Smooth Muscles

Smooth muscles are present in every organ system

- Located in walls of almost every kind of blood vessel
- Located in airway passages (bronchioles)
- Located the walls of the organs of the digestive system
- Located in the passages of the urinary system
- Located in tracts of the reproductive system.

Most often, the smooth muscles are organized into two layers: inner circular and outer longitudinal.
Smooth Muscles

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- When the longitudinal layer contracts, the organ dilates and contracts
- When the circular layer contracts, the organ elongates

Smooth Muscles

- Smooth muscle lacks neuromuscular junctions
- Innervating nerves have bulbous swellings called varicosities
- Varicosities release neurotransmitters into wide synaptic clefts called diffuse junctions
Smooth Muscles

Smooth Muscle Characteristics

- Small and spindle shaped (3 to 6 µm in diameter, 100-500 µm long)
  - Skeletal muscles are 20 times wider, 100 times longer

- Neuromuscular junction receives input from the Autonomic Nervous System: thus involuntary!

- The S.R. is less developed and there are no T-tubules
  - Plasma membrane has many pouchlike infoldings that sequester calcium (= caveolae)
  - Most calcium influx into the cell comes from the extracellular medium

Smooth Muscles

- Smooth muscle contains thick and thin filaments but the organization is different
  - No striations (thus no sarcomeres; hence the term ‘smooth’)
  - No troponin but tropomyosin is present.

Remember that Calcium binds to troponin in skeletal muscle and initiates contraction. This thus indicates that calcium binding to the filaments is not an important step in contraction in smooth muscle!
Smooth Muscles

- Thin filaments are attached to dense bodies, distributed along intermediate desmin filaments.

- In general, actin to myosin ratio is greater than skeletal muscle.

- Thin/thick filaments are arranged diagonally; contraction causes the muscle to twist like a corkscrew.

Contraction in smooth muscles is different from Skeletal Muscle in many aspects.

Many smooth muscle cells have gap junctions; this allows the electrical impulse to flow from one cell to the next.

- Gap junction = electrical synapse
- Results in adjacent cells to exhibit synchronized contractions.
The following are aspects that are similar between skeletal and smooth muscle:

- Actin and myosin interact with each other to promote a sliding mechanism for contraction.
- The trigger for contraction is calcium influx into the cell.
- ATP is the immediate energy source for contractile function.

The following aspects differ; they relate to the detailed steps involved in the excitation contraction process:

1. Under the influence of a stimulus (hormonal or electrical), cytosolic calcium levels increase in the cell. The stimulation causes an influx of calcium, which comes from the extracellular medium, and in turn helps to release calcium from the SR.
2. The elevated Calcium in the cell interacts with a specific calcium binding protein molecule called **Calmodulin**.

The calcium - Calmodulin complex becomes active and can now in turn activate protein kinases

3. Calcium-activated Calmodulin activates a specific kinase called the **myosin light chain kinase** (MLCK).

4. Activated MLCK now transfers a phosphate from ATP to the myosin light chain of the myosin molecule (thus, the myosin light chain becomes phosphorylated)

Myosin light chain is a small protein bound to the myosin head near the neck, and prevents the cross-bridge from swiveling normally, thus hindering combination with the actin.
5. The phosphorylation activates the myosin head, allowing myosin to bind to actin and contraction follows. (a similar cross-bridge cycling as in skeletal muscle)

Smooth Muscles

6. Relaxation occurs when Calcium levels drop back to very low levels. This allows a Myosin Light Chain Phosphatase to dephosphorylate the light chain of myosin and this results in detachment of myosin from actin.
Thus, like skeletal muscle, Calcium is the important initiator of muscle contraction. Intracellular calcium concentrations, therefore, are very important in regulating smooth muscle contraction.

The concentration of intracellular calcium depends upon the balance between

- the calcium that enters the cells,
- the calcium that is released by intracellular storage sites (e.g., SR),
- and removal of calcium either back into storage sites or out of the cell.
There are several signal transduction mechanisms that modulate intracellular calcium concentration and therefore the state of smooth muscle contraction (muscle tone).

Three different mechanisms will be described here: we already discussed the first two when talking about the ANS.

1) Phospholipase C pathway (see in discussion of ANS)
2) Adenylate Cyclase coupled pathway (same)
3) Nitric oxide-cGMP pathway.
4) Stretching

Smooth Muscles

**Phospholipase C pathway**

This pathway depends on signals, such as hormones, that bind to external receptor and activate a G-protein system linked to Phospholipase C.

The result is production of DAG and IP3. IP3 diffuses to the SR and causes opening of Calcium channels.

The calcium sets in motion smooth muscle contraction via Calmodulin.
**Smooth Muscles**

### Phospholipase C pathway

Signal molecules that act via this pathway are for example:

- Norepinephrine (NE) acting via alpha1-adrenoceptors,
- Angiotensin II (AII) acting via AII receptors

These receptors are found in systemic blood vessels and thus result in vaso-constriction of the smooth muscle there (result in increased blood pressure)!

### Adenylate cyclase pathway

This pathway depends on signals, such as hormones, that bind to external receptor and activate a G-protein system linked to Adenylate Cyclase.

- The result is production of cAMP.
- cAMP now activates a different protein kinase that phosphorylates MLCK.
- Phosphorylated MLCK **can not** be activated by calcium-calmodulin complex, which in turn, **cannot** activate the Myosin Light Chain.
- This prevents smooth muscle contraction (which is similar thus to **an inhibition** of smooth muscle contraction).
- Example: epinephrine acting on beta 2 receptors in smooth muscles of bronchioles and coronary blood vessels.
Smooth Muscles

These two examples show the different effects similar signal molecules can have on different organs.

Epinephrine causes relaxation in bronchioles because those smooth muscles contain beta-2 receptors that are coupled to Adenylate Cyclase.

The alpha1 receptors are connected to PLP C and thus cause contraction of the smooth muscle, such as seen in iris dilation (contraction of radial muscles by means of sympathetic stimulation e.g. norepinephrine).

Smooth Muscles

Nitric Oxide pathway

Nitric oxide is a gas. It is highly reactive; that is, it participates in many chemical reactions such as for example car-exhaust and smog. But it turns out NO has many physiological functions as well.

- NO is synthesized within cells by an enzyme **NO synthase** (NOS).

- There are 3 types of genes encoding for a different kind of NOS. All types of NOS produce NO from arginine with the aid of molecular oxygen and NADPH.

\[
\text{Arginine} + 2 \text{ NADPH} + 2 \text{ O}_2 \rightarrow \text{Citrulline} + 2 \text{ NAD} + 2\text{H}_2\text{O} + \text{NO}
\]
Smooth Muscles

- NO diffuses freely across cell membranes. NO is inherently unstable. In addition, there are so many other molecules with which it can interact, that it is quickly consumed close to where it is synthesized. It thus has a very short live span.

- Thus NO acts in a paracrine or even autocrine fashion — affecting only cells near its point of synthesis or effecting the cell it was made by.

The mechanism of many of the actions of NO involves the formation of cGMP.

When NO is formed it readily diffuses out of the cell and into adjacent cells where it binds to soluble guanylyl cyclase.

This enzyme is similar to adenylate cyclase but not coupled to G-proteins. When activated by NO, it produces cGMP from GTP.

If the cells are smooth muscles, the increased cGMP activates a protein kinase that subsequently leads to the inhibition of calcium influx into the smooth muscle cell, and decreased calcium-calmodulin stimulation of myosin light chain kinase. It thus causes smooth muscle relaxation.
Smooth Muscles

The walls of blood vessels have three layers. An internal layer made from epithelial cells called endothelial cells. A middle layer of smooth muscle and an outer layer of connective tissue.

The endothelial layers have the NOS and the formed NO diffuses out into the adjacent smooth muscle cells where it binds to guanylyl cyclase and causes relaxation.

Damage to the lining (endothelial cells) can thus damage NO supply and prevent relaxation, resulting in vasoconstriction and hypertension.

Other effects of NO is that it prevents platelet aggregation.

Unwanted Platelet aggregation within blood vessels can result in plaque buildup, atherosclerosis and spontaneous blood clot formation.

Thus, lack of NO supply may result in atherosclerosis and thrombosis.
Smooth Muscles

Stretching

Some smooth muscles can be activated by stretch. There are two ways this stretch results in contraction; both pathways result in induced myosin light chain phosphorylation

• Stretch causes a depolarization of these smooth muscle cells, leading to generation of action potentials, opening of calcium channels with resulting contraction.

• Stretch works on mechano-sensitive receptors in smooth muscle that are interacting with Ca2+ release channels in sarcolemma and the SR.

Thus these smooth muscles actively resist stretch or distension (e.g., some blood vessels, gut wall muscles and bladder).

Smooth Muscles

Smooth muscle is organized in two categories according to their mode of excitation/stimulation.

Visceral or Single Unit Smooth muscle

These smooth muscles are arranged in sheets or layers and the cells are electrically connected via gap junctions.

Thus, when an action potential occurs anywhere in a cell, it is quickly passed on to the others as a wave and they all contract as a single unit.

As the name implies, they are mostly found in the walls of hollow organs or viscera and are mostly activated by hormones and chemicals.
Smooth Muscles

**Multi Unit Smooth muscle**

- These smooth muscles are different from Single Unit smooth muscles because they consist out of multiple discrete units of smooth muscles.
- These units function independently of each other and must be activated by nerves (similar to motor units in skeletal muscles)

These kind of smooth muscles are mostly found
- walls of larger blood vessels
- large airways to the lungs (bronchi)
- iris of the eye and ciliary body muscles
- base of hair follicles

**Inputs Influencing Smooth Muscle Contractile Activity**

1. Spontaneous electrical activity in the plasma membrane of the muscle fiber
2. Neurotransmitters released by autonomic neurons
3. Hormones
4. Locally induced changes in the chemical composition (paracrine agents, acidity, oxygen, osmolarity, and ion concentrations) of the extracellular fluid surrounding the fiber
5. Stretch