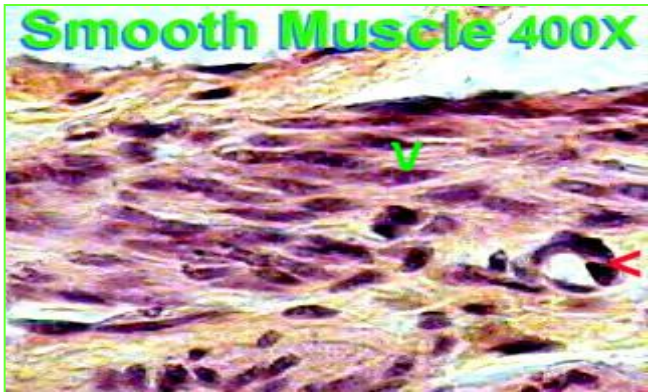
MEDICAL UNIVERSITY – PLEVEN
FACULTY OF MEDICINE
DISTANCE LEARNING CENTER

Lecture № 5

Energy of muscle contraction. Smooth muscles.

Assoc. prof. Boryana Ruseva, MD, PhD
Department of Physiology
Medical University
Pleven



Energy metabolism of muscle contraction

- **Skeletal muscle cells provide with energy using aerobic or anaerobic mechanisms.**

Aerobic mechanism

It performs in mitochondria.

Oxidative phosphorilation -> ATP formation

Anaerobic mechanism

It performs in sarcoplasme.

Glycolysis -> ATP formation

The other source is creatine phosphate (CP)

ADP~P + C ← → ADP + C~P

Fast and Slow Twitch Muscle Fibers

- It is generally accepted that muscle fiber types can be broken down into two main types: **slow twitch (Type I)** muscle fibers and **fast twitch (Type II)** muscle fibers. Fast twitch fibers can be further categorized into **Type IIa** and **Type IIb** fibers.
- These distinctions seem to influence how muscles respond to training and physical activity, and each fiber type is unique in its ability to contract in a certain way.
- Human muscles contain a genetically determined mixture of both slow and fast fiber types. On average, we have about 50 percent slow twitch and 50 percent fast twitch fibers in most of the muscles used for movement.

Fast and Slow Twitch Muscle Fibers

- **Slow Twitch (Type I)**
  The slow muscles are more efficient at using oxygen to generate more fuel (ATP) for continuous, extended muscle contractions over a long time. They fire more slowly than fast twitch fibers and can go for a long time before they fatigue. Therefore, slow twitch fibers are great at helping athletes run marathons and bicycle for hours.

Fast and Slow Twitch Muscle Fibers

- **Fast Twitch (Type II)**
  Because fast twitch fibers use anaerobic metabolism to create fuel, they are much better at generating short bursts of strength or speed than slow muscles. However, they fatigue more quickly.
- **Type IIa Fibers**
  These fast twitch muscle fibers are also known as intermediate fast-twitch fibers. They can use both aerobic and anaerobic metabolism almost equally to create energy. In this way, they are a combination of Type I and Type II muscle fibers.
- **Type IIb Fibers**
  These fast twitch fibers use anaerobic metabolism to create energy and are the "classic" fast twitch muscle fibers that excel at producing quick, powerful bursts of speed. This muscle fiber has the highest rate of contraction (rapid firing) of all the muscle fiber types, but it also has a much faster rate of fatigue and can't last as long before it needs rest.

Muscle work & Muscle fatigue

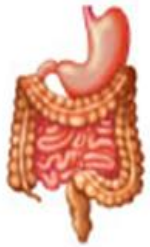
- A = I.H

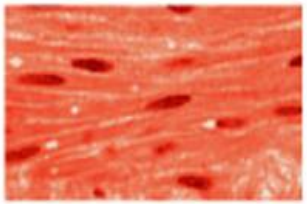
(A- performed work; I- weight of a load; H- distance of shifting load away)

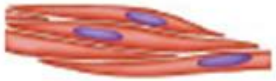
Muscle fatigue – temporally decrease of working capacity of the muscle.

- ***Causes:*** decrease of energetic sources and accumulation of end metabolic products in muscles
- ***Hypertrophy*** of the muscles – increase of the size of the muscles, because of increase of the mass of contractile proteins. It is due to intensive work or usage of steroid anabolic hormones.
- ***Hypotrophy or atrophy*** of the muscles decrease of the size of the muscles, because of decrease of the mass of contractile proteins. It is due to absence of work, because of immobilization or altered transduction of neuronal signals.

Types of muscles

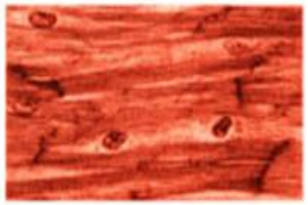






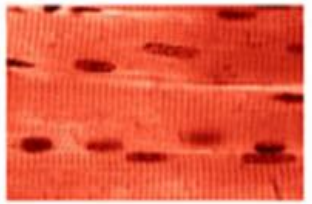
Smooth muscle

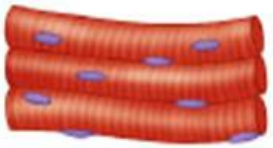
- has spindle-shaped, nonstriated uninucleated fibers.
- occurs in walls of internal organs.
- is involuntary.



Cardiac muscle

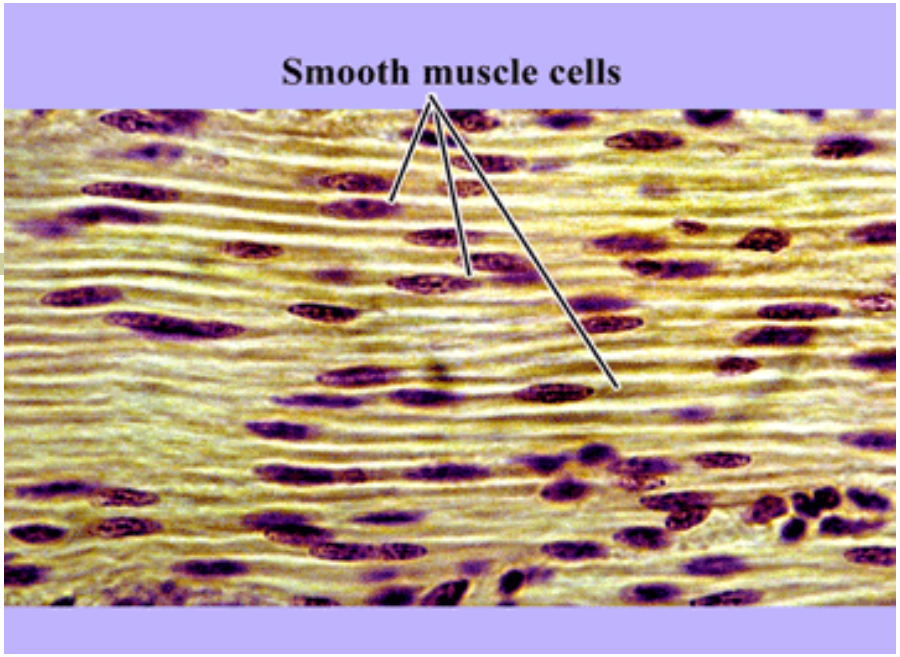
- has striated, branched, uninucleated fibers.
- occurs in walls of heart.
- is involuntary.





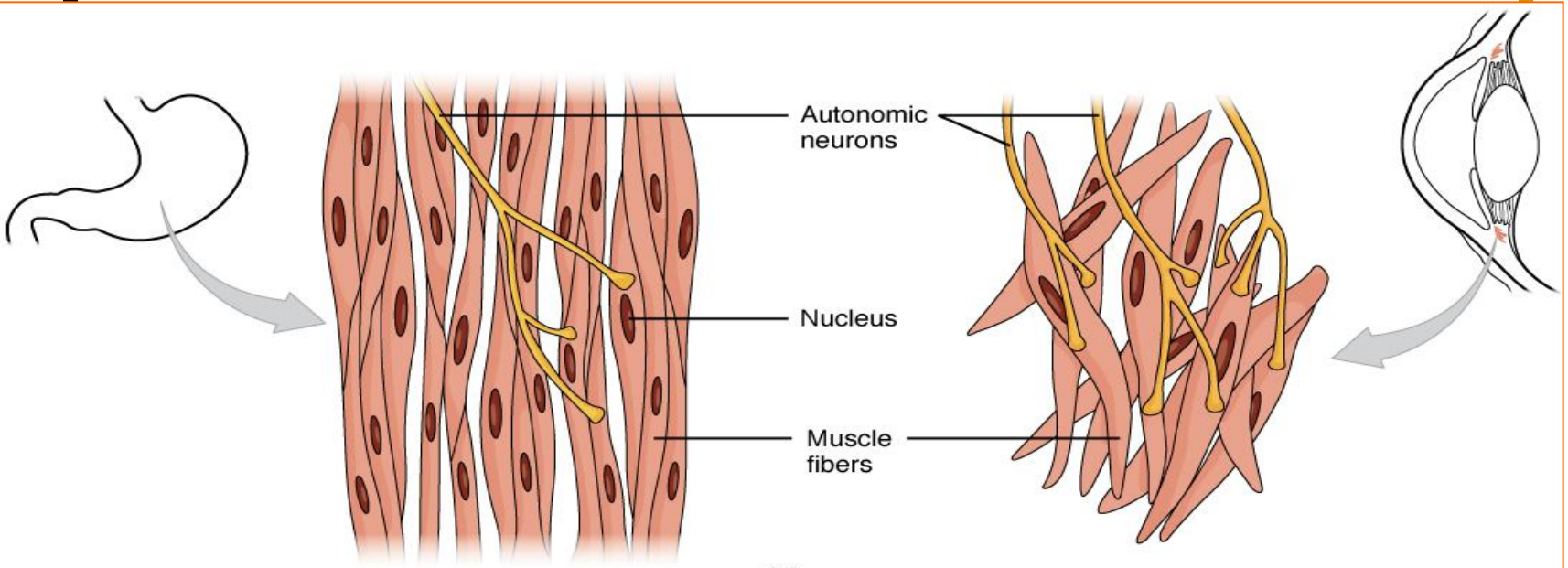
Skeletal muscle

- has striated, tubular, multinucleated fibers.
- is usually attached to skeleton.
- is voluntary.

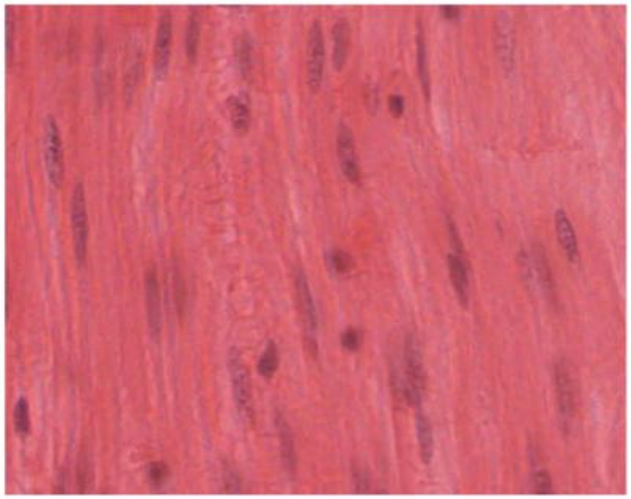


- **Smooth muscle cells are spindle shaped. They have one centrally placed nucleus per cell and are usually organized in small clusters of cells. Fine collagenous, reticular connective tissue separates each cell and the bundles.**

Smooth muscle cells

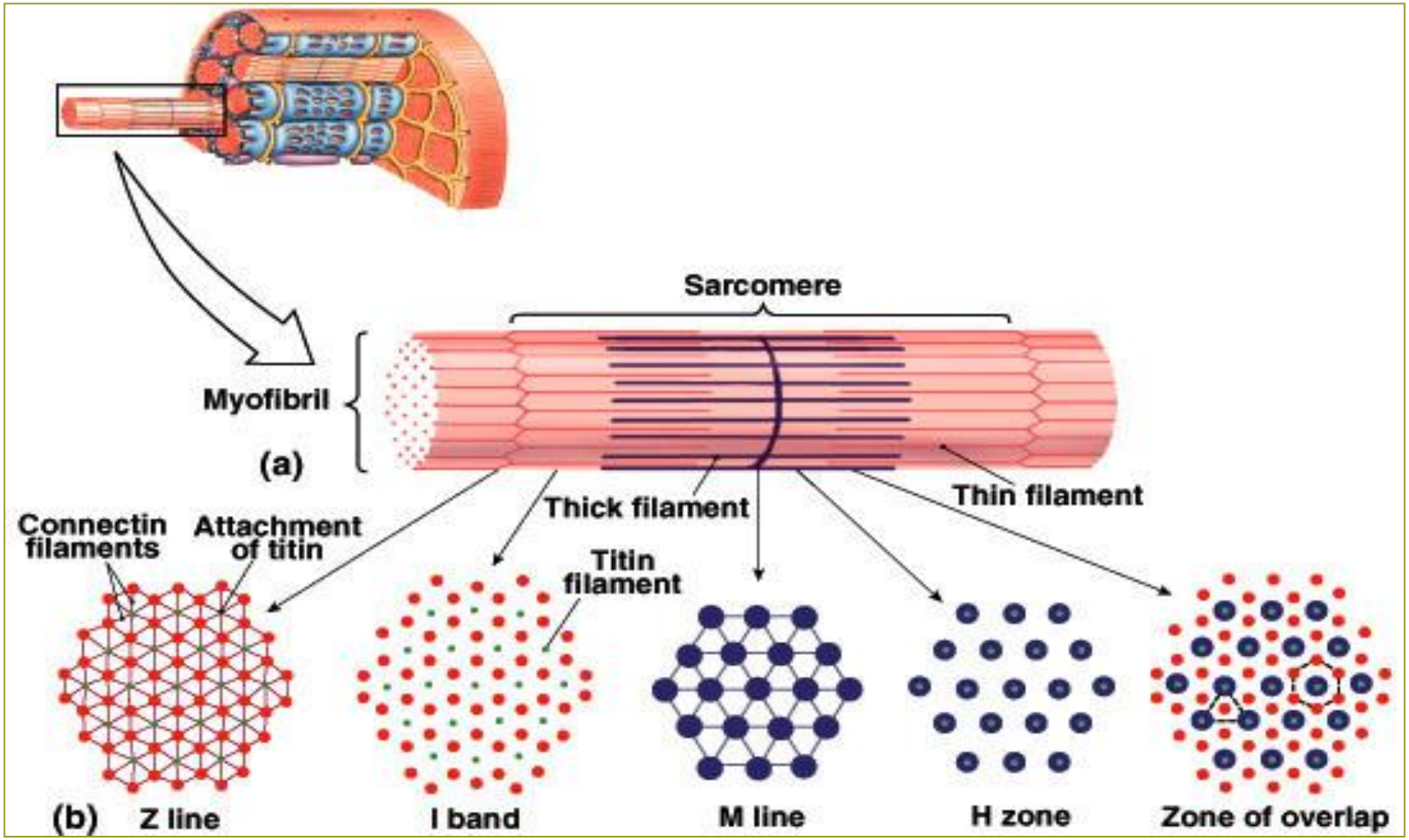


(a)



(b)

Structure of skeletal muscle cells

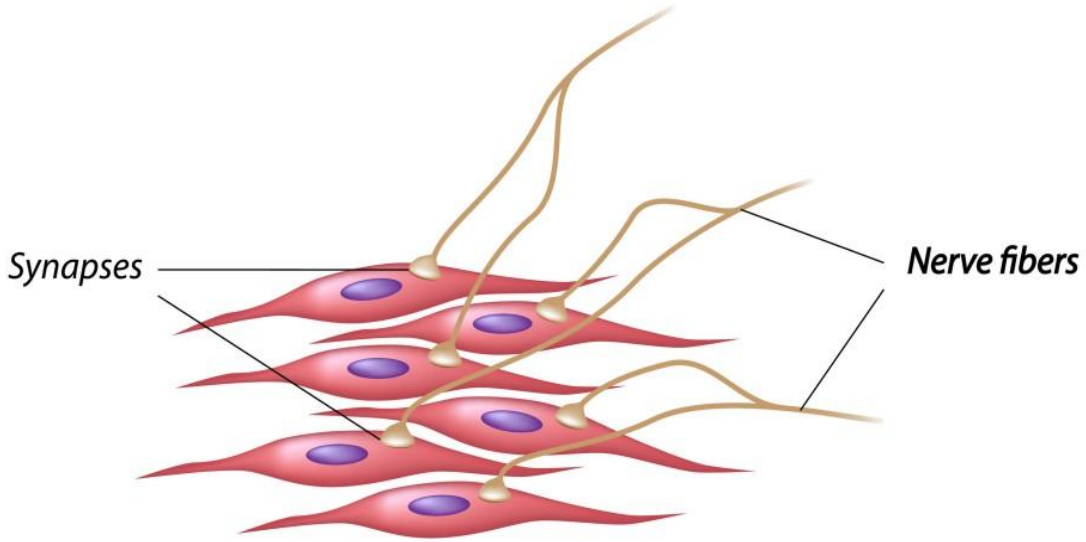


Smooth muscle cells

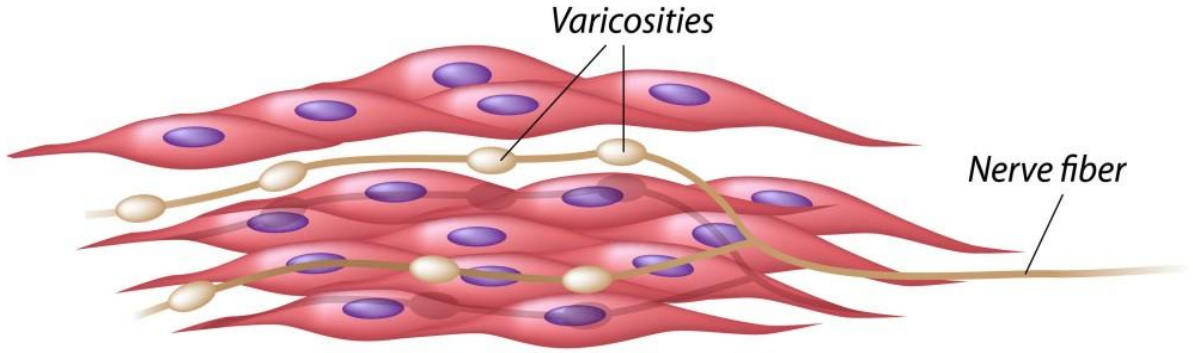
- One way to distinguish smooth muscle from striated muscle is the absence of the regular pattern of sarcomeres (no A, I bands or Z lines). Smooth muscle cells also have only one nucleus. In that sense they are like cardiac muscle cells.
- Smooth muscle cells can be distinguished from connective tissue by their organized appearance. They are usually in a homogeneous bundle or sheet of cells rather than scattered single cells.

Types of smooth muscles

- **Smooth muscle** is an involuntary non-striated muscle. It is divided into two sub-groups; the single-unit (unitary) and multiunit smooth muscle.
- Within single-unit smooth muscle tissues, the autonomic nervous system innervates a single cell within a sheet or bundle and the action potential is propagated by gap junctions to neighboring cells such that the whole bundle or sheet contracts as a syncytium (i.e., a multinucleate mass of cytoplasm that is not separated into cells).
- Multiunit smooth muscle tissues - innervate individual cells; as such, they allow for fine control and gradual responses, much like motor unit recruitment in skeletal muscle.



Multiunit Smooth Muscle

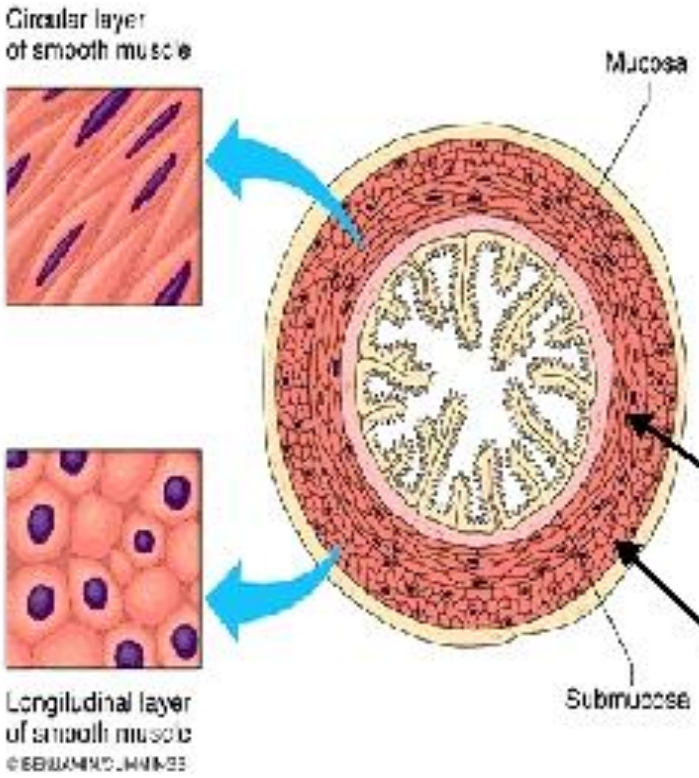


Single-unit Smooth Muscle

Single unit smooth muscles

- Single unit smooth muscles are in sheets lining the walls of hollow organs. For example, you can see rows of smooth muscle cells in the wall of the gastrointestinal tract.
- The smooth muscle cells may be organized in 2-3 layers. One layer may run circularly around the lumen; another layer may be running longitudinally along the length of the organ. In the stomach, there is a layer that runs more diagonally or obliquely.
- Each of these works together to propel food along the organ, or in the case of the stomach, churn the food.

Smooth Muscle Arrangement in the Gut



In the intestine smooth muscle forms two distinct layers, one running along, the other running around the organ. Together these layers cause wave-like peristalsis which propels the contents.

The circular layer runs around the intestine and its contraction causes segmentation

The longitudinal layer runs along the intestine; it causes wave-like contractions.

Multiunit smooth muscles

- Multiunit smooth muscle cells rarely possess gap junctions, and thus are not electrically coupled. As a result, contraction does not spread from one cell to the next, but is instead confined to the cell that was originally stimulated.
- Stimuli for multiunit smooth muscles come from autonomic nerves or hormones but not from stretching.
- This type of tissue is found around large blood vessels, in the respiratory airways, and in the eyes.

Smooth muscle cell ultrastructure

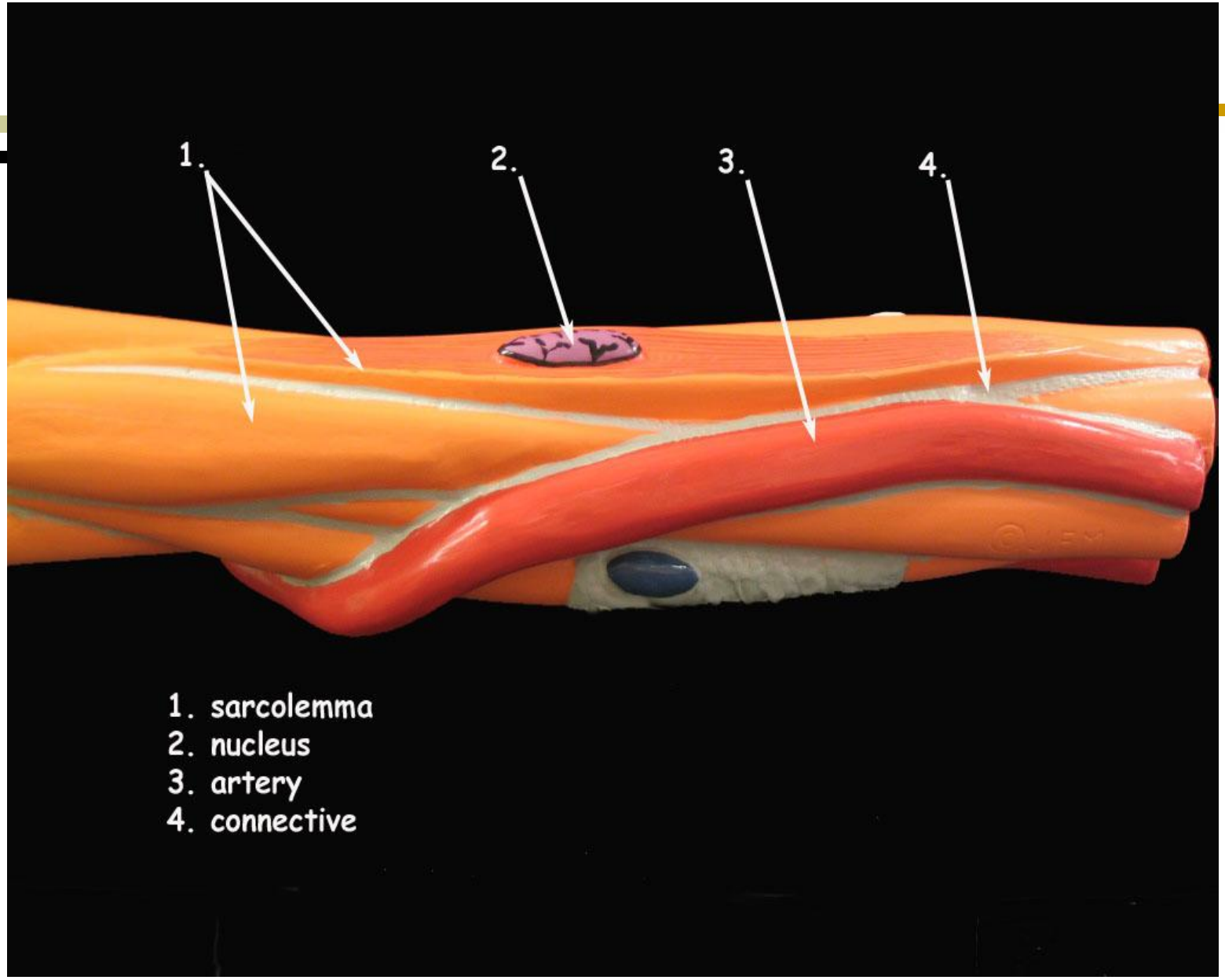
- Smooth muscle cells have a region around the nucleus that is filled with some smooth endoplasmic reticulum (SER) and lots of mitochondria. The mitochondria provide the ATP needed for contraction. The SER provides a site for calcium storage.
- The remainder of the cytoplasm includes contractile filaments broken by focal densities. The thin filaments are actin with tropomyosin. No troponin is present in the smooth muscle cells.
- What other calcium binding protein is found?

  In addition, there are thick filaments that project the heavy meromyosin heads all along their length. Thus, there is a larger surface area for interaction of the myosin with the actin.

Smooth muscle cell ultrastructure

- Focal densities, either in the cytoplasm or at the cell membrane are organizational sites for the thick and thin filaments (actin and myosin) to interact and be held in register.
- Desmin or vimentin filaments also bind at these sites to help hold the filaments together.
- These intermediate filaments help relay the contraction and help to shorten the cell.
- The dense bodies also contain alpha actinin, an actin binding protein. These dense bodies are similar to the Z lines of the striated muscle.

Smooth muscle cells



Smooth muscle cell ultrastructure

- The densities in the membrane are called adherent junctions. Recall the same types of junctions are seen in epithelial cells. We called them “focal adhesions” or “zonula adherents”.
- These provide attachment sites to the connective tissue outside the cell and also helping the muscle cells work together.
- Actin was attached at these sites to actin binding proteins. In the case of smooth muscle, alpha actinin is among the binding proteins.

Smooth muscle cell ultrastructure

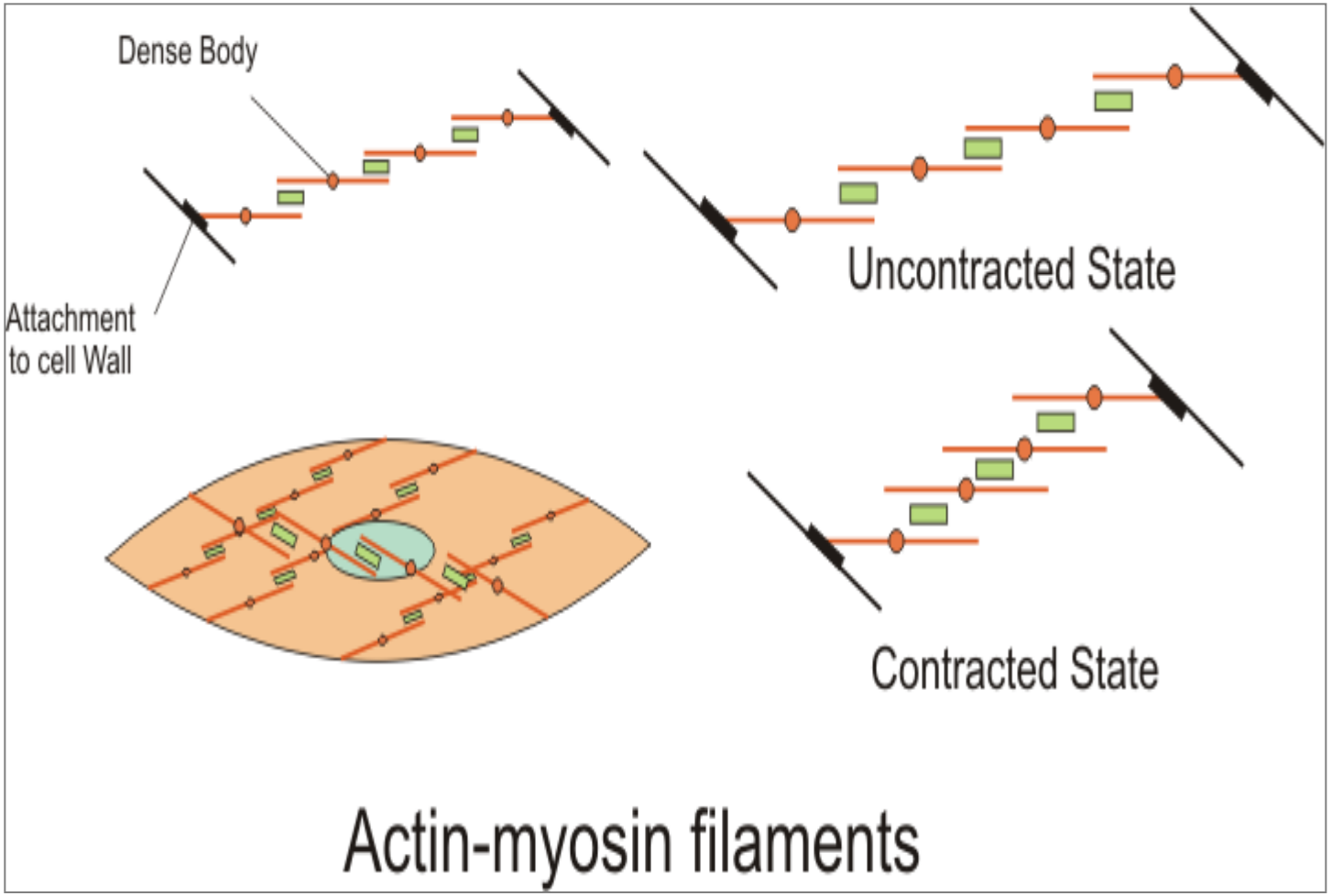
- Also, at the periphery are numerous invaginations of the plasma membrane, which are vesicular or saccular. These are called “caveolae” and are believed to help bring in calcium needed for contraction.
- They are equivalent to the T- tubule system in striated muscle. They work with sarcoplasmic reticulum to sequester calcium when it is not needed for contraction.

Smooth muscle cell ultrastructure

- Finally, smooth muscle cells are interconnected by ‘gap junctions’, which are specialized communication ports between the cells.
- These are regions of many paired connexon molecules that work like molecular pores or channels running between the cells.
- Small molecules or ions can pass from cell to cell via these connexons and they provide communication links that regulate contraction of the entire bundle of smooth muscle.

The ratio of actin to myosin is between 2:1 and 10:1 in smooth muscle, compared to ~6:1 in skeletal muscle and 4:1 in cardiac

muscle. Smooth muscle does not contain the protein troponin



Excitation-contraction coupling

Inducing stimuli and factors

- Smooth muscle may contract spontaneously (via ionic channel dynamics) or as in the gut special pacemakers cells interstitial cells of Cajal produce rhythmic contractions. Also, contraction, as well as relaxation, can be induced by a number of physiochemical agents (e.g., hormones, drugs, neurotransmitters - particularly from the autonomic nervous system).
- Visceral smooth muscle has a *stress-relaxation response*. This means that as the muscle of a hollow organ is stretched when it fills, the mechanical stress of the stretching will trigger contraction.
- Smooth muscle in various regions of the vascular tree, the airway and lungs, kidneys and vagina is different in their expression of ionic channels, hormone receptors, cell-signaling pathways, and other proteins that determine function.

Electrophysiology of Gastrointestinal Smooth Muscle

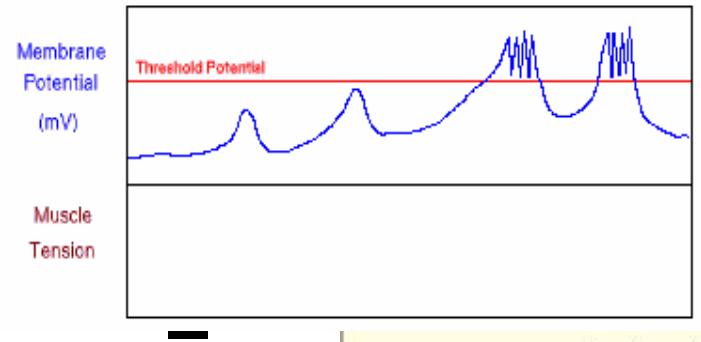
- Normal gastrointestinal motility results from coordinated contractions of smooth muscle, which in turn derive from two basic patterns of electrical activity across the membranes of smooth muscle cells - **slow waves** and **spike potentials**.
- Like other excitable cells, gastrointestinal smooth muscle cells maintain a electrical potential difference across their membranes. The resting membrane potential of smooth muscle cells is between -50 and -60 mV. *In contrast to nerves and other types of muscle cells, the membrane potential of smooth muscle cells fluctuates spontaneously.*
- Because the cells are electrically coupled, these fluctuations in membrane potential spread to adjacent sections of muscle, resulting in what are called "slow waves" - waves of partial depolarization in smooth muscle that sweep along the digestive tube for long distances. These partial depolarizations are equivalent to fluctuations in membrane potential of 5 to 15 mV.

Excitation-contraction coupling

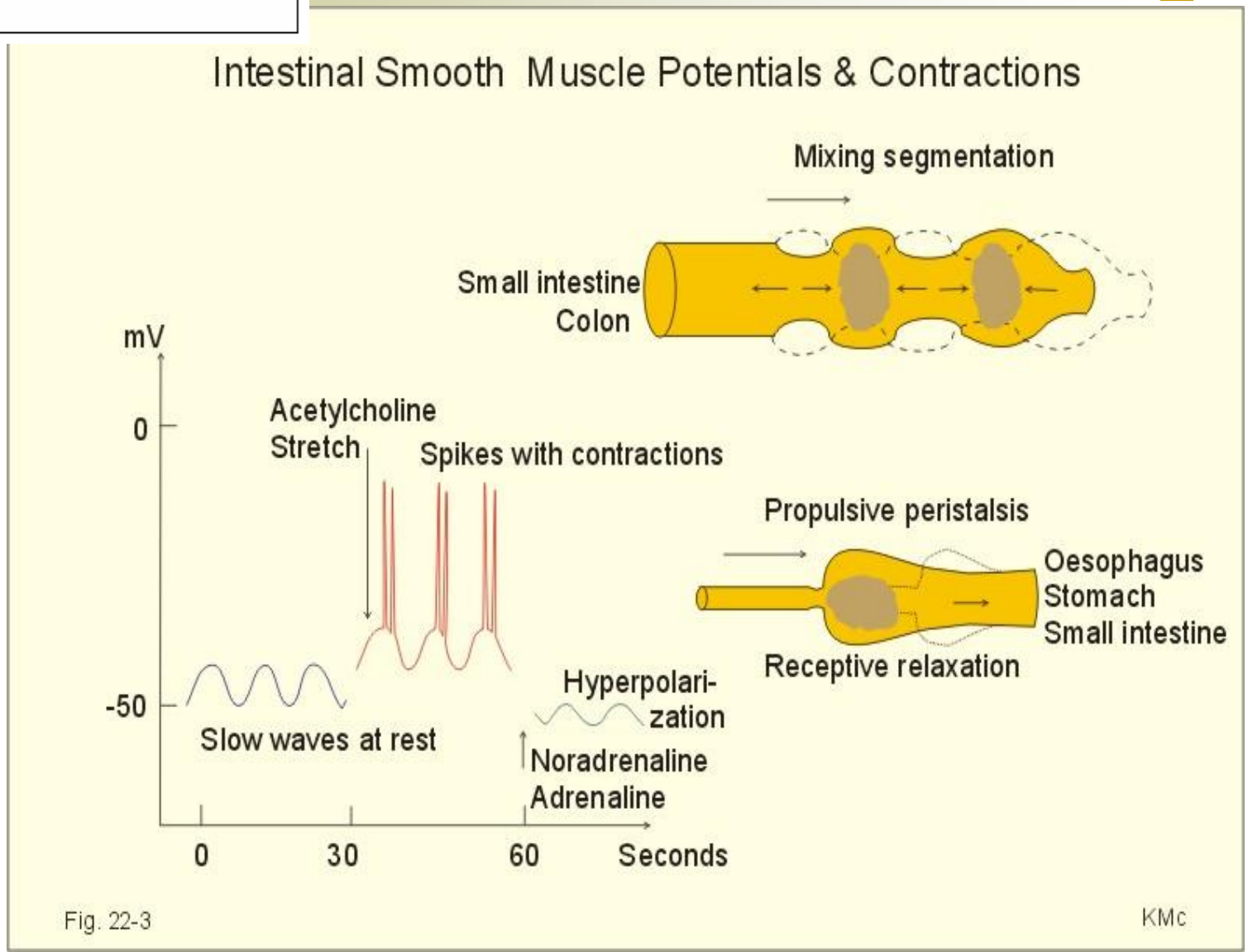
- Although smooth muscle contraction relies on the presence of Ca^{++} ions, smooth muscle fibers have a much smaller diameter than skeletal muscle cells.
- T-tubules are not required to reach the interior of the cell and therefore not necessary to transmit an action potential deep into the fiber.
- Smooth muscle fibers have a limited calcium-storing SR but have calcium channels in the sarcolemma (similar to cardiac muscle fibers) that open during the action potential along the sarcolemma.
- The influx of extracellular Ca^{++} ions, which diffuse into the sarcoplasm to reach the calmodulin, accounts for most of the Ca^{++} that triggers contraction of a smooth muscle cell.

Excitation-contraction coupling

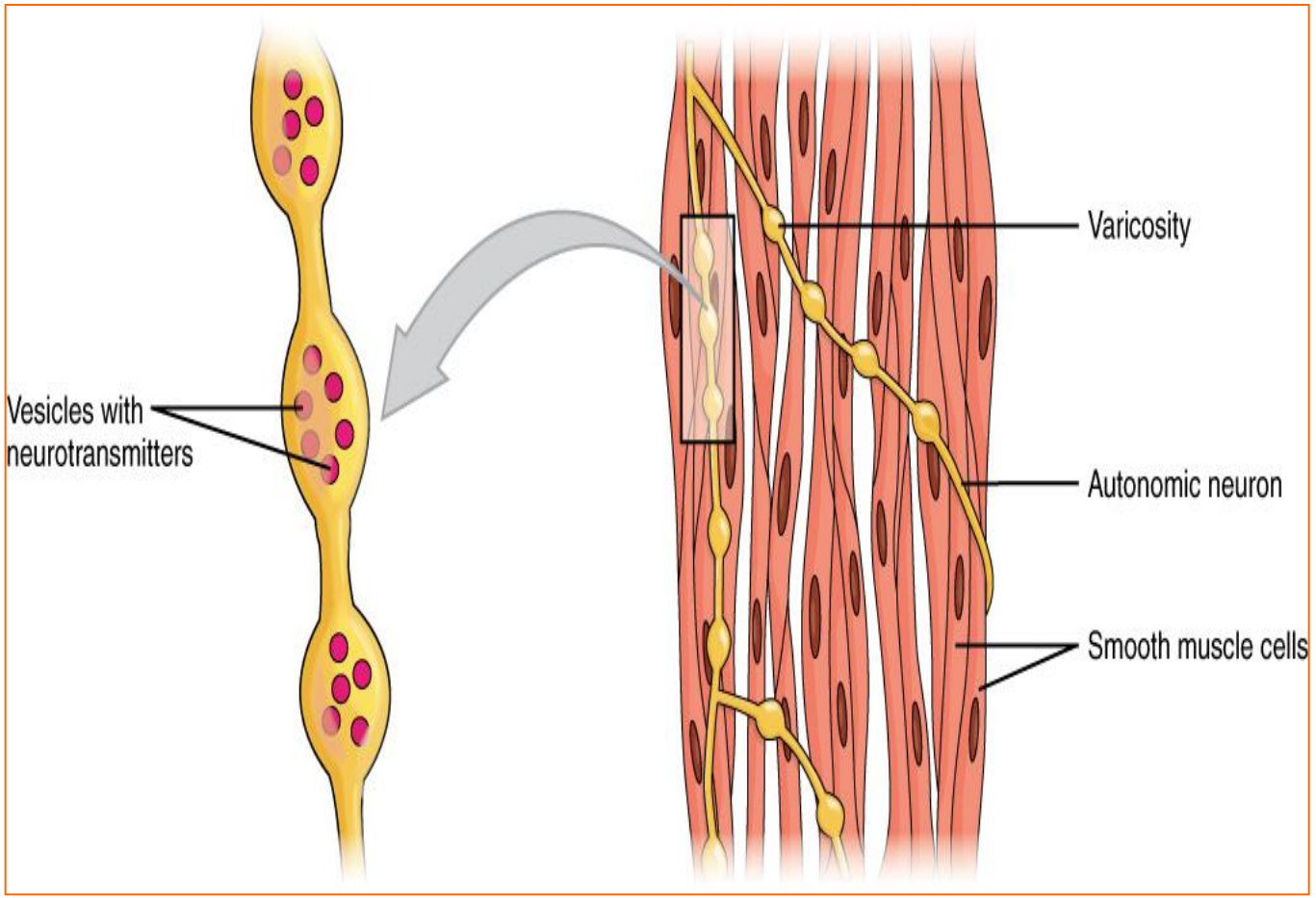
- Muscle contraction continues until ATP-dependent calcium pumps actively transport Ca^{++} ions back into the SR and out of the cell.
- However, a low concentration of calcium remains in the sarcoplasm to maintain muscle tone.
- This remaining calcium keeps the muscle slightly contracted, which is important in certain tracts and around blood vessels.



The action potentials of visceral smooth muscle occur in one of two forms: (1) spike potentials or (2) action potentials with plateaus.



A series of axon-like swelling, called varicosities or "boutons," from autonomic neurons form motor units through the smooth muscle.



Spread of impulse

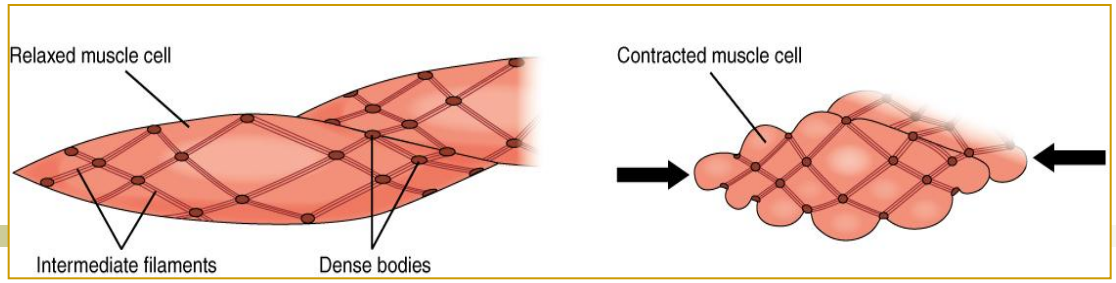
- To maintain organ dimensions against force, cells are fastened to one another by adherens junctions. As a consequence, cells are mechanically coupled to one another such that contraction of one cell invokes some degree of contraction in an adjoining cell.
- Gap junctions couple adjacent cells chemically and electrically, facilitating the spread of chemicals (e.g., calcium) or action potentials between smooth muscle cells. Single unit smooth muscle displays numerous gap junctions and these tissues often organize into sheets or bundles which contract in bulk.

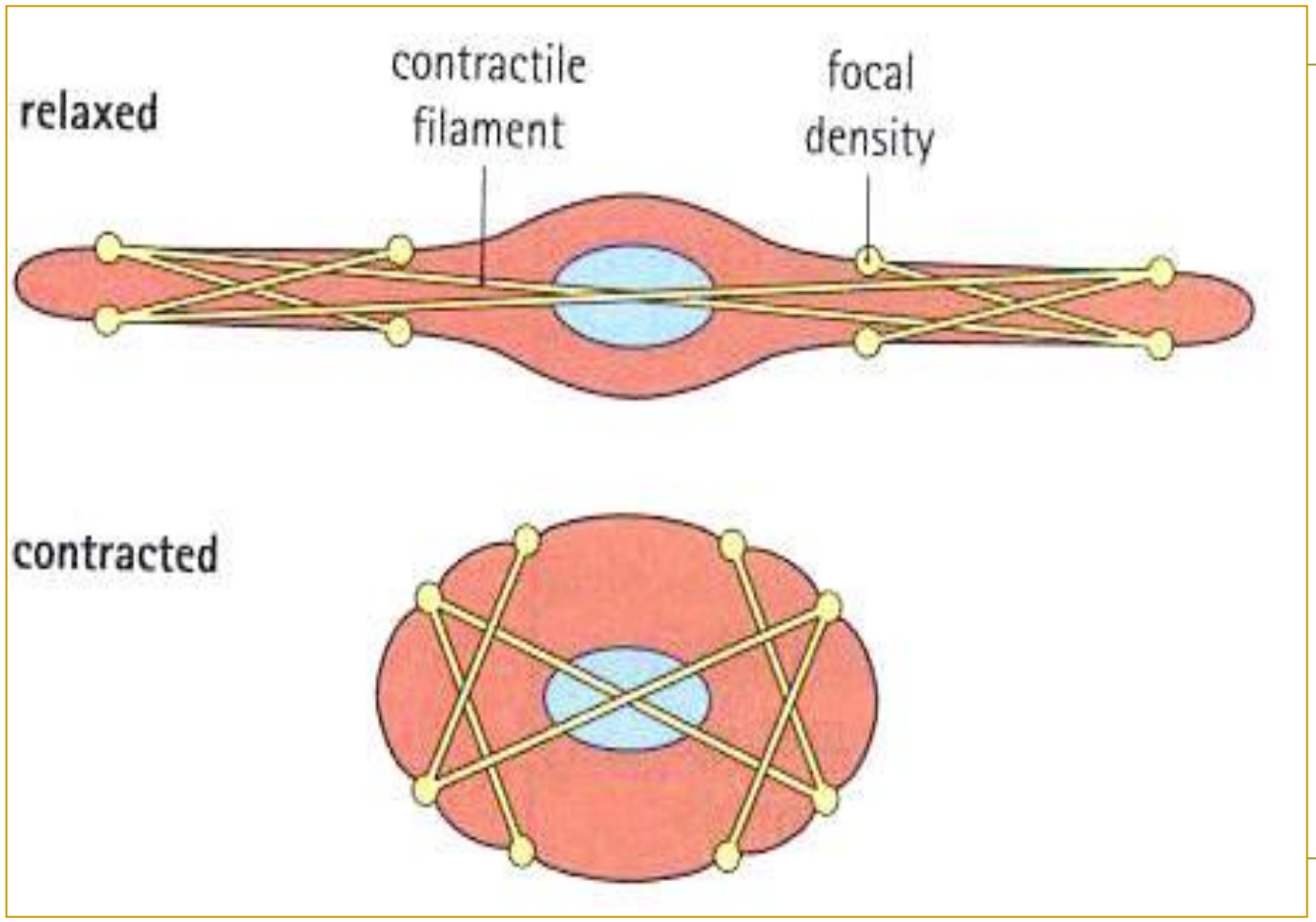
Contraction

- Smooth muscle contraction is caused by the sliding of myosin and actin filaments (a sliding filament mechanism) over each other. The energy for this to happen is provided by the hydrolysis of ATP. Myosin functions as an ATPase utilizing ATP to produce a molecular conformational change of part of the myosin and produces movement. Movement of the filaments over each other happens when the globular heads protruding from myosin filaments attach and interact with actin filaments to form crossbridges. The myosin heads tilt and drag along the actin filament a small distance (10-12 nm). The heads then release the actin filament and then changes angle to relocate to another site on the actin filament a further distance (10-12 nm) away. They can then re-bind to the actin molecule and drag it along further.

Contraction

- This process is called crossbridge cycling and is the same for all muscles. Unlike cardiac and skeletal muscle, smooth muscle does not contain the calcium-binding protein troponin.
- Contraction is initiated by a calcium-regulated phosphorylation of myosin, rather than a calcium-activated troponin system.
- Crossbridge cycling causes contraction of myosin and actin complexes, in turn causing increased tension along the entire chains of tensile structures, ultimately resulting in contraction of the entire smooth muscle tissue.





The top view shows a relaxed smooth muscle cell. Note the focal densities and the network of actin and myosin filaments.

When contracted, the filaments slide together and pull the cell to a more rounded appearance.

Sheets of smooth muscle cells work together because they are interconnected by gap junctions and connective tissue.

Contraction

- Smooth muscle may contract ***phasically*** with rapid contraction and relaxation, or ***tonically*** with slow and sustained contraction.
- The reproductive, digestive, respiratory, and urinary tracts, skin, eye, and vasculature all contain this tonic muscle type.
- This type of smooth muscle can maintain force for prolonged time with only little energy utilization.
- There are differences in the myosin heavy and light chains that also correlate with these differences in contractile patterns and kinetics of contraction between tonic and phasic smooth muscle.

The contraction process proceeds along the following steps:

- Step 1. Wave of depolarization along membrane from the neuromuscular junction or adjacent cells.
- Step 2. Calcium is released from caveolae and endoplasmic reticulum
- Step 3. Calcium binds to calmodulin
- Step 4. Calcium-calmodulin complex activates and unfolds myosin light chain kinase
- Step 5. ATP is used to phosphorylate myosin light chain kinase (this is unique to smooth muscle).
- Step 6. Phosphorylated light chain kinase is activated so it can bind actin.
- Step 7. Works like an ATPase to bind actin and move along the F actin chain.

To stop the contraction:

- **Step 1. Reduction in calcium levels**
- **Step 2. Calmodulin calcium complex dissociates**
- **Step 3. Myosin light chain kinase is inactivated.**
- **Step 4. Myosin phosphatase dephosphorylates the myosin light chain**
- **Step 5. Actin binding site is masked**

Relaxation

- Myosin light-chain phosphatase dephosphorylates the myosin light chains and thereby inhibits contraction.
- In general, the relaxation of smooth muscle is by cell-signaling pathways that increase the myosin phosphatase activity, decrease the intracellular calcium levels, hyperpolarize the smooth muscle, and/or regulate actin and myosin dynamics.

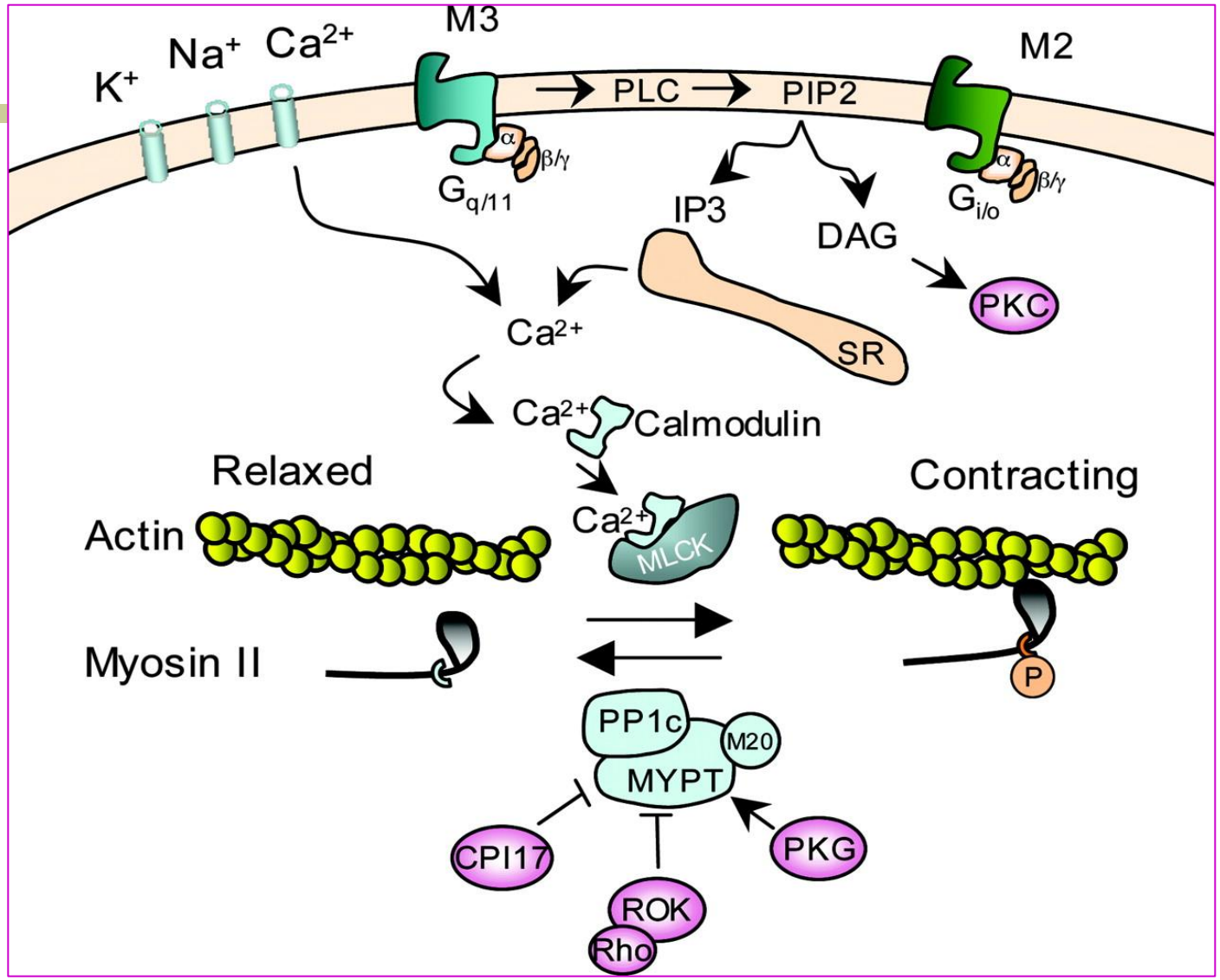
Relaxation-inducing factors:

- The relaxation of smooth muscle can be mediated by the endothelium-derived relaxing factor - nitric oxide, endothelial derived hyperpolarizing factor (either an endogenous cannabinoid, cytochrome P450 metabolite, or hydrogen peroxide), or prostacyclin (PGI_2).
- Nitric oxide and PGI_2 stimulate soluble guanylate cyclase and membrane bound adenylate cyclase, respectively. The cyclic nucleotides (cGMP and cAMP) produced by these cyclases activate Protein Kinase G and Proten Kinase A and phosphorylate a number of proteins. The phosphorylation events lead to a decrease in intracellular calcium (inhibit L type Calcium channels, inhibits IP3 receptor channels, stimulates sarcoplasmic reticulum Calcium pump ATPase).
- The endothelium derived hyperpolarizing factor stimulates calcium sensitive potassium channels and/or ATP sensitive potassium channels and stimulate potassium efflux which hyperpolarizes the cell and produces relaxation.

Innervation via the autonomic nervous system

- Smooth muscle can either receive innervation via the autonomic nervous system, or hormones through the blood system can regulate them. Some muscle responds to both types of regulation.
- Innervation involves nerve endings forming synapses with smooth muscle cells. They are usually in the form of swellings of axons which contain synaptic vesicles (norepinephrine or acetylcholine are two neurotransmitters).
- For instance, most blood vessels respond to norepinephrine and epinephrine (from sympathetic stimulation or the adrenal medulla) by producing vasoconstriction (this response is mediated through alpha 1-adrenergic receptors). Blood vessels in skeletal muscle and cardiac muscle respond to these catecholamines producing vasodilation because the smooth muscle possess beta 2- adrenergic receptors.
- Parasympathicus causes excitation and contraction through m-cholinergic receptors.

Muscarinic receptor signaling pathways that regulate the contractile system in smooth muscle.



External substances

- An example of hormonal control would be found in the uterus, which is under the influence of oxytocin. This would be active particularly during labor and delivery.
- Generally, arterial smooth muscle responds to carbon dioxide by producing vasodilation, and responds to oxygen by producing vasoconstriction.
- Bronchiole, smooth muscle that line the airways of the lung, respond to high carbon dioxide producing vasodilation and vasoconstrict when carbon dioxide is low.
- Further different smooth muscle tissues display extremes of abundant to little sarcoplasmic reticulum so excitation-contraction coupling varies with its dependence on intracellular or extracellular calcium.

What is the difference between single unit (unitary) or multiunit muscle groups?

- A multiunit system receives fine innervation allowing for regulation of individual cells.
- The cells that control the opening of the iris are innervated individually.
- A single unit (unitary) innervation pattern has a neuromuscular junction that serves a sheet or bundle of muscle fibers.
- The cells that receive the stimulus in turn transmit it to other cells via the gap junctions (nexus). Some muscle has both types of innervation patterns.

Energy of contraction

- Because most smooth muscles must function for long periods without rest, their power output is relatively low, but contractions can continue without using large amounts of energy.
- Some smooth muscle can also maintain contractions even as Ca^{++} is removed and myosin kinase is inactivated/dephosphorylated. This can happen as a subset of cross-bridges between myosin heads and actin keep the thick and thin filaments linked together for a prolonged period, and without the need for ATP.
- This allows for the maintaining of muscle “tone” in smooth muscle that lines arterioles and other visceral organs with very little energy expenditure.

Благодаря за вниманието!