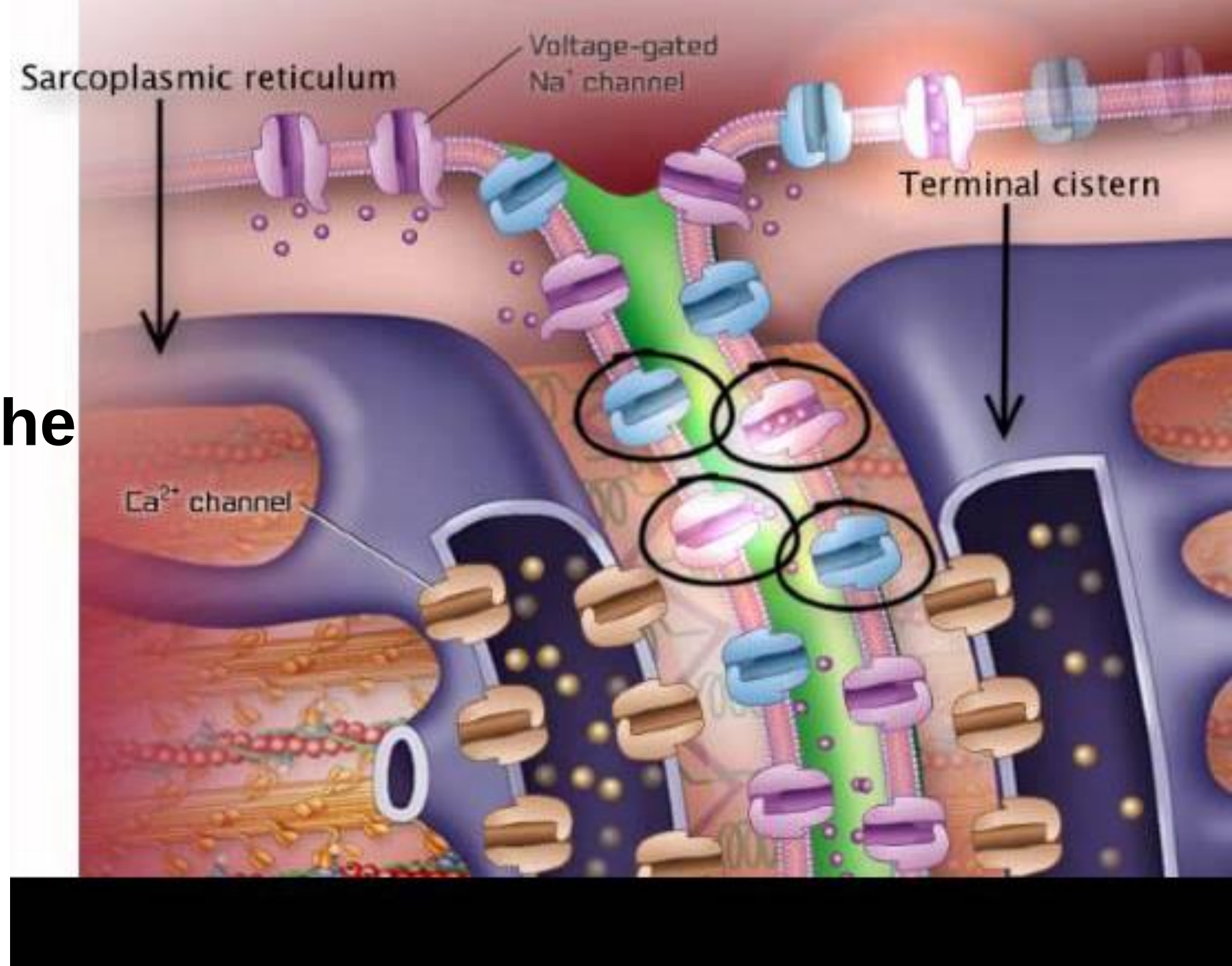
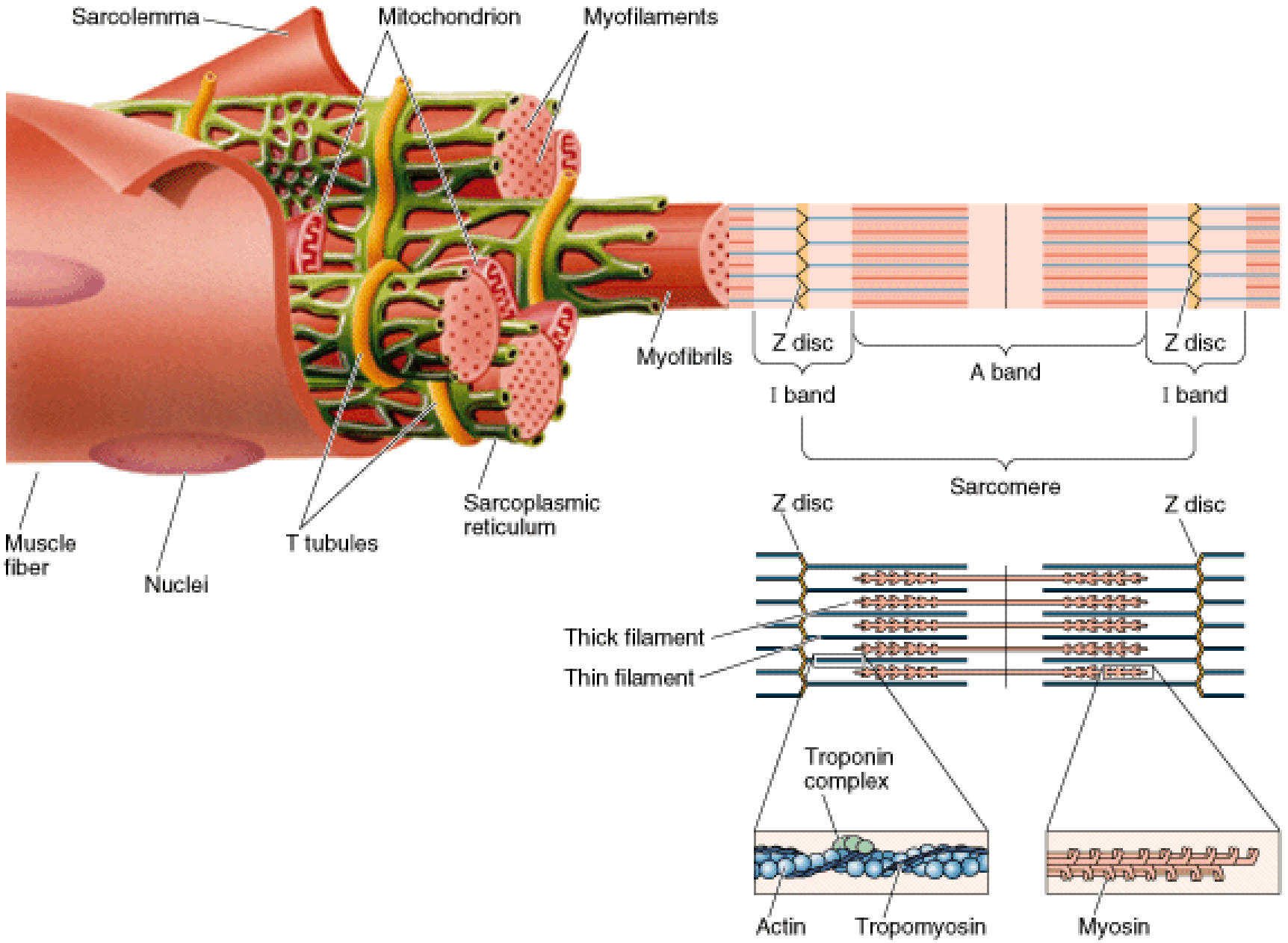
Calcium and Excitation-Contraction Coupling in the Heart-2

Assoc. Prof. Erkan Tuncay



▶ Organization of a Muscle Fiber

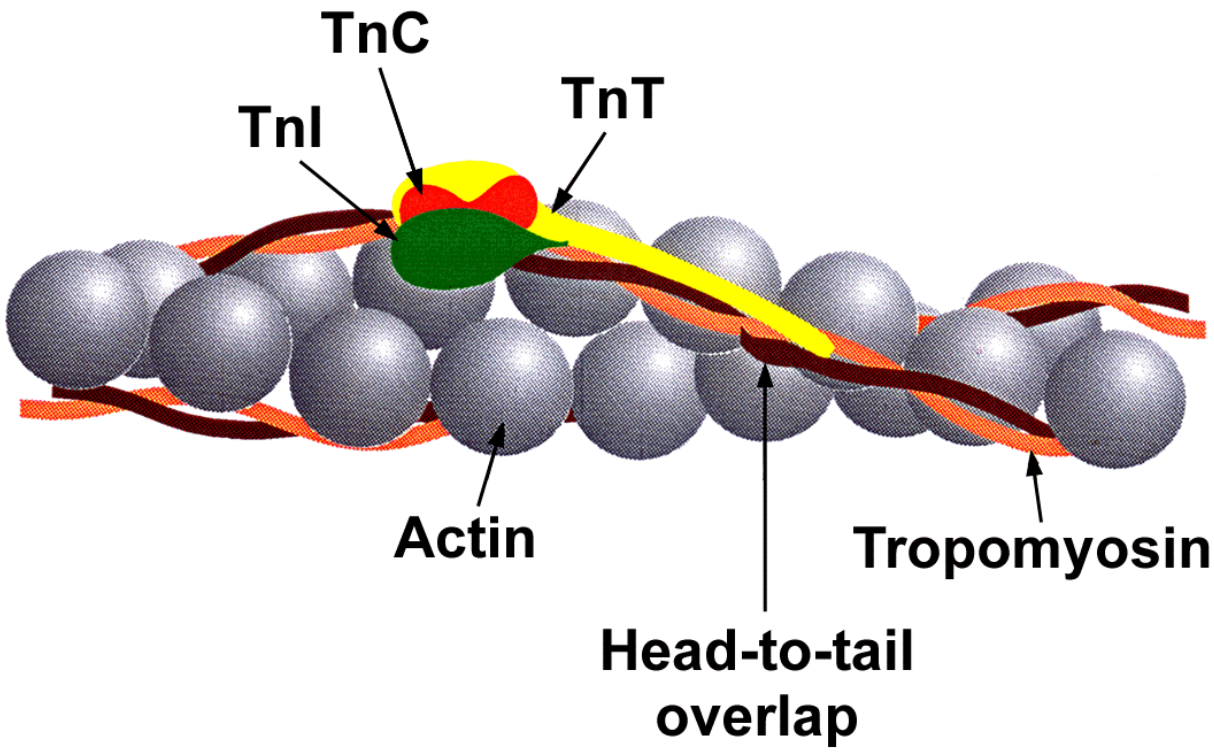


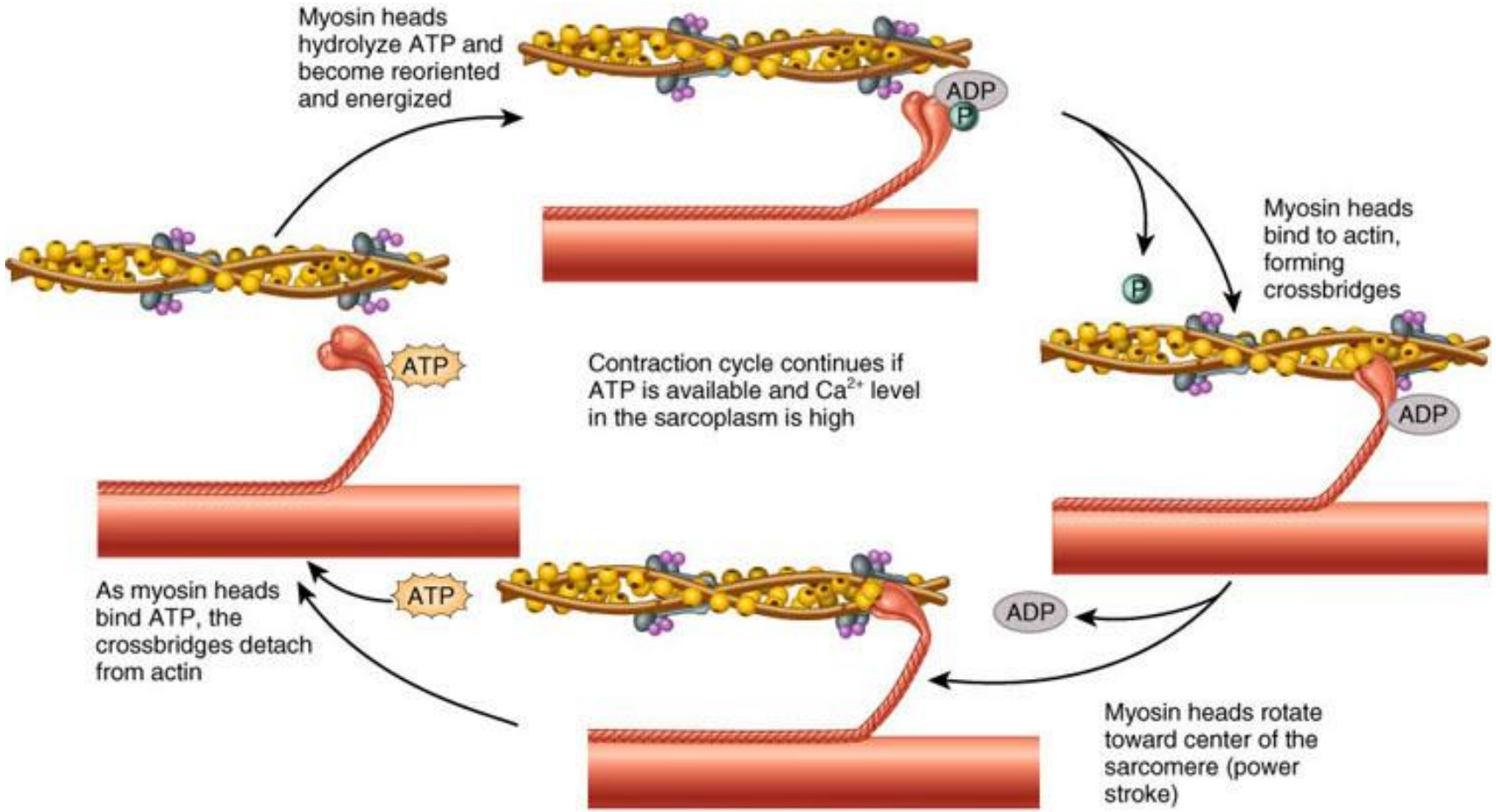
- Muscle → Myofilaments → Myofibrils→ Sarcomers→ Filaments (Thick & thin) → Proteins
  - Every myofilaments contains thusands of myofibrils
  - Every myofibrils contains poritens;

a) **Contractile proteins**: myosin and actin.
b) **Regulatory proteins**: *tropomyosin and troponin*
c) **Structural proteins**: titin

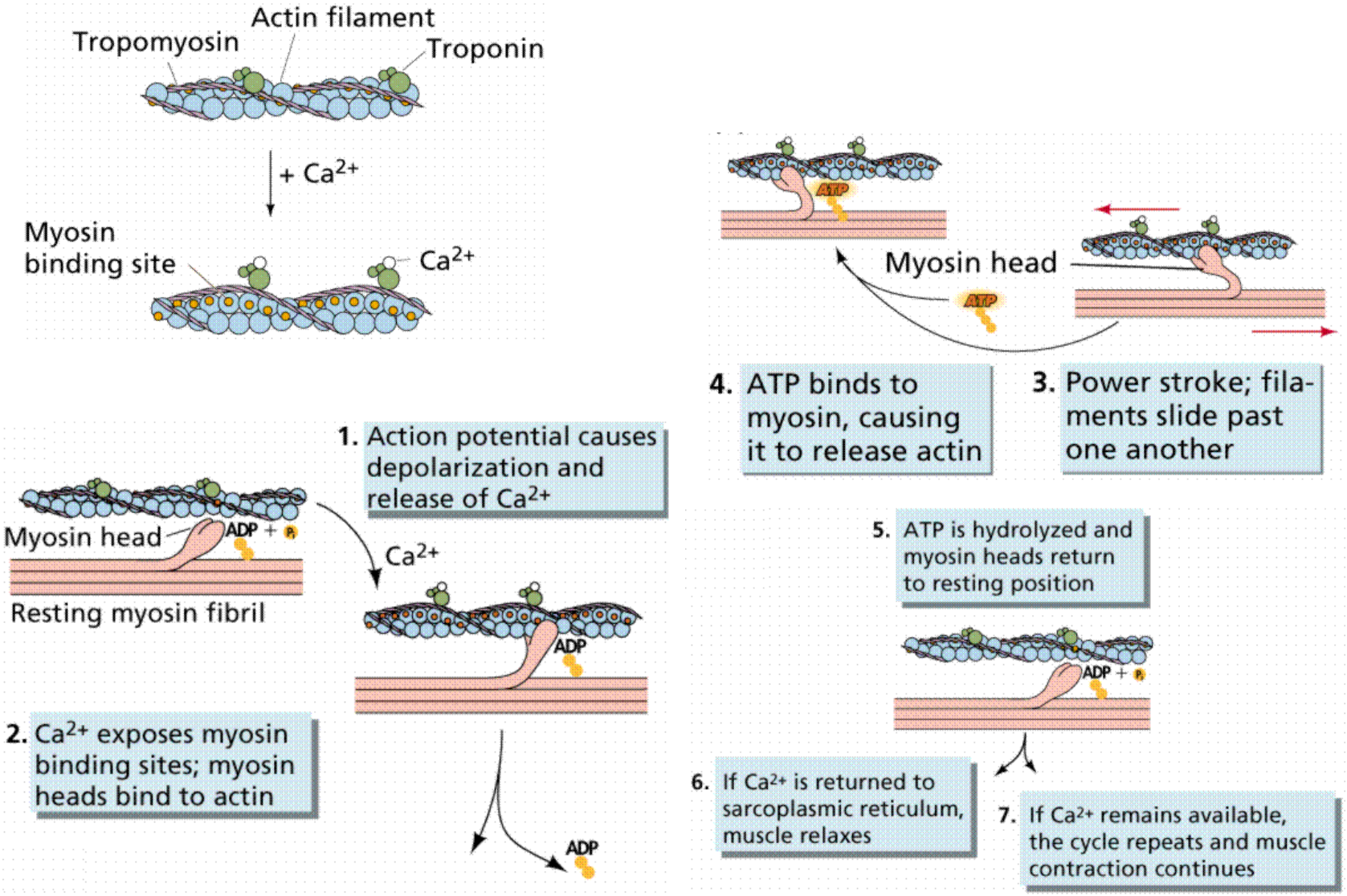
Troponin

- Troponin is a complex of three regulatory proteins, troponin C (TnC), troponin T (TnT), and troponin I (TnI), which are integral to non-smooth muscle contraction in cardiac muscle. They are located between actin filaments of muscle tissue. TnC binds to calcium ions and produces conformational change in TnI. TnT binds to tropomyosin and TnT binds to actin.

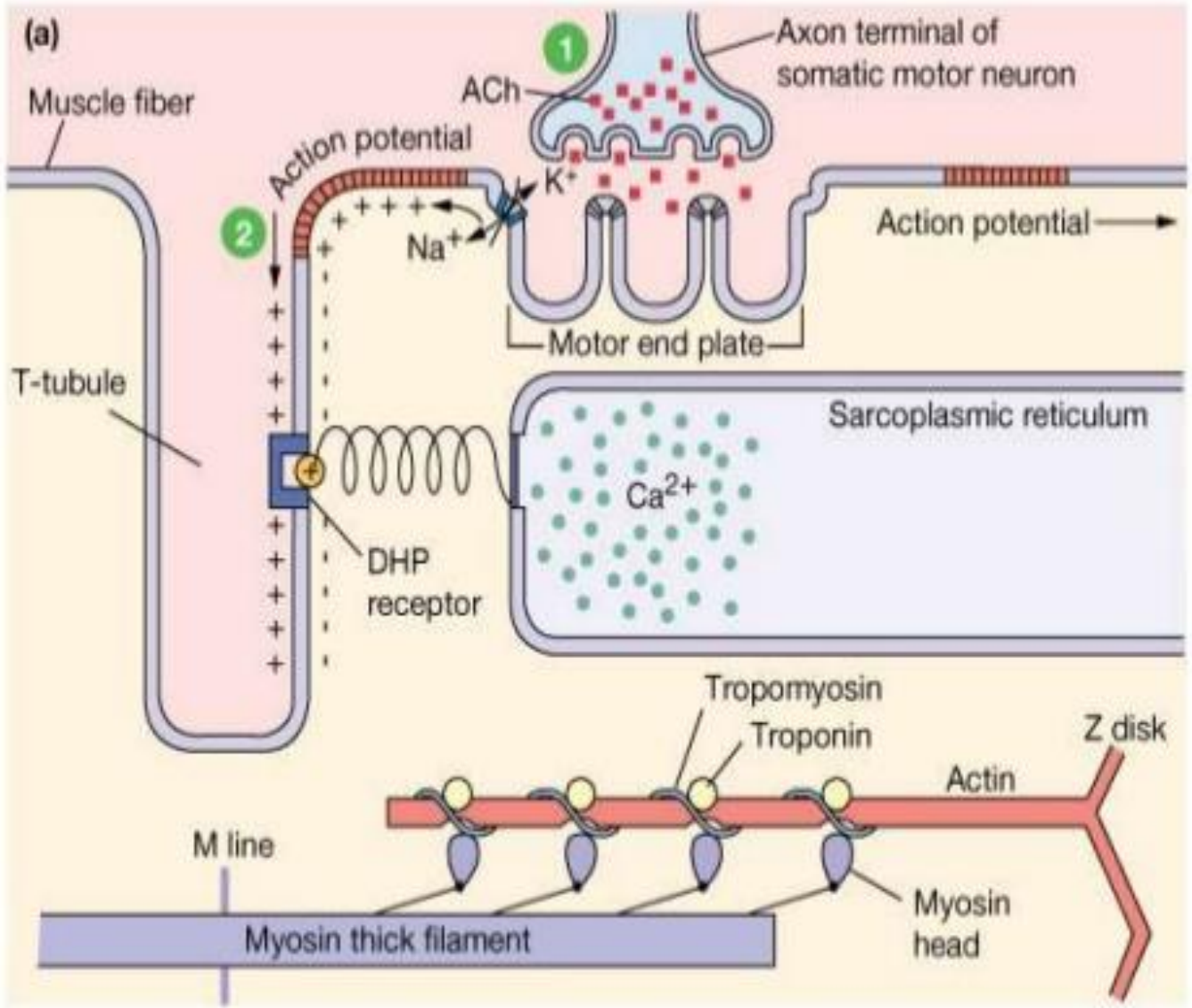




The sliding filament model

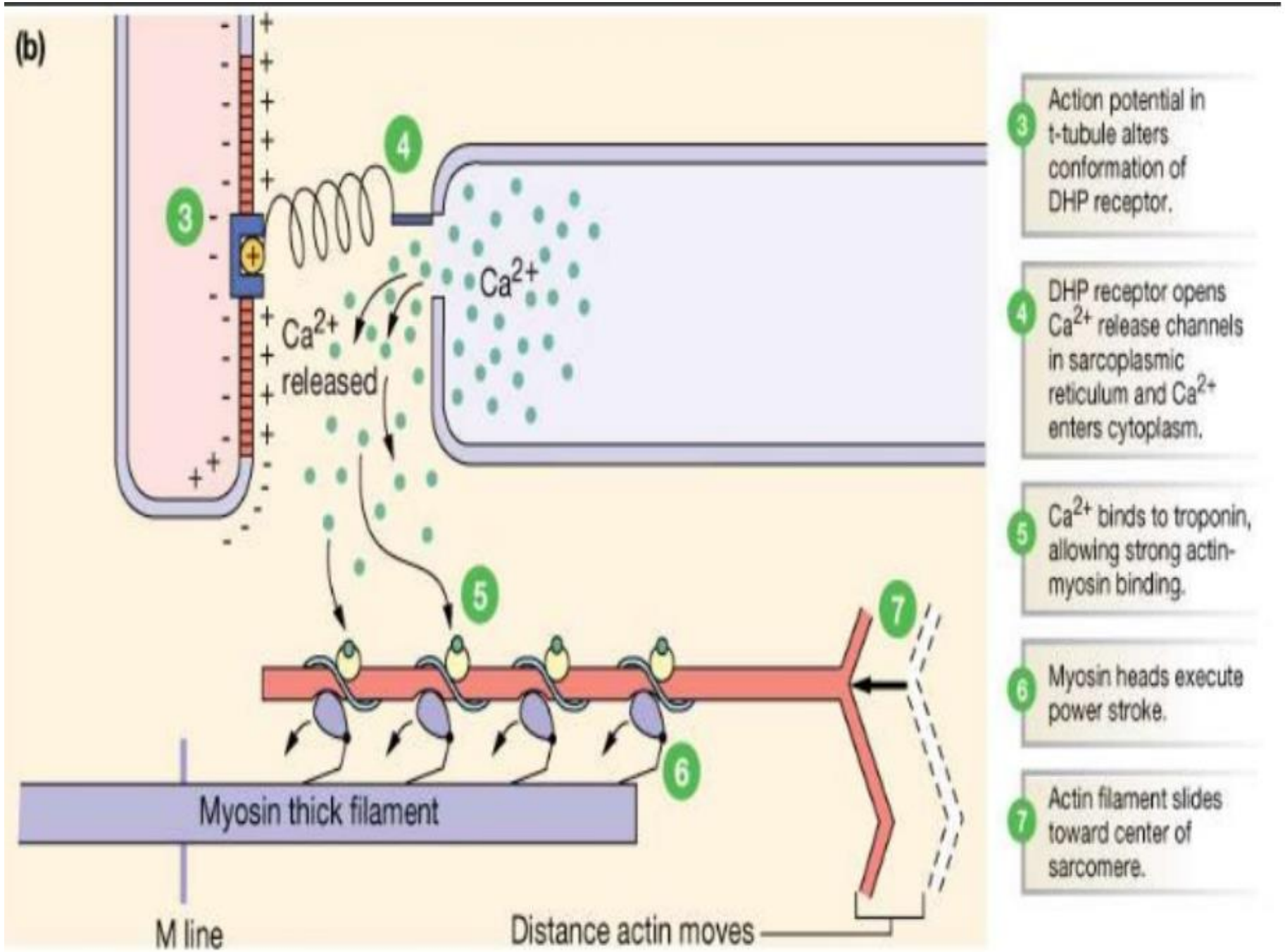


Skeletal Muscle Contraction: EXCITATION CONTRACTION COUPLING

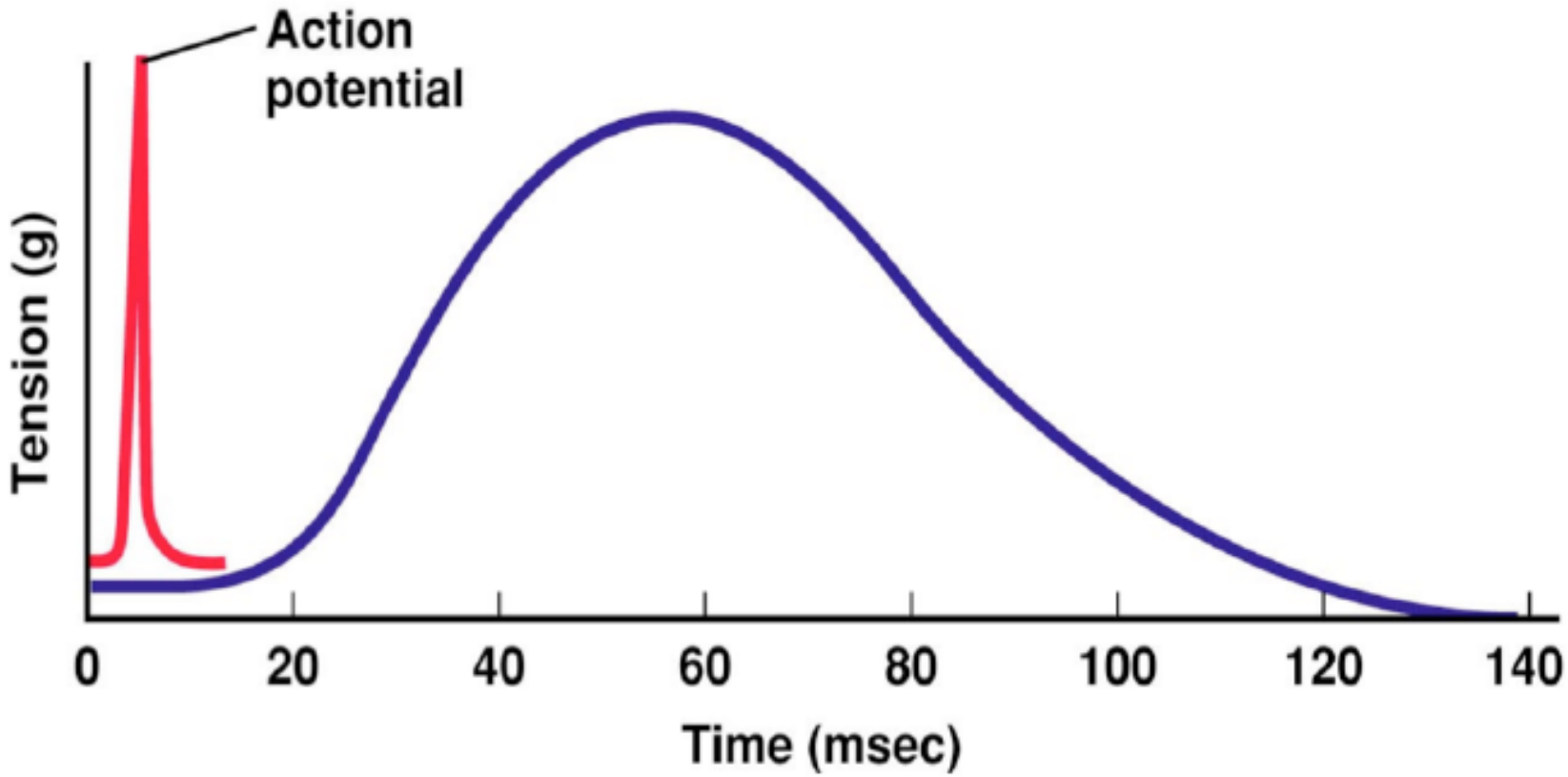


1. Somatic motor neuron releases ACh at neuromuscular junction.

2. Net entry of Na^+ through ACh receptor-channel initiates a muscle action potential.


(b)
3
4
Ca^{2+} released
Ca^{2+}
5
6
7
Myosin thick filament
M line
Distance actin moves
3 Action potential in t-tubule alters conformation of DHP receptor.
4 DHP receptor opens Ca^{2+} release channels in sarcoplasmic reticulum and Ca^{2+} enters cytoplasm.
5 Ca^{2+} binds to troponin, allowing strong actin-myosin binding.
6 Myosin heads execute power stroke.
7 Actin filament slides toward center of sarcomere.

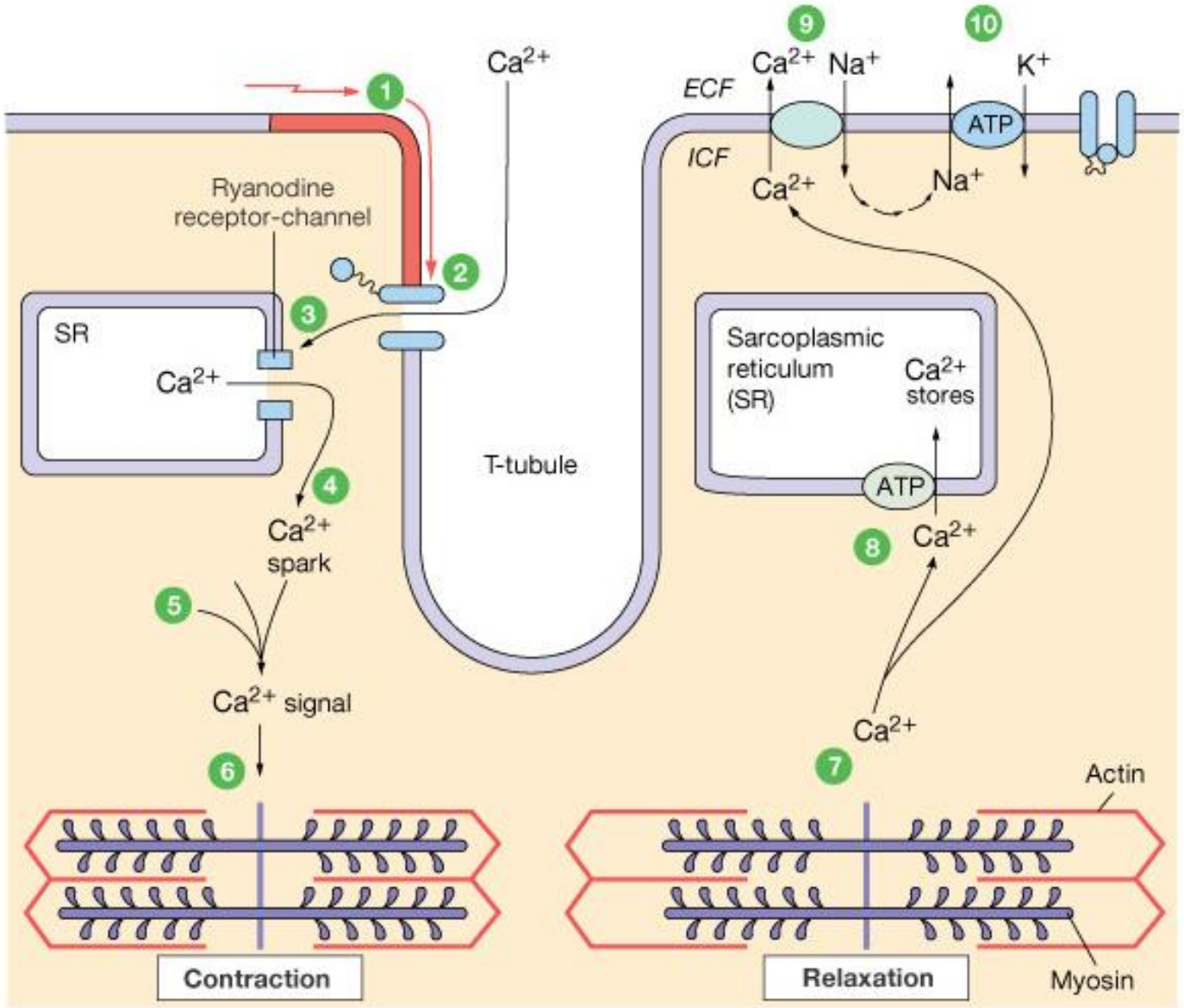
Skeletal muscle: Acion potential and contraction relationship



Summary of Actions of Skeletal Muscle Cell Contraction

1. Nerve impulse cause nerve to release acetylcholine.
2. ACh travels across neuromuscular junction, binding to muscle cell membrane.
3. ACh binding initiates an electrical impulse which travels across membrane and into T tubules.
4. Impulse stimulates release of Ca^{+2} from SR.
5. Ca^{+2} binds with t-t complex of the actin filaments, shifting it's position, exposing myosin binding sites.
6. Myosin binds to actin; Ca^{+2} presence also causes enzymatic actions of myosin to breakdown ATP into ADP + P + energy.
7. Energy of ATP degradation causes shape change of myosin head, pulling actin molecule toward center of sacromere.
8. After sliding, a new ATP binds to myosin, breaking the myosin-actin bond, releasing the myosin head.
9. If Ca^{+2} is still present, the process repeats itself until sacromere has shortened completly.
10. If a nerve impulse ceases, the Ca^{+2} is reabsorbed by the SR and the muscle relaxes.

Mechanism of Cardiac muscle contraction



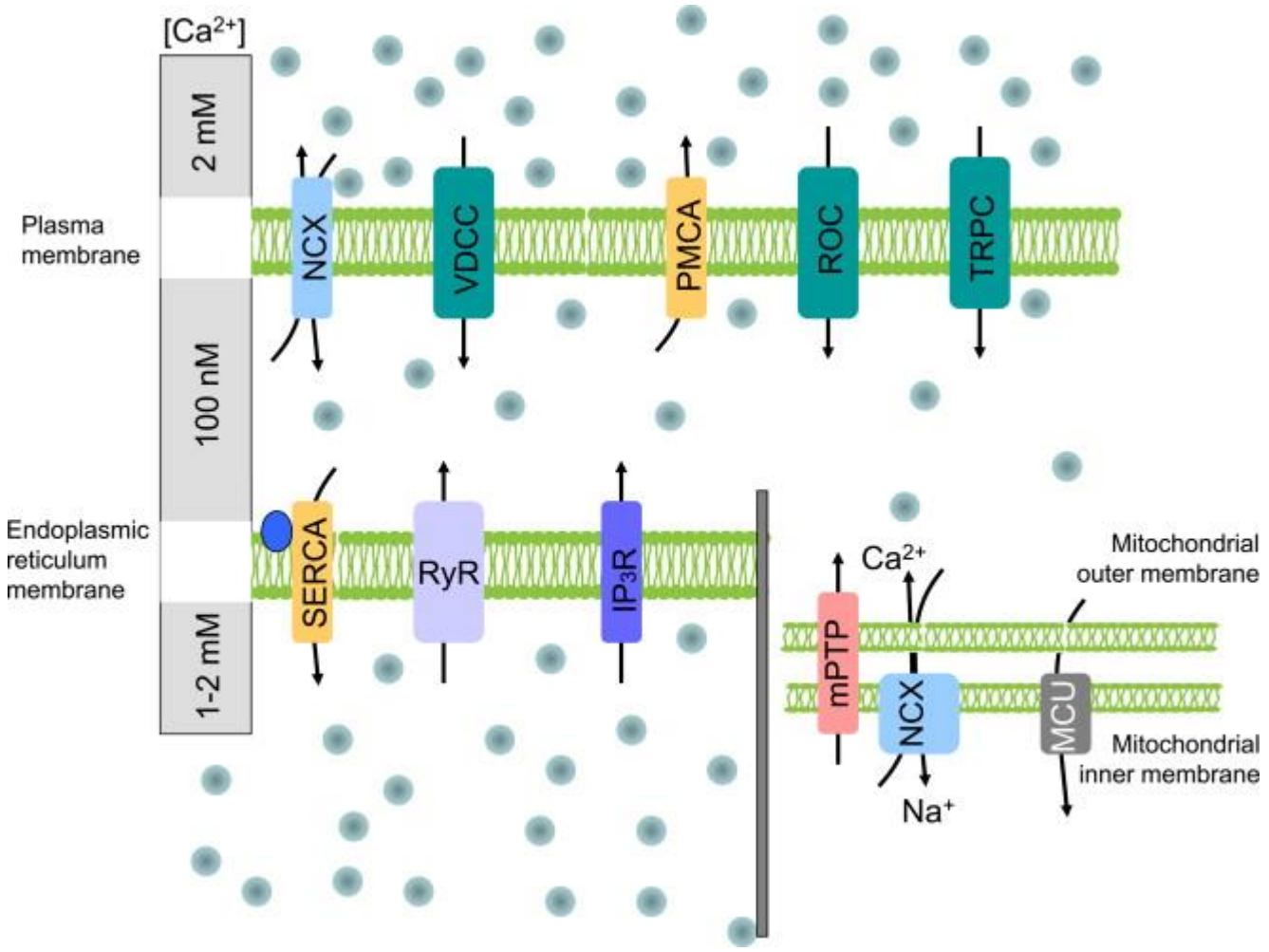
1. Action potential enters from adjacent cell.
2. Voltage-gated Ca^{2+} channels open. Ca^{2+} enters cell.
3. Ca^{2+} induces Ca^{2+} release through ryanodine receptor-channels (RyR).
4. Local release causes Ca^{2+} spark.
5. Summed Ca^{2+} sparks create a Ca^{2+} signal.
6. Ca^{2+} ions bind to troponin to initiate contraction.
7. Relaxation occurs when Ca^{2+} unbinds from troponin.
8. Ca^{2+} is pumped back into the sarcoplasmic reticulum for storage.
9. Ca^{2+} is exchanged with Na^{+}.
10. Na^{+} gradient is maintained by the Na^{+}-K^{+}-ATPase.

Summary of Actions of Cardiac Muscle Cell Contraction

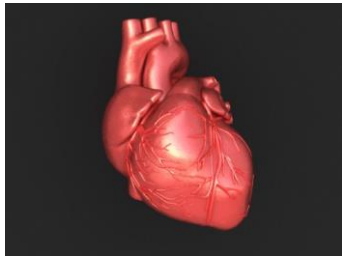
1. An action potential, induced by the pacemaker cells in the sinoatrial (SA) and atrioventricular (AV) nodes, is conducted to contractile cardiomyocytes through gap junctions.
2. As the action potential travels between sarcomeres, it activates the calcium channels in the T-tubules, resulting in an influx of calcium ions into the cardiomyocyte.
3. Calcium in the cytoplasm then binds to cardiac troponin-C, which moves the troponin complex away from the actin binding site. This removal of the troponin complex frees the actin to be bound by myosin and initiates contraction.
4. The myosin head binds to ATP and pulls the actin filaments toward the center of the sarcomere, contracting the muscle.
5. Intracellular calcium is then removed by the sarcoplasmic reticulum, dropping intracellular calcium concentration, returning the troponin complex to its inhibiting position on the active site of actin, and effectively ending contraction as the actin filaments return to their initial position, relaxing the muscle.

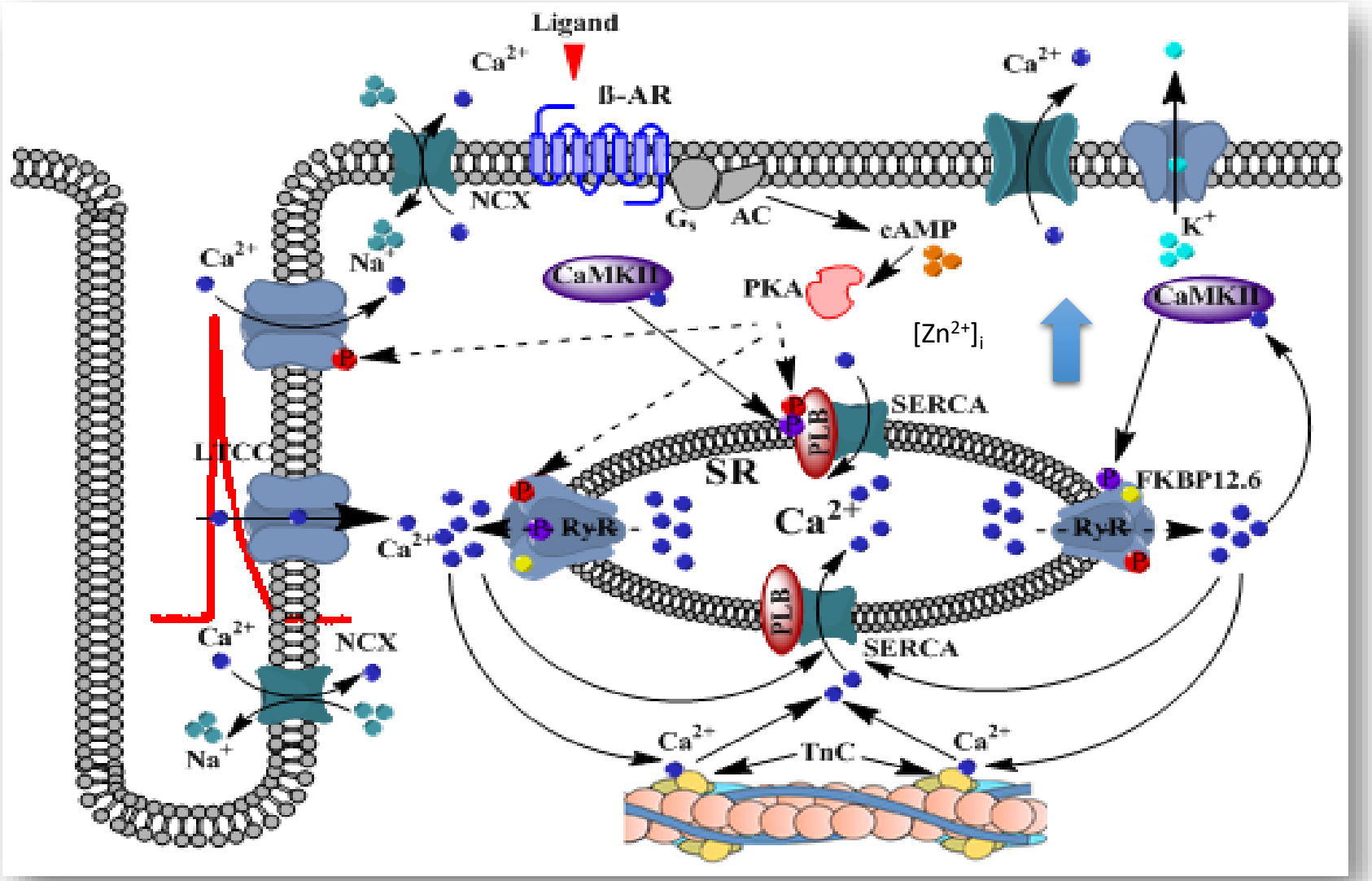
Calcium mechanisms in cells

- NCX – sodium/calcium exchanger
- VDCC – voltage gated calcium channels
- PMCA – pmca plasma membrane calcium atpase
- ROC – receptor operated channels;
- TRPC – Transient Receptor Potential Canonical channels
- SERCA – sarko/endoplazmik retikulum kalsiyum ATPaz
- RyR – ryanodin receptors
- IP3R – inositol 1,4,5-trisphosphate receptors;
- mPTP – mitochondrial permeability transition pore;
- MCU – mitochondrial uniporter

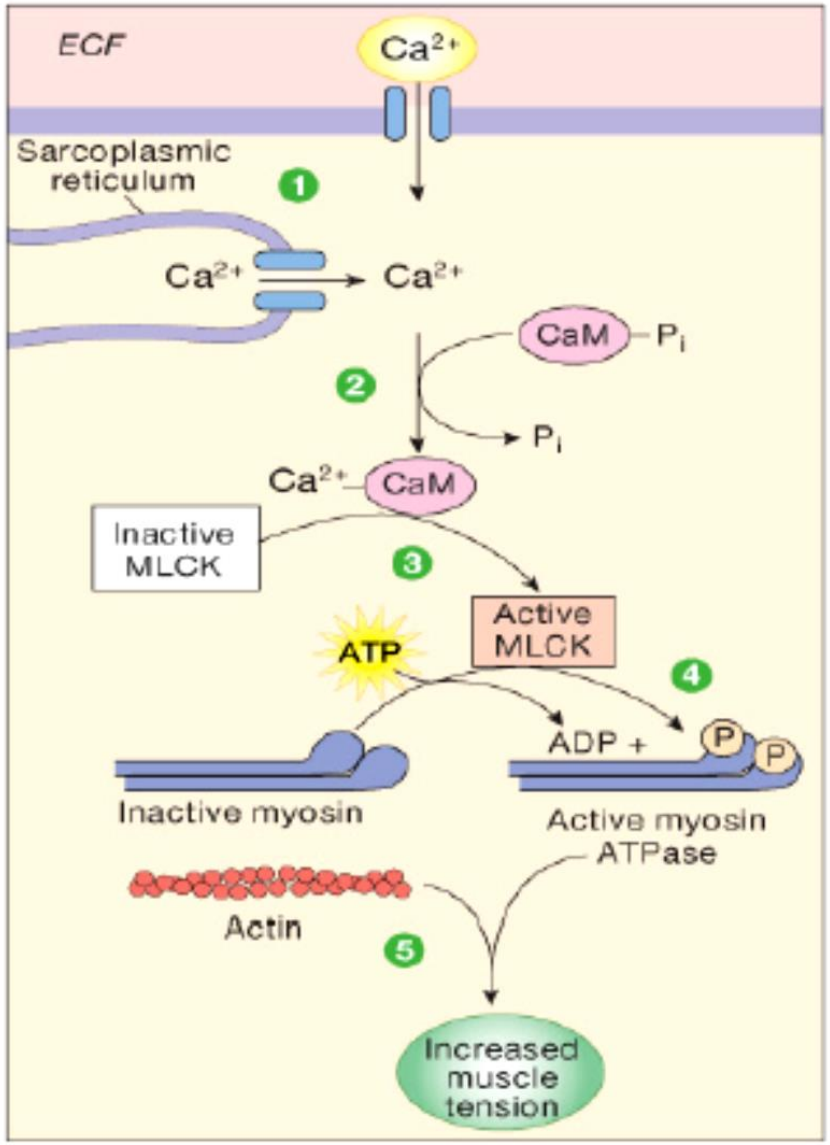


Calcium homeostasis in heart



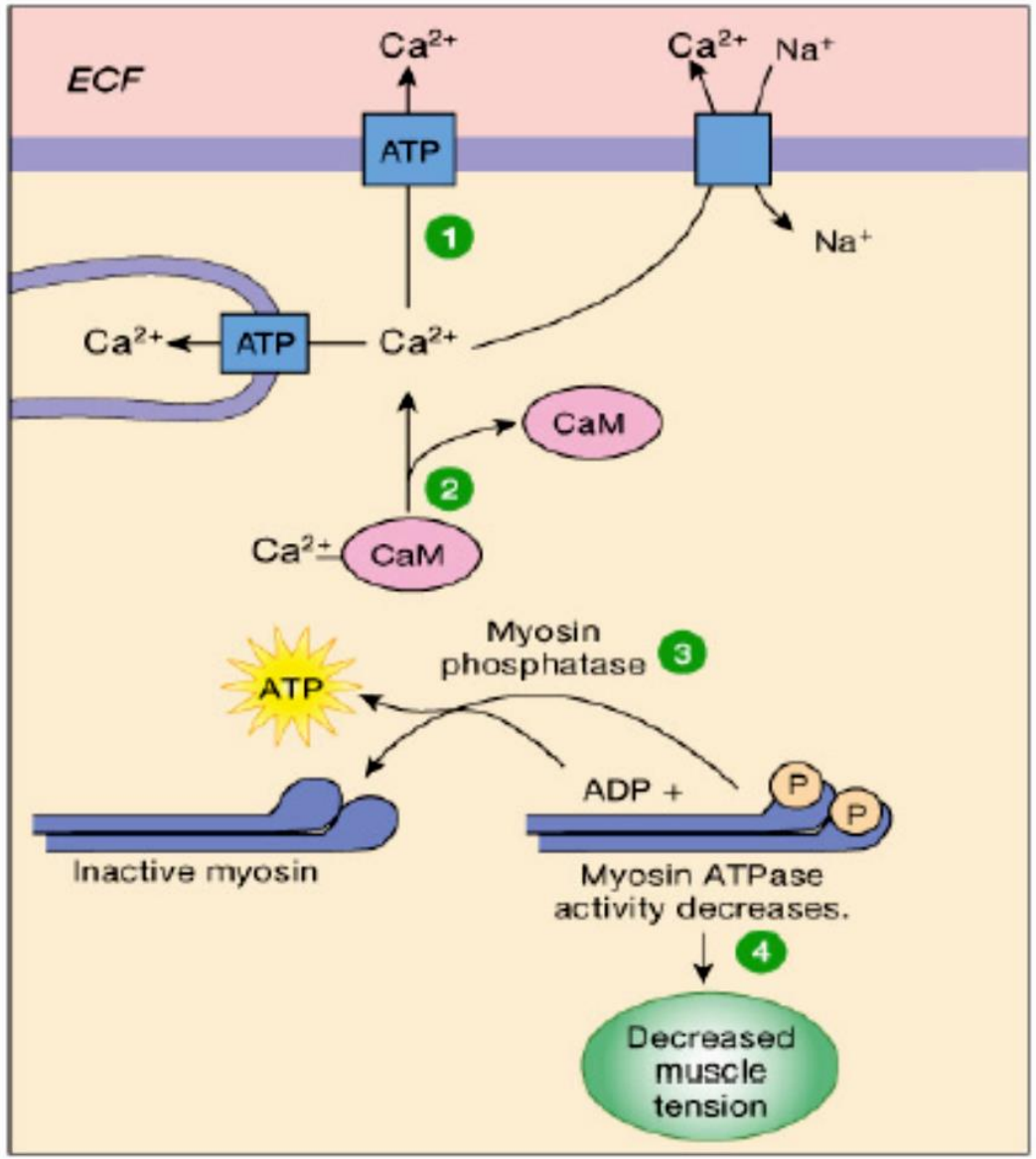


SMOOTH MUSCLE CONTRACTION AND RELAXATION



1. Intracellular Ca^{2+} concentrations increase when Ca^{2+} enters cell and is released from sarcoplasmic reticulum.
2. Ca^{2+} binds to calmodulin (CaM).
3. Ca^{2+}–calmodulin activates myosin light chain kinase (MLCK).
4. MLCK phosphorylates light chains in myosin heads and increases myosin ATPase activity.
5. Active myosin crossbridges slide along actin and create muscle tension.

Düz Kasın Kontraksiyonu: Mekanizma



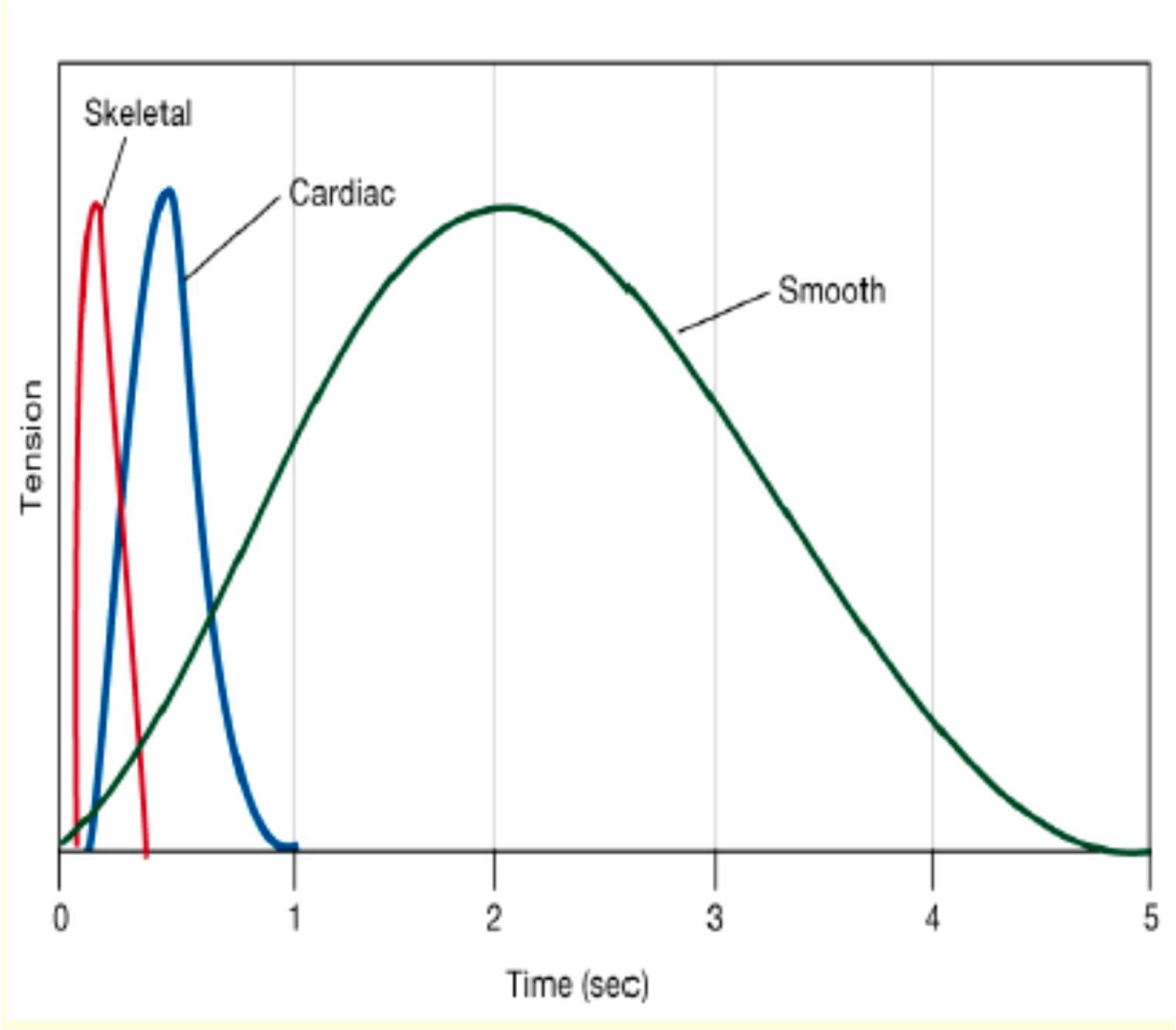
1. Free Ca^{2+} in cytosol decreases when Ca^{2+} is pumped out of the cell or back into the sarcoplasmic reticulum.

2. Ca^{2+} unbinds from calmodulin (CaM).

3. Myosin phosphatase removes phosphate from myosin, which decreases myosin ATPase activity.

4. Less myosin ATPase results in decreased muscle tension.

Muscle contraction types



Types of Contractions

Isotonic (dinamic) contraction:

The most simple contraction is when the muscle contract without any or little attachment. The length of the muscle is then reduced but the tone has not changed. This is called **isotonic** (= same tone).