

Smooth Muscle

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Learning objectives

- **Plasticity of smooth muscle**
- **Electrical activity of smooth muscle**
- **Mechanism of contraction**
- **Excitation contraction coupling**
- **Latch phenomenon**

Plasticity of smooth Muscle

- **Smooth muscle behaves → Viscous mass**
- **Than → Rigid structure tissue**
- **This property referred as →**
- **Plasticity of smooth muscle**

Example of Plasticity of Smooth Muscle

- **Tension exerted by smooth muscle walls of Urinary bladder....**
- **Measured as → Different degree of distention**
- **As fluid infused in to bladder via catheter**

Example of Plasticity of Smooth Muscle

- **Initially** → **Tension** → **Increases**
- **Relatively little**
- **As** → **Volume** → **Increased**
- **Because of** → **Plasticity of the bladder wall**

Example of Plasticity of Smooth Muscle

- **A point will be reached**
- **At which →**
- **Bladder contracts forcefully.....**

Electrical activity in Smooth Muscle

- **Membrane potential** → **No true “Resting value”**
- **Relatively Low** → **When the tissue is Active**
- **Higher** → **When tissue is Inhibited**

Periods of relative Quiescence

- **Values of resting potential (RMP)**
- **Ranges from**
- **- 20 to -65 mV (Ref. → Ganong chapter 5 Page:114)**

Membrane Potentials in Smooth Muscle

- **Normal resting state**
- **The intracellular potential**
- **- 50 mV to -60mV (*Ref. Gyuton*)**
- ***30 mV less negative* than in skeletal muscle**

Membrane Potentials in Smooth Muscle

- **Quantitative level (RMP)**
- **Depends on**
- **Momentary condition of the muscle**

2 Types of Smooth Muscle

1. **Multi-unit smooth Muscle**
2. **Unitary or Single unit (Visceral) smooth Muscle**

Unitary Smooth Muscle

- **Unitary does not mean → single muscle fiber**
- **Unitary means**
- **Whole mass of**
- **Hundred to thousands of smooth muscle fibers**
- **Contract together as a single unit**

Example of Unitary smooth muscle →

- *“Visceral / Syncitial smooth muscle” because*
 1. Walls of most of hollow Viscera of body
 2. GUT (Genitourinary tract)
 3. Bile ducts
 4. Ureters
 5. Uterus and many blood vessels

Action Potentials in Unitary Smooth Muscle

- *Divergent electrical activity*

Action Potentials in Unitary Smooth Muscle

- **Action potential in *Unitary smooth Muscle***
- **Or *Visceral smooth muscle***
- **Occurs in same way as in the skeletal muscle**

Action potentials of Visceral Smooth Muscles

- **Two (2) forms:**

1. **Spike potentials**

2. **Action potentials with Plateaus**

Spike Potentials

- **Typical *spike* potential** → As of *skeletal muscle*
- **In most types of Unitary smooth muscle**
- ***Duration: 10 to 50 milliseconds***

Spike Potentials

- *Slow sine wave-like fluctuations*
- Shoot → The zero potential line
- Sometimes → Do not shoot zero line

Spike Potentials → Elicited by

- **Electrical stimulation by...**
 1. **Actions of the hormones on smooth muscles**
 2. **Actions of transmitters substances from nerve fibers**
 3. **By stretch**
 4. **Spontaneous generation in muscle fiber itself**

Action potentials with Plateau

- Onset of action potential →
- Similar to → Typical Spike Potential

Action potentials with Plateau

- **Instead of**
- *Rapid repolarization*
- **Of muscle fiber membrane**
- *As in Spike Potential*

Action potentials with Plateau

- *Repolarization is → Delayed*
- **For several 100**
- **To as much as 1000 milliseconds (1 second)**

Importance of the Plateau

- Plateau Account for *Prolonged contraction*
- Occurs in some types of smooth muscles
- *Ureters and Uterus*
- *Some types of vascular smooth muscles*

Ca²⁺ Generating **the Smooth Muscle Action potential**

- **Smooth muscle have**
- **More → → → *Voltage-Gated Ca²⁺ Channels***
- **Than does skeletal muscle**
- ***Few → Voltage-gated Na⁺ Channels***

Na⁺ Participate little role → Smooth Muscle AP

- **Na⁺ participate little in genesis of the AP**
- **In most smooth muscle**

Ca²⁺ Generating the Smooth Muscle Action potential

- **Ca²⁺ ions flow**
- **In to the interior of the fiber**
- **Mainly responsible for the Action potential**

Ca²⁺ Generating the Smooth Muscle Action potential

- **Role of Ca²⁺ ions is in**
- **Same**
- **Self regenerative way as**
- **In nerve fiber & skeletal muscle fiber**

Prolonged Action potentials of smooth muscle

- **Ca²⁺ channels → Open**
- **Many times *more slowly* and for *Longer period***
- **Than → Na⁺ Channels**

Ca²⁺ Performs → 2 Tasks

- **Same Ca²⁺ acts**
- **Directly on the smooth muscle contractile mechanism**
- **To cause contraction + Generating AP**

Self excitatory smooth muscles

- **Some smooth muscles e.g.**
- **Visceral smooth muscles of GUT**
- **Self-excitatory**
- **Action potentials arise within smooth muscle cells**
- ***“Without an extrinsic stimulus”***

Self excitatory smooth muscles

- **Often associated with**
- *Basic slow wave rhythm of membrane potential*

Slow wave of Visceral smooth muscle

- **NOT → Action potential**
- **NOT → Self-regenerative process**
- **But → Self excitatory**
- **NOT → Spreads progressively on muscle fibers**

Slow wave of Visceral smooth muscle

- **Local property of smooth muscle fibers**
- **Make → The muscle mass**

Cause of Slow Wave Rhythm

- **Unknown**

Slow Wave Rhythm may be →

- **Waxing (Increase) & Waning (Decrease)**
- **of Pumping of Sodium (Na^+) ions**
- **Outward through the**
- **Muscle fiber membrane**

Slow Wave Rhythm → Membrane → More Negative

- Membrane become → *More negative*
- When sodium (Na^+) is pumped rapidly
- Outward

Slow Wave Rhythm → Membrane → More Negative

- Membrane become
- *Less negative*
- Sodium (Na^+) pump becomes *less* → Active

Slow Wave Rhythm may be →

- **Increased**
- **Decreased**
- **Conductance of the Ion channels rhythmically**

Importance of Slow Wave Rhythm

- **When**
- **Strong enough → Initiate action potentials**

Importance of Slow Wave Rhythm

- **Slow waves themselves**
- **Can not cause → Muscle contraction**

Peak of Negative Slow wave →

- Rises in → the Positive direction
- About → - 35 mV

Importance of Slow Wave Rhythm

- **-35 mV → Approximate threshold**
- **For eliciting action potentials (AP)**
- *In most visceral smooth Muscle*

Action potential develops

- **Spreads → Over the muscle mass**
- **Then → Contraction occurs**

Explain why...???

- **Slow wave are called → Pacemaker Wave**

Repetitive Spike potentials (mV)

- **At each peak of the slow wave**
- **One or more action potential occurs**
- **Elicits →**
- **A series of rhythmic contractions of smooth muscle**

Slow wave rhythm → Pacemaker Wave

- **Elicits →**
- **A series of**
- **Rhythmic contractions of smooth muscle mass**

Slow wave rhythm → Pacemaker Wave

- **Control**
- **The rhythmical contractions of the GUT**

Explain what will happen & Why...?

- **When gut overfilled by intestinal contents...?**

Excitation of visceral smooth muscle By Muscle Stretch

- **Visceral (Unitary) smooth muscle**
- **Stretched sufficiently →**
- **Spontaneous action potentials**
- **Usually generated**

Excitation of visceral smooth muscle By Muscle Stretch

- **Spontaneous action potential generated....**
 - 1. The normal slow wave potentials**
 - 2. Decrease in the overall negativity of membrane potential → By the stretch itself**

Excitation of visceral smooth muscle By Muscle Stretch

- **Allows gut wall → Extensively stretched**
- **To contract**
- **Automatically & Rhythmically**

Excitation of visceral smooth muscle By Muscle Stretch...

- **When gut overfilled by intestinal contents**
- *Local automatic contractions*
- **Often set up *peristaltic waves* →**

Excitation of visceral smooth muscle By Muscle Stretch...

- **Peristaltic waves → Move the contents**
- **Away from → *The overfilled intestine***
- **Usually *in the direction of the Anus***

Multiunit Smooth Muscle

- Composed of *Discret smooth muscle fibers*
- *Each fiber contracts independently of others*
- Innervated by → Single nerve ending
- As in skeletal muscle fiber

Example of Multiunit smooth muscle →

- 1. Ciliary muscles of the Eye**
- 2. Iris of the eye**
- 3. Nictitating membrane that covers the eyes in some lower animals**
- 4. Piloerector muscle**

Depolarization of Multiunit Smooth Muscle

- **Muscle of the iris of the eye**
- **The piloerector muscle of each hair**
- **Contract → In response to Nerve stimuli**

Depolarization of Multiunit Smooth Muscle

- **The nerve endings secret**
- **Acetylcholine in c/o → Multi-unit smooth muscle**
- **Norepinephrine in c/o →**
- **Others Multiunit muscles**

Depolarization of Multiunit Smooth Muscle

- **In both cases...**
- **Ach & NE cause**
- **Depolarization of the smooth muscle membrane**
- **In turn elicit contraction**

Depolarization of Multiunit Smooth Muscle

- **Action potentials**
- **Do NOT develops**

No Action potential → Multiunit Smooth Muscle

- **The fibers are too small**
- **To generate an Action Potential**

Junction Potential → Multiunit

- **Small smooth muscle cells**
- **Even without action potential**
- **Local depolarization → Junctional Potential**
- **Caused by Nerve transmitter**

Junction Potential → Multiunit

- **Junctional potential**
- **Spreads → “Electronically”**
- **Over the entire fiber → Muscle contraction**

Action Potential Elicited in Visceral Smooth Muscle

- **In Visceral smooth muscle**
- **When action potentials are elicited**
- **30 to 40 smooth muscle fibers**
- **Must depolarize simultaneously**
- **Before self propagating Action potential**

Contraction Without Action Potential

- **Half of all smooth muscle contraction**
- **Initiated by stimulatory factors**
- **Directly act on the smooth muscle contractile machinery**

Contraction Without Action Potential

- **Non-Nervous**
- **Non-Action potential Stimulating factors :**
 1. **Local chemical factors**
 2. **Various Hormones**

Smooth Muscle Excitation

- 1. Hormones**
- 2. Local Tissue factors**

Local Tissue Chemical Factors

- **Contraction of**
 - 1. Arterioles**
 - 2. Meta-arterioles**
 - 3. Precapillary sphincters**

Smooth muscle →

- **Highly contractile**
- **Respond to changes in local chemical conditions**
- **Surrounding interstitial fluid**

Local Tissue Chemical Factors

- **Lack of oxygen (Hypoxia / Anoxia) →**
- **In local tissues**
- **Smooth muscle → Relaxation → Vasodilation**

Local Tissue Chemical Factors

- **Excess of Carbon dioxide (CO_2) \rightarrow Hypercapnia**
- **In local tissues**
- **Vasodilation**

Local Tissue Chemical Factors

- **Increased $[H^+]$ (Fall pH) →**
- **Increased Vasodilation**

Other Factors → Local Vasodilation

1. Adenosine
2. Lactic acid
3. Increased K^+ ions (**Hyperkalemia**)
4. Decreased Ca^{2+} ion (**Hypocalcaemia**)
5. Increased body temperature

Effects of Hormones on Smooth Muscle

- **Some have profound effects**
- **Some have little effects**

Effects of Hormones on Smooth Muscle

1. **Nor-epinephrine**
2. **Epinephrine**
3. **Acetylcholine**
4. **Angiotensin**
5. **Vasopressin (ADH)**
6. **Oxytocin**
7. **Serotonin**
8. **Histamine**

Effects of Hormones on Smooth Muscle

- **Hormone causing → Contraction of smooth muscle**
- **When muscle membrane contains**
- *Hormone-gated excitatory receptors*
- **For respective hormone**

Effects of Hormones on Smooth Muscle

- **Hormone causing → Inhibition of smooth muscle**
- **When muscle membrane contains**
- *Inhibitory receptors*
- **For respective hormone**

Mechanism of Smooth Muscle **Excitation**

- **Hormones receptors →**
- **In smooth muscle membrane**
- **Open the → Na⁺ & Ca²⁺ ion channels**
- **Depolarize the membrane as Nerve Stimulation**

Mechanism of Smooth Muscle **Excitation**

- **Action potential → Results**
- **Rhythmical action potentials →**
- **Already occurring**
- **May be enhanced**

Source of Calcium Ions → Contraction

- **Contractile process in smooth muscle**
- **Is activated by Ca^{2+}**
- **As in skeletal muscle**

Source of Calcium Ions → Contraction

- **Source of Calcium ions**
- **Differed from skeletal muscle**
- **In skeletal muscle all Ca^{2+} ions derived from**
- **“Sarcoplasmic reticulum” (Only source)**

Source of Calcium Ions → Contraction

- **“Sarcoplasmic reticulum” → In Skeletal muscle**
- **Is rudimentary**
- **In most smooth muscle**

Source of Calcium Ions → Contraction

- **Most type of smooth muscle**
- **Almost all Ca^{2+} → Cause contraction**
- **Enter smooth muscle cell from → The ECF**

Almost all the Ca^{2+} enter from \rightarrow ECF

- **Enter smooth muscle cell from \rightarrow the ECF**
- **At the time of Action potential**
- **Or**
- **Other stimulus (Hormone / Local tissue factors)**

Ca²⁺ ions Concentration → ECF

- **High in ECF → 10⁻³ molar**

Ca²⁺ ions Concentration → Smooth muscle

- **Low in smooth muscle cell sarcoplasm →**
- **10⁻⁷ molar**

Smooth muscle cell action potential

- **Is caused Mainly by →**
- **Influx of Ca^{2+} ions in to muscle cell**

Smooth muscle fibers →

- **Extremely small**
- **In contrast to Skeletal muscle**

Ca²⁺ ions Diffusion →

- **All parts of the smooth muscle**
- **Elicit contraction**

Time for Ca^{2+} ions Diffusion

- 200 – 300 milliseconds
- Called → *Latent period*
- Before contraction begin
- 50 times more than latent period of skeletal muscle

Ca²⁺ entry by Hormone-activated Ca²⁺ channels

- Opening of *Hormone activated Ca²⁺ channels*
- **DOES NOT** cause an **Action potential**
- **NOT** much changes in **RMP**
- **Because** enough **K⁺** ions move to the exterior at
the same time

Enough Ca^{2+} ions moves to the exterior

- **At the same time**
- **Maintain**
- **Normal membrane potential**

Ca²⁺ entry by Hormone-activated Ca²⁺ channels

- **DOES NOT** cause an **Action potential**
- **NOT** much changes in **RMP**
- **Even though contraction continues**
- **As long as Ca²⁺ channels → Open**

It is Ca^{2+} ions cause \rightarrow Contraction

- **Not change in membrane potential**

Role of the Sarcoplasmic reticulum

- **SR** → **“Rudimentary”** in most of smooth muscle
- **Some** smooth muscle cells contain
- **Moderately developed** →
- **Sarcoplasmic reticulum (SR)**

Sarcoplasmic tubule of smooth Muscle

- **Small invaginations of the cell membrane**
- *Caveoli*
- *Caveoli* → **Abut against the surface of**
- **Sarcoplasmic tubules**

Caveoli believed → Rudimentary analog

- **Of the Transverse tubules system of skeletal muscle**

When the Action Potential transmitted

- **In to *Caveoli* →**
- **Excite → Ca^{2+} ion release**
- **From the Abutting sarcoplasmic tubule**

Release of Ca^{2+} ions from Sarcoplasmic tubule

- **In same way**
- **Action potentials in skeletal muscle**
- **Transverse (T) tubules cause release of Ca^{2+}**
- **Longitudinal (L) sarcoplasmic tubules**

More extensive Sarcoplasmic reticulum

- **In smooth muscle fiber**
- **More rapid → Contraction → Less latent period**

Because

- **Ca²⁺ entry**
- **Through the cell membrane is much slower**
- **Than internal release of Ca²⁺**
- **From Sarcoplasmic Reticulum (SR)**

Explain what will happen why..?

- 1. To smooth muscle when Extracellular Ca^{2+} fall below low level...**
- 2. Force of contraction of smooth muscle dependent on ECF Ca^{2+} ion concentration**

Effect of ECF Ca^{2+} ion Concentration

- **Extracellular \rightarrow ECF $[\text{Ca}^{2+}]$**
- **No effect on the**
- **Force of contraction of skeletal muscle contraction**

ECF Ca^{2+} ion Concentration \rightarrow Falls

- **Low level \rightarrow**
- **Smooth muscle contraction \rightarrow Almost Ceases**

ECF Ca^{2+} ion Concentration \rightarrow Falls

- **Immersed smooth muscle \rightarrow Low Ca^{2+} medium**
- **Several minutes \rightarrow**
- **Sarcoplasmic reticulum (SR) loses \rightarrow Ca^{2+} supply**

ECF Ca^{2+} ion Concentration \rightarrow Falls

- **Force of contraction of smooth muscle**
- **Usually is**
- **Dependent on the Extracellular fluid (ECF)**
- **Ca^{2+} ion concentration**

Calcium Pump → Relaxation of Smooth Muscle

- **To cause relaxation of smooth muscle contraction**
- **Necessary to remove the Ca^{2+} ions from the Intracellular fluid (ICF)**
- **Around Actin & Myosin filaments**

Calcium Pump → For Relaxation

- **Ca²⁺ - ATPase active transport pumps**
- **Pumps Ca²⁺ ions out of the**
- **Smooth muscle fiber**
- **Back into → The sarcoplasmic reticulum (SR)**

Explain why...?

- **Duration of smooth muscle contraction is in seconds**
- **Rather than 100th to 10th of a second as occurs in skeletal muscle**

Calcium Pump → For Relaxation

- Calcium pump of smooth muscle → Slow acting
- Than
- Fast-acting sarcoplasmic reticulum pump in skeletal muscle

Regulation of Contraction by Ca^{2+}

- **Initialization of contraction** →
- *Increased* → **Intracellular Ca^{2+} ions**

Ca²⁺ Ion Concentration →

- **High In ECF → 10⁻³ molar**
- **Low In smooth muscle Cell sarcoplasm → 10⁻⁷**

molar

[Ca²⁺] Increased by →

- **Voltage-Ligand gated Plasma membrane channels**

Efflux from intracellular stores through

- **RyR (Rynodine Receptors)**
- **Inositol Triphosphate receptor (IP_3R)**

Increased Concentration of Ca^{2+}

- **Caused by:**
 - 1. Nerve stimulation of the smooth muscle fiber**
 - 2. Hormonal stimulation**
 - 3. Stretch of the fiber**
 - 4. Changes in the chemical environment of the fiber**

Initialization of smooth muscle contraction →

- *Increased*
- **Intracellular [Ca²⁺] ions**

Smooth Muscle / Skeletal Muscle

- **Smooth muscle → Do not have Troponin**
- **Skeletal muscle contraction**
- **Troponin: Regulatory Protein**
- **Activated by Ca^{2+} ions to cause**

Smooth Muscle → Calmodulin

- **In place of Troponin**
- **Large amount of regulatory protein**
- *Calmodulin*

Smooth Muscle → Calmodulin

- **Lack of Troponin in → Smooth muscle prevents**
- **Ca²⁺ Activation via**
- **Troponin binding**

Smooth Muscle → Calmodulin

- **Similar to Troponin → Reacts with Ca^{2+} ions**
- **Cause contraction in →**
- **Different manner**

Calmodulin → Similar to Troponin

- **Reacts with 4 Ca^{2+} ions**

Calmodulin different to Troponin

- **Manner in which**
- **It initiate contraction**

Calmodulin → Initiate contraction by

- **Activating myosin cross bridges**

Calmodulin- Ca^{2+} Joins with MLCK

- Ca^{2+} ions bind with → Calmodulin
- Calmodulin-Calcium combination
- Joins with → Myosin Kinase →
- Phosphorylating Enzyme

Myosin must be Phosphorylated →

- **Myosin in smooth muscle**
- **Must be → Phosphorylated**
- **For activation of → Myosin ATPase**

In skeletal muscle →

- **Phosphorylation of Myosin**
- **Dephosphorylation of Myosin**
- **Also occur in Skeletal muscle**
- **But Phosphorylation is**
- **NOT necessary for activation of ATPase**

Calmodulin – Calcium combination

- **Ca²⁺ ions bind with → Calmodulin**
- **Joins with and activates → Myosin kinase**

Calmodulin- Ca^{2+} Complex

- **Activates**
- **Calmodulin-dependent myosin light chain kinase**

(MLCK)

Ca²⁺-Calmodulin dependent myosin light kinase

- **One of the light chain of each myosin head**
- **Called the *Regulatory chain* → Phosphorylated**
- **Response to this myosin kinase (MLCK)**

Myosin light kinase (MLCK) →

- **Enzyme catalyzes**
- **Phosphorylation of Myosin light chain**
- **On Serine at Position 19**
- **Increasing its → ATPase activity**

Regulatory chain → NOT → Phosphorylated

- **The attachment-detachment**
- **Cycling of myosin head**
- **With Actin filament does not occur**

Regulatory chain → Phosphorylated

- **Head of Myosin filament → Capability**
- **Of binding with the Actin filament**
- **Proceeding entire cycle of contraction as skeletal muscle**

Relaxation of the smooth muscle

- Closing of the \rightarrow Ca^{2+} channels
- Lowering of the \rightarrow
- Cytoplasmic Ca^{2+} concentrations
- By the action of
- Ca^{2+} -ATPase active transport pumps

Relaxation of the smooth muscle

- Under these conditions...
- **Calmodulin** → **Dissociates from Myosin light-chain kinase (MLCK)**
- **Inactivating this enzyme**

Cessation of Smooth Muscle contraction

- **When Ca^{2+} ions concentration \rightarrow Falls**
- **Below \rightarrow critical level**
- **Processes automatically reversed**
- **Except \rightarrow Phosphorylation of Myosin head**

Myosin Light Chain Phosphatase

- **Located** → Fluids of Smooth muscle cell
- **Myosin** → Dephosphorylated
- **Splits** → Phosphate from Regulatory light chain
- **Cycling Stops** → Contraction ceases

Dephosphorylation → Inhibits

- **Inhibits → The cross bridge**
- **From binding to Actin and**
- **Producing another power stroke**

Amount of Myosin Light Chain Phosphatase

- **Time required for**
- **Relaxation of the smooth muscle contraction**
- **Determined →**
- **By the amount of active Myosin phosphate in the cell**

Binding of Acetylcholine to Muscarinic Receptors



Increased Influx of Ca^{2+} Into the Cell



Activation of Calmodulin-dependent Myosin light chain Kinase



Phosphorylation of Myosin



Increased Myosin ATPase Activity

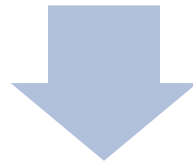


Binding of Myosin to Actin → Contraction

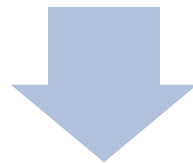
Dephosphorylation of Myosin



By Myosin Light Chain Phosphatase



Relaxation or Sustained Contraction



Due to Latch Bridge and Other Mechanisms

Latch Phenomenon

- **Successive recycling of the Myosin head**
- **During succeeding seconds , minutes**
- **Heads release and attach**
- **Further along the Actin filament**

Latch Phenomenon

- **Length of the Smooth muscle**
- **Eventually changes**
- **When Tension of the smooth muscle**
- **Returns nearly to its original value**

Latch Phenomenon

- **Myosin cross-bridges**
- **Cause contractile force**
- **Almost same as had been previously**