Mechanisms of smooth muscle contraction and relaxation and latch mechanism

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Smooth Muscle Contraction

- Thin filaments are attached to plasma membrane or dense bodies (analogous to Z line)

- Filaments are oriented diagonally to the long axis of the cell
  - During shortening plasma membrane regions between attachment points balloon out

Smooth Muscle Contraction

- Sliding-filament mechanism
  - Less myosin, more actin
  - No regular alignment
  - Maximal tension developed by smooth muscles is similar to that of skeletal muscle

- The isometric tension produced by smooth muscle fibers varies with fiber length
  - Tension development is highest at intermediate lengths and lower at shorter or longer lengths
  - Significant force is generated over a relatively broad range of muscle lengths compared to that of skeletal muscle

Excitation-Contraction Coupling in Smooth Muscles

- The contraction of smooth muscles is triggered by a sharp rise in the Ca^{2+} concentration within the cytoplasm
  - calcium-induced calcium release
    - Sustained smooth muscle contraction
  - inositol triphosphate (IP3) produced at the plasma membrane due to stimulation by a hormone

Smooth Muscle Contraction

- Changes in cytosolic Ca^{2+} concentration

- Cross-bridge cycling in smooth muscle is controlled by a Ca^{2+} -regulated enzyme that phosphorylates myosin
  - Ca^{2+} -calmodulin myosin light chain kinase

- Only the phosphorylated form of smooth muscle myosin can bind to actin and undergo cross-bridge cycling

Sliding Filaments Mechanism

1. Ca^{2+} binds to calmodulin

2. The Ca^{2+}–calmodulin complex binds to myosin light-chain kinase (MLCK), activates the enzyme

3. Active myosin light-chain kinase then uses ATP to phosphorylate myosin light chains in the globular head of myosin

4. Phosphorylation of myosin drives the cross-bridge away from the thick filament backbone, allowing it to bind to actin

5. Cross-bridges go through repeated cycles of force generation as long as myosin light chains are phosphorylated

Smooth Muscle Contraction

- *ATP hydrolysis determines the rate of cross-bridge cycling and shortening velocity*
- Smooth muscle myosin has very low rate of ATPase activity
  - 10-100 times less than skeletal muscle
  - Much slower muscle shortening
  - Because of slow rate of energy usage, smooth muscles does not undergo fatigue

Smooth Muscle Relaxation

- Myosin light-chain phosphatase (MLCP)
  - myosin dephosphorylation
  - continuously active
- Relaxation or contraction depends on the ratio between kinase and phosphotase
  - i.e. Cytosolic Ca^{2+}
- Latch state
  - when stimulation is persistent and the cytosolic Ca^{2+} concentration remains elevated, the rate of ATP hydrolysis by the cross-bridges declines even though isometric tension is maintained
    - sphincter muscles of the gastrointestinal tract (prolonged contraction)
  - tension can be maintained in an almost rigor-like state without movement
  - Much slow dissociation of cross-bridges from actin

Sources of Cytosolic Ca^{2+}

1. the sarcoplasmic reticulum
2. extracellular Ca^{2+} entering the cell through plasma membrane Ca^{2+} channels

Sarcoplasmic reticulum

- Smaller in smooth muscle
- No T-tubules
  - Small cell diameter and slow rate of contraction
- Attached membrane at some sites (action potentials are coupled to Ca^{2+} release)
- Second messanger related Ca^{2+} release in some types (coupled to extracellular signals)

Extracellular calcium

- Voltage-sensitive and ligand gated Ca^{2+} channels in the plasma membranes of smooth muscle cells
  - Increased flow into the cell

Ca^{2+} Removal

- Active transport of Ca^{2+} back into the sarcoplasmic reticulum and out of the cell (slower → longer contraction)

- Only a portion of the cross-bridges are activated in a smooth muscle fiber in response to most stimuli
  - *Graded* tension

- Smooth muscle tone
  - the cytosolic Ca^{2+} concentration is sufficient to maintain a low level of basal cross-bridge activity in the absence of external stimuli

Membrane Activation

- Receives multiple inputs, with the contractile state of the muscle dependent on the relative intensity of the various inhibitory and excitatory stimuli

- All changes Ca^{2+} concentration

- Ca^{2+} mediated action potentials

- Graded depolarizations (or hyperpolarizations) in membrane potential, depende on the number of open Ca^{2+} channels