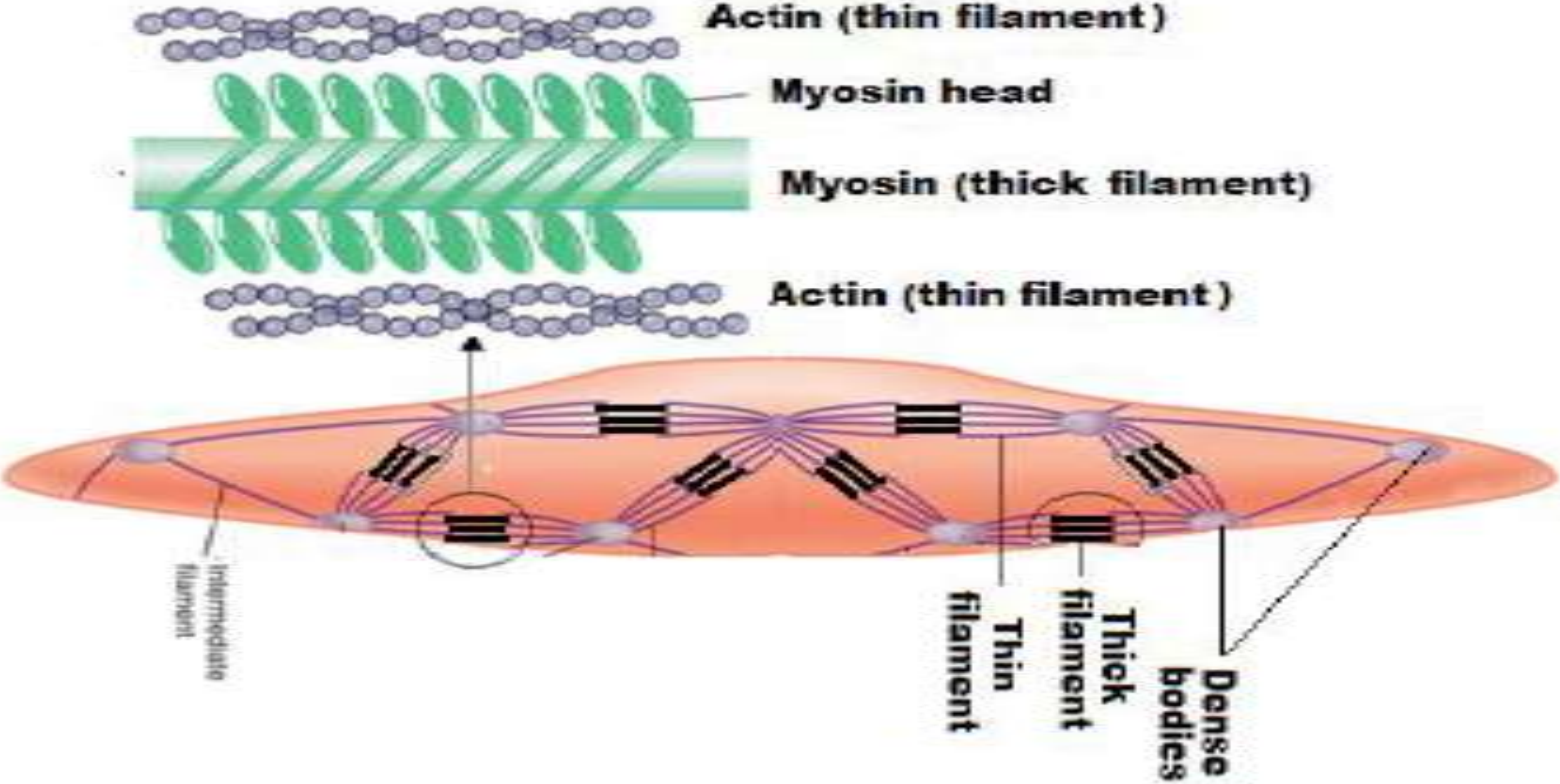
(b) Relaxation



The difference between smooth, skeletal, and cardiac muscles:

1. Histological differences :

- Smooth muscle cells are small, no striations seen in smooth muscle cells (absence of sarcomeres).
- No T-tubules.
-No troponin (except cardiac muscles).
-The thick and thin filaments are dispersed throughout the cell. Thin filaments (actin) are anchored into dense bodies (a Z-line equivalent) which are either anchored to the cell membrane but most of them float within the cytoplasm and hold together by intermediate filaments .
-The junction between the nerve terminal (**somatic nerve fiber**) and skeletal muscle fiber is called **neuromuscular junction** while those between the nerve terminals **(autonomic nervous system)** and smooth muscles are called **contact** or **diffuse junction.**
- The neurotransmitter at the neuromuscular junction of skeletal muscle is only acetylcholine; while of smooth muscle is acetylcholine or norepinephrine. Smooth muscle is innervated by the **autonomic and enteric nervous systems** while skeletal muscles are innervated by somatic sensory and motor neurons.



Smooth muscle and its contractile apparatus.

The difference between smooth muscle and skeletal muscles

1. Histological differences

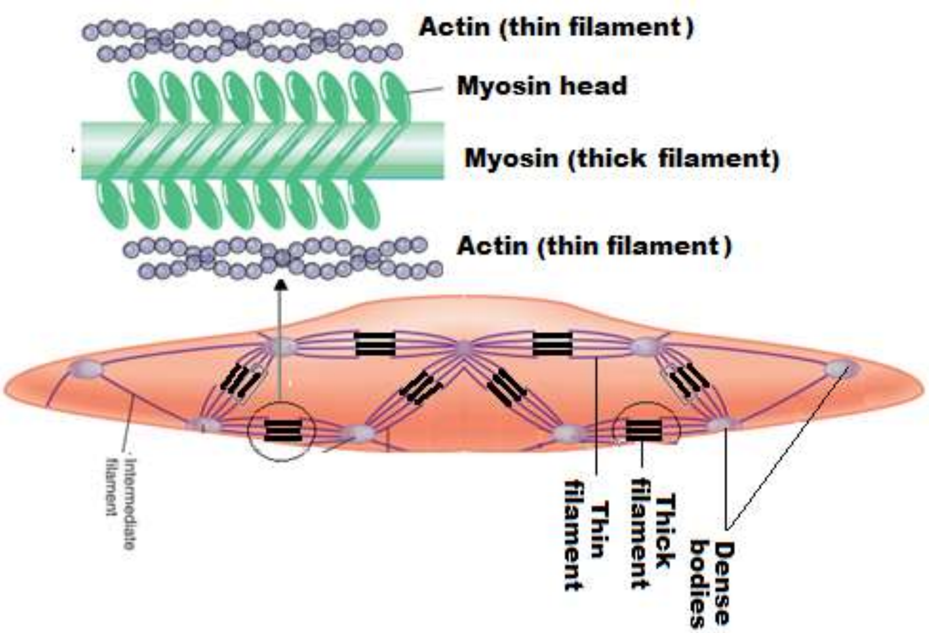
❖Smooth muscle cells are small

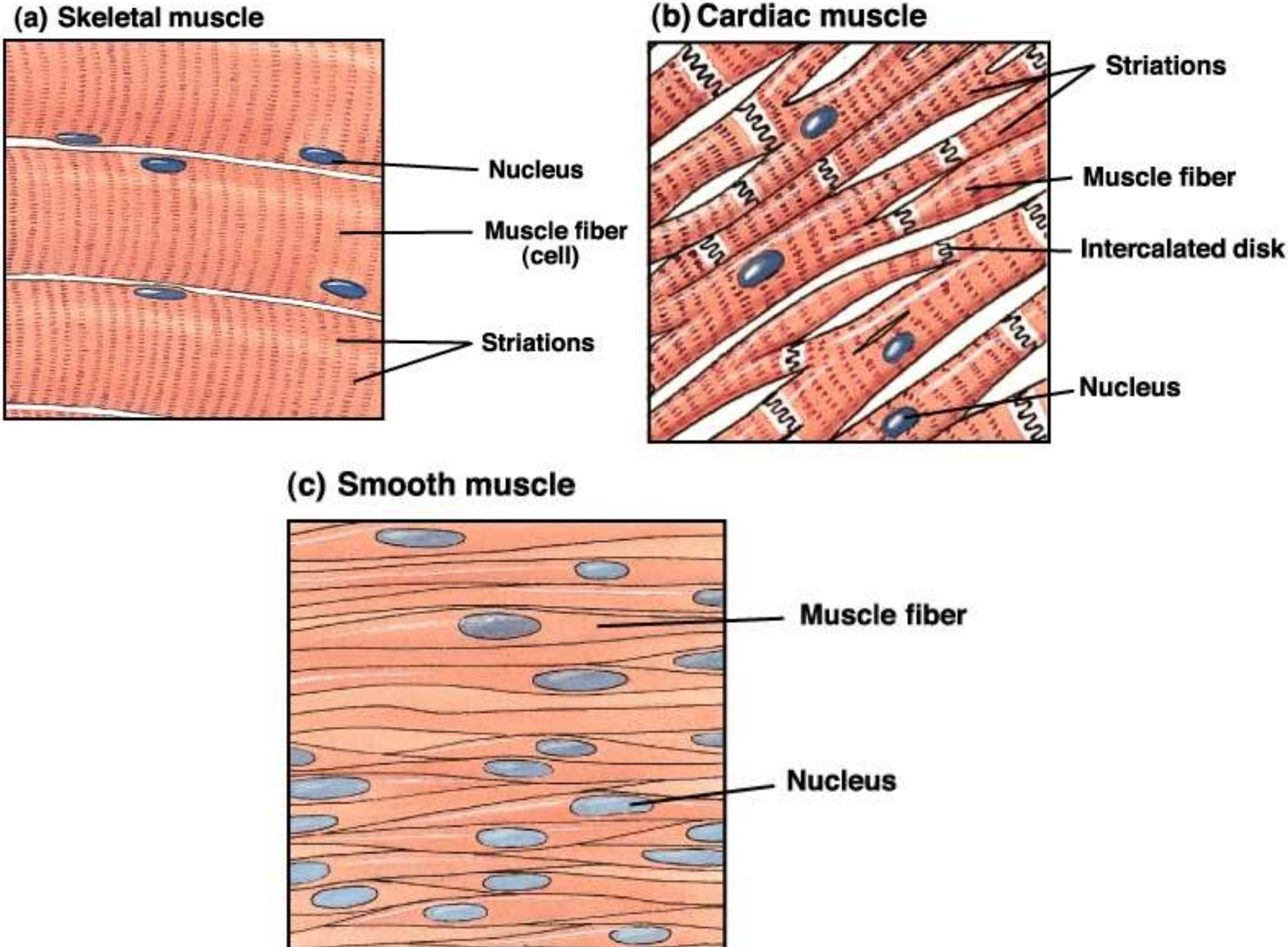
❖No striations (absence of sarcomeres)

❖No T-tubules

❖The thick and thin filaments are dispersed throughout the cell. Thin filaments (actin) are anchored into dense bodies (a Z-line equivalent) which are either anchored to the cell membrane but most of them float within the cytoplasm and hold together by Intermediate filaments

❖No Troponin




(a) Skeletal muscle
Nucleus
Muscle fiber (cell)
Striations
(b) Cardiac muscle
Striations
Muscle fiber
Intercalated disk
Nucleus
(c) Smooth muscle
Muscle fiber
Nucleus

2. Differences in muscle contraction:

In smooth muscles are **rhythmical** tissues, **the contraction time is longer**, **less energy** is required to sustain the same tension of contraction relative to skeletal muscles, **can be shorten a far greater percentage of its length** compare to skeletal muscle.

In addition, the maximum **force of smooth muscle contraction per cm cross-sectional area is greater** than the skeletal muscle contraction. However, the cross-bridge cycle in smooth muscle is considerably slower than in skeletal muscle, which allows for a longer contraction time and higher maximal force of contraction. An important characteristic of visceral smooth muscle is its ability to contract in response to stretch.

3. Differences in membrane potential:

In **normal resting state**, the membrane potential of smooth muscle is less negative than in skeletal muscle and some of them have no fixed value but actually have a **slow wave potential**. The **action potentials** of visceral smooth muscle occur in two different forms: (1) **Spike potential** as those seen in skeletal muscle and (2) **Action potential with plateau**. The smooth muscle cell membrane **has far more voltage-gated Ca^{2+} channels and few voltage-gated Na^{+} channels** than skeletal muscle fiber. Therefore, Na^{+} participates little in the generation of the action potential in most smooth muscle.

Instead, the flow of Ca^{2+} ions to the interior of the fiber is mainly responsible for the action potential and the initiation of the smooth muscle contraction.

Cardiac muscle: Cardiac muscle physiology can best be understood through reviewing the differences with skeletal muscles.

1. Histological differences: Cardiac muscle is striated like skeletal muscle but otherwise differs from it in many structural and physiological ways. Cardiac myocytes (muscle cells), or cardiocytes, are relatively **short, thick, branched cells**. They usually have **one centrally placed nucleus** (but it can be more) (skeletal muscle cell is multinucleated). The sarcoplasmic reticulum (SR) **lacks terminal cisternae** (it has foot-like sacs associated with the T tubules). The cardiac muscles are made up of many cardiac muscle cells **connected in series with each other** at the **intercalated discs**, which are the cell membranes that separate individual cardiac muscle cell from each other. At the intercalated disc free diffusion of ions and action potential from one cardiac cell to another occurs through gap junctions. It also has **especially large mitochondria**, which fill about 25% of the myocyte; skeletal muscle fibers, by comparison, have much smaller mitochondria that occupy only 2% of the fiber.

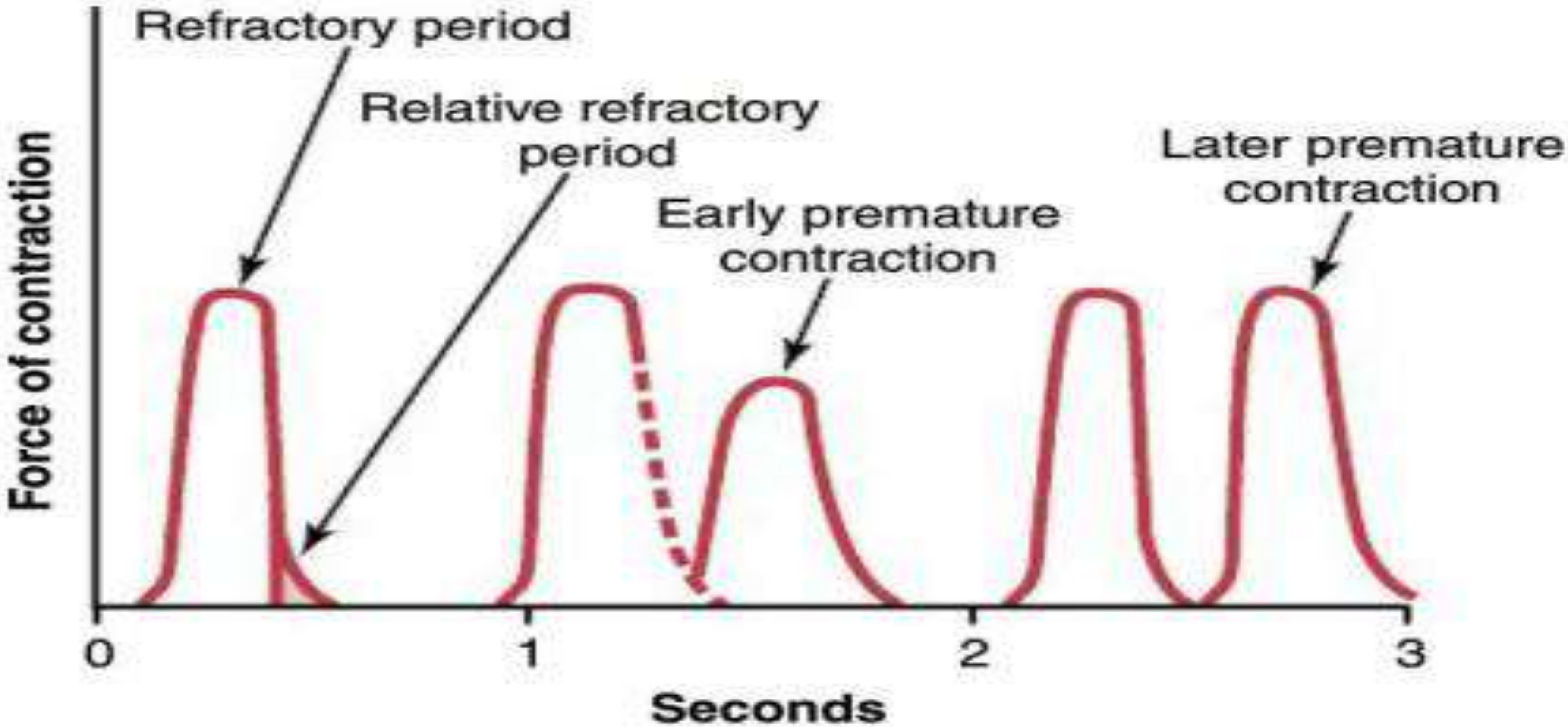
2. The action potentials of the cardiac muscle fibers (atria, ventricles and Purkinje fibers) characterized by the **presence of plateau**, which causes the prolongation of action potential in the cardiac muscle. The myocytes contract as long as the action potential is in its plateau.

The duration of cardiac action potential is much longer (calcium influx prolongs the duration of the action potential and produces a characteristic plateau phase) than in nerve or skeletal muscle fiber. In a typical nerve, the action potential duration is about 1 ms.

In skeletal muscle cells, the action potential duration is approximately 2-5 ms. In contrast, the duration of cardiac action potentials range from 200 to 400 ms. In nerve and muscle cells, the depolarization phase of the action potential is caused by an opening of sodium channels. This also occurs in non-pacemaker cardiac cells (atrial and ventricular muscles). However, in cardiac pacemaker cells (sinoatrial and atrio-venticular nodes), calcium ions are involved in the initial depolarization phase of the action potential.

3. The cardiac muscle is absolutely refractory during most of the action potential. Therefore, tetanization of the type seen in skeletal muscle cannot occur. An electrical stimulus can sometimes initiate a new spike at the very end of the action potential, i.e. at the relative refractory period.

4. The strength of cardiac contraction depends on the concentration of Ca^{2+} ions in the ECF that pass through T-tubules and on the Ca^{2+} released from endoplasmic reticulum. In contrast, the strength of skeletal muscle contraction is hardly affected by the ECF Ca^{2+} concentration because its contraction is caused almost entirely by Ca^{2+} ions released from sarcoplasmic reticulum inside the skeletal muscle fiber itself.



Force of ventricular heart muscle contraction, showing also duration of the refractory period and relative refractory period, plus the effect of premature contraction. Note that premature contractions do not cause wave summation, as occurs in skeletal.

5. Metabolism of cardiac muscle: Cardiac muscle **depends almost exclusively on aerobic respiration** to make ATP. It is very rich in
myoglobin (a short-term source of stored oxygen for aerobic respiration) and glycogen (stored energy).
Cardiac muscle, therefore, is more vulnerable to an oxygen deficiency.
Because it makes little use of anaerobic fermentation or the oxygen debt mechanism, **it is not prone to fatigue**.

2- Muscle contraction differences

❖Long single twitch contraction time

❖Less energy is required to sustain the same tension of contraction

❖Able to shorten a far greater percentage of its length

❖the maximum force of smooth muscle contraction per cm cross-sectional area is greater than the skeletal muscle contraction

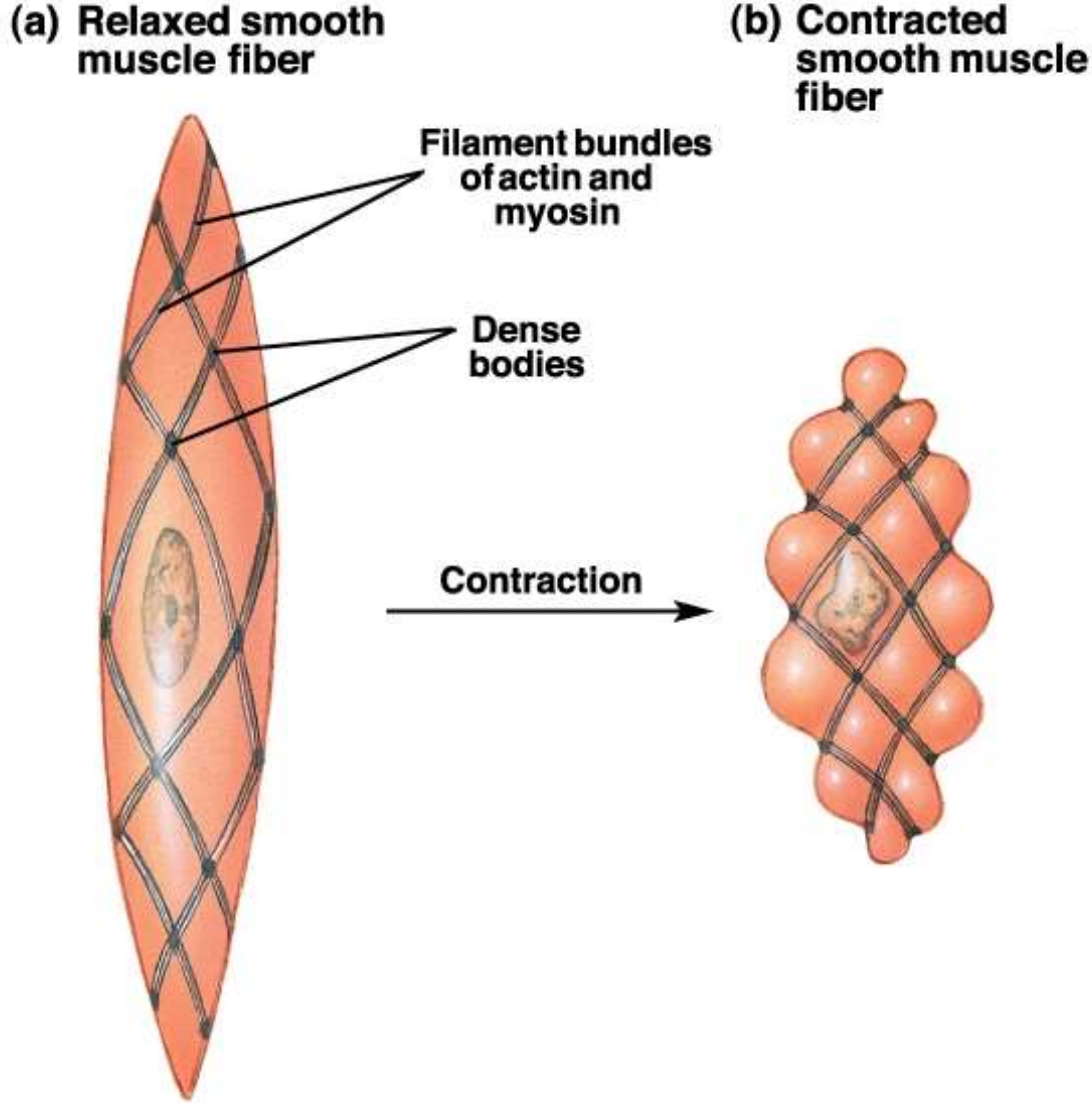
❖Contraction can be initiated by nerve impulses or by hormones and other factors

❖Both contraction and relaxation are due to the presence of excitatory and inhibitory receptors at their membranes

❖Some smooth muscle is self-excitatory

❖Tonic contraction of smooth muscle caused mainly by local tissue factors or circulating hormones such as angiotensin, vasopressin, or norepinephrine and to less extent by nervous and action potential stimulating factors

❖The main source of Ca ions that initiate the contraction process in smooth muscle is from sarcoplasmic reticulum and/or ECF


(a) Relaxed smooth muscle fiber
(b) Contracted smooth muscle fiber
Filament bundles of actin and myosin
Dense bodies
Contraction

3-The membrane potential differences

❖The resting membrane potential of smooth muscle is usually about –50 to –60 mv

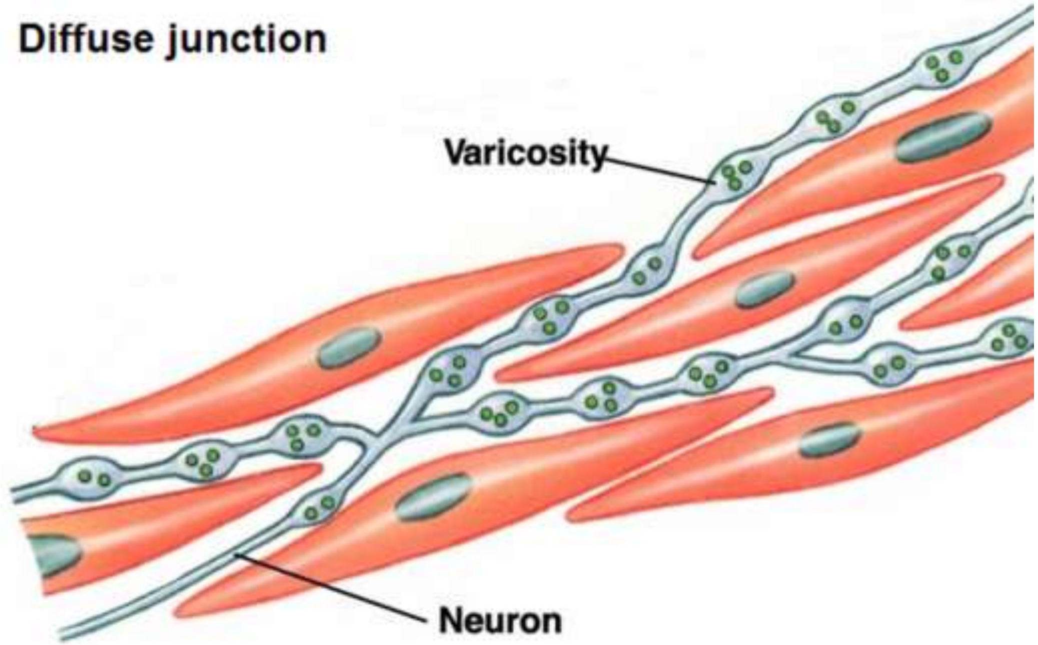
❖The action potentials of visceral smooth muscle occur in two different forms

❖The smooth muscle cell membrane has far more voltage-gated Ca channels and few voltage-gated Na channels than skeletal muscle fiber

❖The junction between the nerve terminals and smooth muscles are called diffuse junction

❖The neurotransmitter at the neuromuscular junction of skeletal muscle is only acetylcholine, while of smooth muscle are acetylcholine or norepinephrine

❖ Stress-relaxation of smooth muscle



Cardiac muscle

- **1. Histological differences**
- **2. The action potentials**
- **3. The cardiac muscle is absolutely refractory**
- **4. The strength of cardiac contraction** depends on the concentration of Ca^{2+} ions
- **5. Metabolism of cardiac muscle:** Cardiac muscle **depends almost exclusively on aerobic respiration** to make ATP.

Table 4.2: summary of the differences among the three types of muscles

	Skeletal muscles	Cardiac muscles	Smooth muscles
Microscopic appearance	Striated; actin and myosin arranged in sarcomeres	Striated; actin and myosin arranged in sarcomeres	Not striated; no sarcomeres, actin anchored into dense bodies and cell membrane
Innervation	Somatic nervous system (alpha motor neurons)	Autonomic nervous system	Autonomic nervous system
Level of Control	Under voluntary control	Under involuntary Control	Under involuntary control
Presence of Troponin	Yes	Yes	No
Presence of T Tubules	Yes	Yes	No
Source of Increased Cytosolic Ca^{2+}	Sarcoplasmic reticulum	From ECF and from sarcoplasmic reticulum	From ECF and from sarcoplasmic reticulum
Site of Ca^{2+} regulation	Troponin in thin filaments	Troponin in thin filaments	Myosin in thick filaments
Presence of Gap Junctions	No	Yes	Yes in single-unit smooth muscle
Length–Tension Relationship	Yes but limited	Yes	No