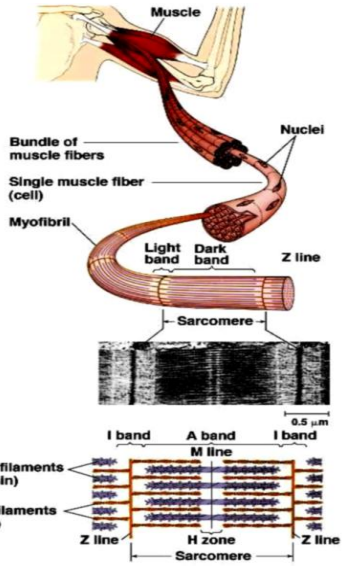
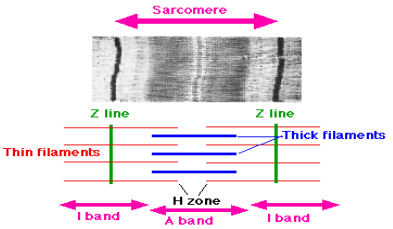
Muscle

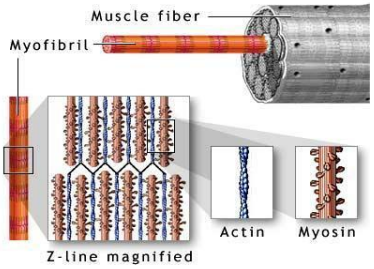
Types of muscles

2 Types → Striated muscle → Skeletal muscles, Cardiac muscles
2 Types → Smooth muscles



Skeletal muscles





Morphology (structure)

Skeletal muscles *each contains* **muscle fibers** *each contains* **myofibrils** *each contains* **filaments**

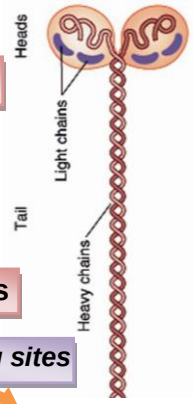
Myosin protein

2 Heavy chains — Coil around each other ⇨ a helix
- **Tail**
- **Body**
- **2 Arms** → **Has 2 hinges**
  - One hinge with the body
  - 2nd hinge with the head

4 light chains

Cross bridges

2 Heads → **Has 3 binding sites**
- Actin binding site
- ATP binding site
- catalytic site (hydrolyzes ATP)



Thin filament proteins (3 types)

(1) Actin	(2) Tropomyosin	(3) Troponin
• The ***backbone*** of thin filaments • Formed of ***2 chains*** (coil around each other ⇨ a ***helix***) • Each actin molecule has (***active site***) with which cross brides of myosin combine during muscle contraction	• ***Long filaments*** present in the groove between the 2 chains of actin • ***covers the active sites*** on actin during relaxation	3 globular protein molecules **1- Troponin I:** has a strong affinity & binds with actin (I-band) **2- Troponin T:** has a strong affinity & binds with tropomyosin **3- Troponin C:** has a strong affinity & binds with Ca^{+2}

Tubular system: *2 networks*

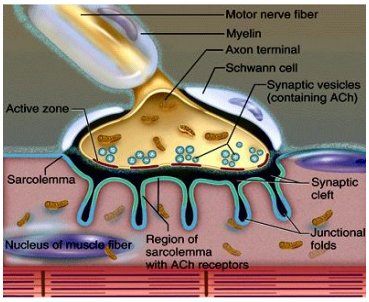
(1) Transverse (T) tubule	(2) Sarcoplasmic reticulum (SR)
• ***Invagination*** on the surface of muscle membrane ***at the junction of A & I bands.*** • ***Conducts action potential to the SR.*** • Contains ***extracellular fluid***. • Contains ***a voltage sensitive*** (***DHP***) ***receptor*** that opens the ryanodine Ca^{+2} release channels on the SR membrane.	• Networks of membranous channels ***surround each myofibril & run parallel with it*** • It has high conc. of Ca^{+2} (for muscle contraction) • The ends of SR (***terminal cisternae***) contact with T tubules by foot processes. • SR membrane contains (***ryanodine receptor***) that contain foot process & Ca^{+2} release channel

Physiologic anatomy of neuromuscular junction

1- Axon terminals (end feet): contains ***A.Ch. vesicles***.

2- Motor end plate (MEP) contains ***A.Ch. receptors***

3- Synaptic cleft contains ***A.Ch. esterase*** enzyme.



Neuromuscular transmission

Sequence of events during N.M. transmission

1- The nerve impulse ***reaches the nerve ending*** ⇨ ↑↑ permeability to Ca^{+2}

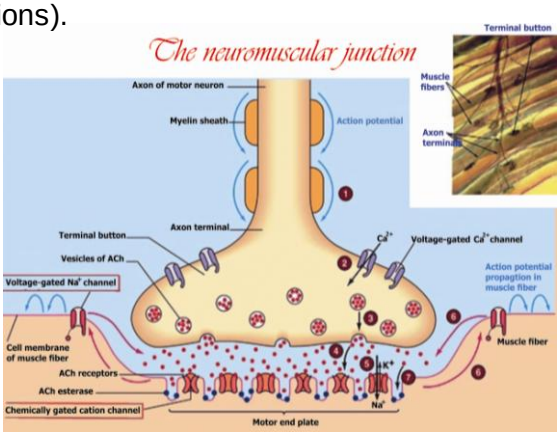
2- ***Ca^{+2} enter*** the nerve endings ⇨ rupture of vesicles ⇨ ***exocytosis A.Ch***.

3- A.Ch ***diffuses to the muscle*** ⇨ ***binds*** to its receptors in M.E.P. ⇨ ***activation of ligand-gated channels*** (Na^+ entry > K^+ exit) ⇨ ***depolarization*** at motor end plate (***end plate potential "EPP"***)
EPP is graded, non-propagated response

4- ***EPP depolarizes*** the adjacent muscle membrane ***to its firing level*** ⇨***action potentials*** are ***generated*** on either side of M.E.P & ***conducted*** in both directions ⇨ initiate muscle contraction

5- ***A.Ch*** (dissociated from receptors) is ***hydrolyzed*** rapidly by ***choline esterase*** enzyme (to prevent it from causing multiple muscles contractions).

Miniature EPP: at rest, few vesicles containing A.Ch rupture spontaneously & release A.Ch ⇨ minute depolarization at MEP
The number of ruptured vesicles α Ca^{+2} conc. & 1/α Mg^{+2} conc. at MEP



Properties of N.M transmission

(1) It is ***unidirectional*****:** (in one direction only from the nerve to the muscle).

(2) There is a **delay** about 0.5 mSec: (represents the time for events of N.M. transmission)

(3) **Easily fatigued**: due to repeated stimulation & exhaustion of A.Ch vesicles.

(4) **Effect of ions:** Excess Ca^{+2} ⇨ ↑↑ release of A.Ch ⇨ ↑↑ transmission.
Excess Mg^{+2} ⇨ ↓↓ release of A.Ch ⇨ ↓↓ transmission.

(5) **Effect of drugs:**

(a) Drugs stimulate N.M transmission	(b) Drugs block N.M transmission
1- Drugs have A.Ch-like action (Methacholine, carbachol & nicotine small dose) They are not destroyed by choline esterase **2- Anticholine esterase:** (neostigmine, physostigmine & DFP). They inactivate cholinesterase ⇨ ↑↑ A.Ch	**(Curariform drugs)** ⇨ Prevent passage of impulses at MEP. ***Curare:*** competes with A.Ch for the receptor sites on the membrane.

Myasthenia Gravis: Muscle weakness & easy fatigability:
- It is a serious & sometimes fatal disease (in case of respiratory muscles paralysis).
- It is an autoimmune disease (autoantibodies against patient's A.ch receptors)
- Treatment: anticholine esterase (e.g. neostigmine) ⇨ ↑↑ A.Ch to affect normal muscles activity

Changes following skeletal muscle stimulation

❶ Electrical changes ❷ Excitability changes ❸ Mechanical changes ❹ Metabolic changes

(1) Electrical changes following skeletal muscles stimulation *similar to those in nerve but:*

1- Resting membrane potential **(– 90 mV.)**
2- Action potential precedes contraction by **(2 mSec)**
3- Action potential lasts **(2 – 4 mSec)**.
4- Conduction velocity **(5 m/sec)**.

(2) Excitability changes following skeletal muscles stimulation *similar to nerve*

- **ARP:** coincides with the ascending limb & part of the descending limb of the spike potential
- **ARP:** coincides with the latent period of the mechanical response.
- As the muscle begins to contract, it regains its excitability.

(3) Mechanical changes following skeletal muscles stimulation:

Molecular mechanism of muscle contraction (the contractile response)
(Excitation - Contraction (EC) coupling): 4 steps

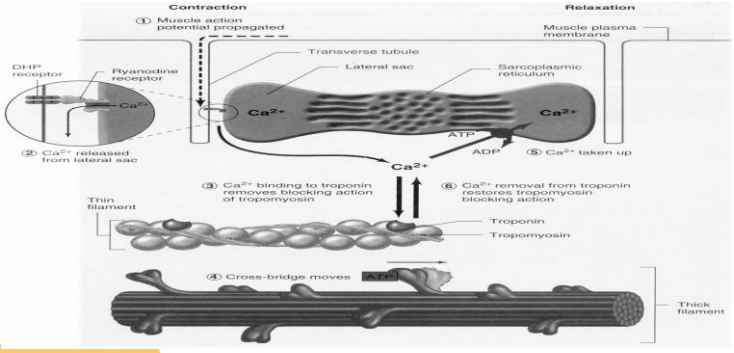
(1) Release of Ca^{+2}: propagation of A.P. into the T tubules ⇨ opening of the Ca^{+2} channels on terminal cisternae(TC) ⇨ Ca^{+2} flow out of the SR into the cytoplasm.

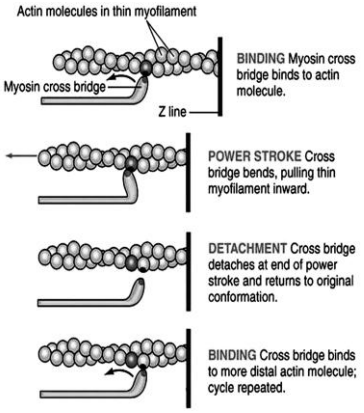
(2) Activation of muscle proteins: Ca^{+2} binds to troponin C (undergoes conformational changes)
⇨ Tropomyosin is moved away ⇨ uncovering the binding site on actin.
⇨ Cross bridges from myosin combines with the binding site on actin & contraction begins

(3) Generation of tension: by cycling of the cross bridges: 4 steps:

1st step	*2nd step*	*3rd step*	*4th step*
Binding of actin & myosin	***Bending*** of cross bridges ⇨ sliding of actin over myosin • The ***energy needed*** for bending is obtained from hydrolysis of ATP	***Release*** (detachment) of the cross bridges from actin • ***ATP is needed*** to ↓↓ affinity of cross bridges for active sites • If ATP is not available, the thick & thin filaments cannot be separated (muscle contracture)	***Return*** of the cross bridges to their original site to act in another cycle • cycling continues as long as Ca^{+2} is attached to troponin & energy is available.

(4) Relaxation: Ca^{+2} is removed by ***Ca^{+2} pump*** on the SR membrane ⇨ ↓↓ intracellular Ca^{+2} conc.
⇨ troponin returns to its original conformational state.
Tropomyosin covers the binding site of actin & cycling stops.





All or none law

A single skeletal ms. fiber obeys all or none law

- ***The skeletal ms. fiber contracts maximally or does not contract at all.***
- A threshold stimulus produces maximal contraction provided that other conditions remain constant

The muscle twitch: a brief contraction followed by relaxation caused by a single action potential

Types of contraction of skeletal muscles

	(1) Isotonic contraction	(2) Isometric contraction
1- Ms. Length	Shortens	***Constant***
2- Ms. Tension	***Constant***	Highly increased
3- Time	More	Less
4- Energy	More	Less
5- Work	Done (load is moved)	Not done (load is not moved)
6- Mechanical efficiency	% of energy input converted into work 20 — 25 %	0 %
7- Force of contraction is measured by	Velocity & degree of muscle shortening	Degree of developed muscle tension
8- Function	Movement of part of the body or the body as a whole	Tenses a part of the body & maintains the body against gravity
Example	Contraction of biceps to lift an object	Contraction of quadriceps to stiff the knee joint

Muscles can contract both isometrically & isotonically (mixture of the 2 types)

Factors affecting skeletal muscle contraction

1. Type of muscle
2. Stimulus factor
3. Length – tension relationship
4. Load – velocity relationship
5. Muscle fatigue

(1) Type of muscle fibers (2 types)

1- Slow (red) fibers (type I)	2- Fast (pale) fibers (type IIb)
• ***Small*** muscle fibers. • Innervated by ***small slowly conducting*** motor neurons. • ***Contain:*** large numbers of oxidative enzymes ***More*** mitochondria ***(aerobic metabolism)*** ***More*** myoglobin (store O_2 for need). ***More*** blood supply (supply more O_2) • ***Have:*** low ATPase activity	• ***Large*** muscle fibers. • Innervated by ***large rapidly conducting*** motor neurons • ***Contain:*** large amount of glycolytic enzymes for glycolytic process ***(anaerobic metabolism)*** ***Less*** myoglobin. ***Less*** blood supply. ***Less*** mitochondria. • ***Have:*** high ATPase activity – extensive SR
Slow contractile mechanism ***High*** resistance to fatigue e.g. back muscles & soleus muscle	***Rapid*** contractile mechanism ***Less*** resistance to fatigue e.g. muscles of the hand & extraocular muscles

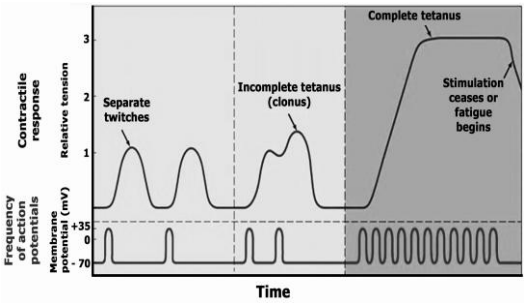
(2) Stimulus factors

a- Strength of stimulus: ↑↑ strength of stimulus ⇨ ↑↑ no. of activated ms. fibers ⇨ ↑↑ ms. contraction

b- Frequency of stimulation: ↑↑ frequency of muscle stimulation ⇨ ↑↑ force of contraction
(because ↑↑ Ca^{+2} release from the SR each time the muscle is stimulated)

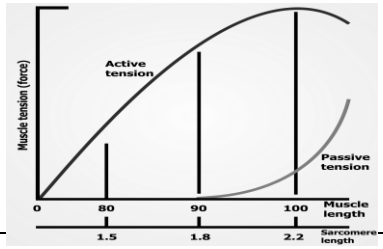
According to frequency of stimuli, there are:

- ***Complete tetanus:*** (with ***high frequency***) fusion of contractions with no relaxation
- ***Incomplete tetanus:*** (with ***moderate frequency***). contractions with incomplete relaxation
- ***Separate twitches:*** progressive ↑↑ in force of contraction during each successive twitch until a plateau value (uniform tension)



Treppe "Stair case phenomenon"
cause: ↑↑ levels of intracellular Ca^{+2}

(3) Length – Tension relationship

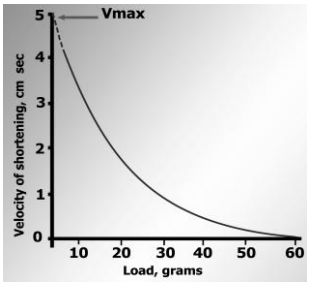


Starling's law:

The greater the initial ms. fiber length (preload), ***the more*** will be the active tension developed during its isometric contraction ***within limits***

Sarcomere length		
(a) Maximal force occurs at 2.2μ	**(b) More than 2.2 μ**	**(c) Less than 2.2 μ**
At this length, there is a maximal number of cross bridges. This is the resting length of the muscles inside the body	Some cross bridges do not have actin filaments to combine with ⇨ ↓↓ force of contraction.	Ends of the 2 actin filaments overlap ⇨ ↓↓ number of cross bridges ⇨↓↓ force of contraction

(4) Load-Velocity relationship



- ↑↑ after load ⇨ ↓↓ velocity & degree of muscle shortening.
- Maximal velocity of shortening (Vmax) occurs when there is no external load (zero load)
- Vmax is theoretical, because load can not be zero

(5) Muscle fatigue

- Prolonged & strong contraction of muscle ⇨ ***muscle fatigue*** (↓↓ strength of contraction, ↑↑ its duration & relaxation becomes incomplete).
- ***Causes:*** (a) ↑↑ metabolites (as lactic acid) ⇨ ↑↑ intracellular acidity.
  (b) ↓↓ muscle ATP, glycogen & creatine phosphate.
  (c) ↓↓ blood flow ⇨ loss of nutrients & O_2 supply.
  (d) ↓↓ transmission at N.M. junction.

(4) Metabolic changes following skeletal muscles stimulation

(Energy sources & muscle metabolism)

I- During rest **II- During contraction** **III- During recovery**

I- During rest

skeletal muscles consumes ***energy for:***

a- maintenance of RMP b- synthesis of chemical substances c- production of muscle tone

II- During contraction

Energy consumption is markedly ↑↑

- **ATP** is the only immediate energy source for contraction.
- **ATP** is hydrolyzed anaerobically into ADP. Myosin acts as the enzyme ATPase.
- **ATP** inside muscles is enough for maximal contraction for only (5 – 6 seconds).
- **ATP** is continuously reformed **by 3 metabolic mechanisms:**

(1) Phosphocreatine	(2) Glycogen lactic acid system	(3) Aerobic system
ADP + Creatine Phosphate → ATP + Creatine • Energy transfers from phosphocreatine to ATP within a small fraction of sec • Phosphagen energy system (phosphocreatine + ATP) can provide maximal muscle power for (10 – 15 sec.) enough for 100m. running • Creatine phosphate is later restored by the reverse reaction during muscle relaxation.	***Glucose + 2 ATP (or glycogen + 1 ATP) —anaerobic glycolysis (in cytoplasm)→ 2 lactic acid + 4 ATP*** • Provides (30 – 40 sec.) excess muscle activity + (10 – 15 sec.) provided by the phosphagen system. • Enough for 200-800 meters running. • Lactic acid ⇨ severe muscle fatigue • Removal of lactic acid by: a- Some of lactic acid ⟶ pyruvic acid b- Much of lactic acid ⇨ glucose (by the liver) ⇨ glycogen stores in muscles c- It is used as a fuel in the heart.	***Glucose + 2ATP (or glycogen + 1 ATP) O_2 ⟶ $6CO_2 + 6H_2O + 40ATP$*** • Oxidation of food stuffs in the mitochondria to provide energy (glucose, fatty acids & amino acids). • Provides unlimited time for ms activity as long as nutrients & O_2 are available.

III. During recovery (Oxygen Debt) *Extra post-exercise O_2 consumption:*

Definition: Oxygen consumption during recovery (after exercise) in excess of the resting basal oxygen consumption.

This extra O_2 consumption is used for: (1) **Re**moval of excess lactate.
(2) **Re**formation of ATP & creatine phosphate.
(3) **Re**filling of myoglobin with oxygen.

Motor unit: the motor neuron & the muscle fibers supplied by it

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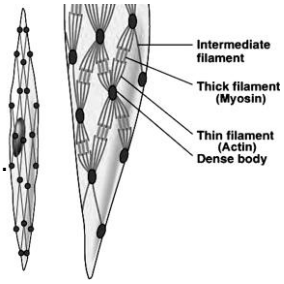
Smooth muscles

Types (2)

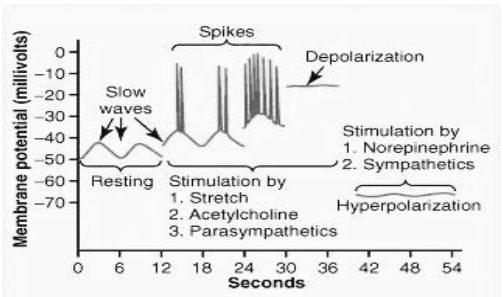
Visceral (single unit) smooth muscles	Multiunit smooth muscles
Site: in the walls of hollow viscera.	**Site:** e.g. ciliary muscle & iris of the eye.
Fibers are ***aggregated*** & have ***"gap junctions"***	The fibers are ***separated***
Action potential ***can spread*** from 1 cell to another	Action potential ***cannot spread***
The whole muscle ***acts as one unit***.	Each fiber contracts **independently** of others
The muscle is spontaneously active & ***affected by*** hormones, chemical & neuro-transmitters	The muscle is ***densely innervated*** & contraction is under ***neural control***

Structure



(1) Thin, fusiform (**spindle-shaped**) cells (5 – 10 µ wide & 10 – 500 µ long).
(2) **No** sarcomeres, **no** interdigitating thick & thin filaments ⇨ **no** striations,
(3) **No** troponin-tropomyosin complex. **No** T tubules & SR is poorly developed.
(4) The thin filaments are attached to ***dense bodies***.
(5) Cross-bridges cycle similar to that of striated ms.

Electrical activity of smooth muscles

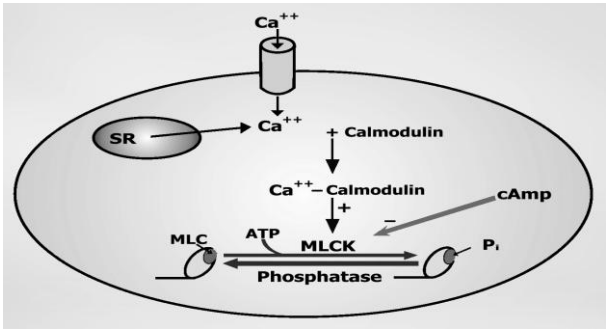


- RMP is **unstable** (average **– 50 to – 60 mV.**)
- Waves are **superimposed** on the RMP (e.g. slow sine waves of the gut).
- These waves **cannot cause** muscle contraction.
- When **wave potential** reaches **–35mV,** action potential occurs.
- The action potentials of smooth muscle **has (2 forms):**

1- Spike potentials	2- Action potential with plateau
• Duration of the spike (50 mSec). • Similar as in skeletal ms. or on top of slow waves or rhythmically (pace maker potential)	• Like that of cardiac ms. • Plateau ⇨ delayed repolarization ⇨ prolonged contraction

Contraction process of smooth muscles

Excitation – contraction (E –C) coupling:



(1) Binding of cytoplasmic Ca^{+2} to calmodulin.
(2) The ***calcium – calmodulin complex***
⇨ activates myosin light chain kinase (***MLCK***)
⇨ ***phosphorylates*** the regulatory light chain on the head of myosin molecule
⇨ ATP hydrolysis & ***cross bridge cycling***.
(3) The phosphorylated cross bridges continue to cycle until they are ***dephosphorylated*** by ***myosin light chain phosphatase*** (***MLCP***) during relaxation.
(4) ***Relaxation*** occurs when the intracellular Ca^{+2} conc. fall & the MLCK becomes inactive

Mechanical properties of smooth muscles differ from those of striated muscles

(1) Smooth muscles contracts slower than skeletal muscles
(dependent on the phosphorylation of the myosin light chain)

(2) The dephosphorylated cross - bridges remain attached to actin
latch-bridges: (smooth ms has the ability to maintain tone with little energy consumption)

(3) Ca^{+2} enter the cells in a variety of ways:
a- During depolarization of the cell membrane ⇨ open ***voltage gated Ca^{+2} channels***.
b- When smooth ms is stimulated by a neurotransmitter ⇨ open ***receptor activated Ca^{+2} channels*** or release Ca^{+2} from sarcoplasmic reticulum through inositol triphosphate ***(IP_3) gated Ca^{+2} channels***

(4) The level of cytoplasmic Ca^{+2} in smooth muscles is determined by:
a- The rate of ***Ca^{+2} entry*** by Ca^{+2} influx & Ca^{+2} release from sarcoplasmic reticulum
b- The rate of ***Ca^{+2} removal*** from cytoplasm of smooth muscle actively into SR or out of the cell

Characteristics of contraction of smooth muscles

(1) Spontaneous contractions (even, if there is no nerve supply)
⇨ rhythmic contractions or tetanic from (muscle tone).

(2) Role of nerve supply: do not initiate activity, but ***regulate*** the activity of smooth muscles

(3) Contractions are controlled by:

a- Motor neurons

b- Stimulatory factors:
(1) Stretch: allows a hollow organ to contract & evacuate when it is distended.
(2) Cold: ↑↑ contraction of plain muscles.
(3) Local factors: Acid, ↑↑ CO_2 & ↓↓ O_2 cause relaxation.
Alkali & ↑↑ K^+ cause contraction.
(4) Humoral factors

(4) Relation of length to tension (plasticity)
The smooth muscle is plastic i.e. if it is stretched ⇨ 1st the tension is increased.
⇨Then the tension is gradually decreased to normal.
Value: it allows hollow viscus to be filled without much increase in pressure.
Urine can accumulate in the urinary bladder without much increase in pressure.
Cause: readjustment of the position of the myosin cross-bridges on the thin filaments.

(5) Smooth ms contraction uses less ATP than skeletal ms. ⇨ it is ***fatigue resistant***