

What does the following have in common?

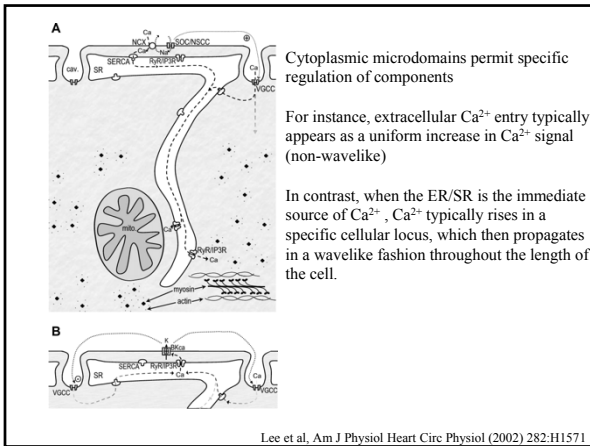
Expulsion of newborn from the uterus
Wheeze of asthma
Spasm of coronary arteries

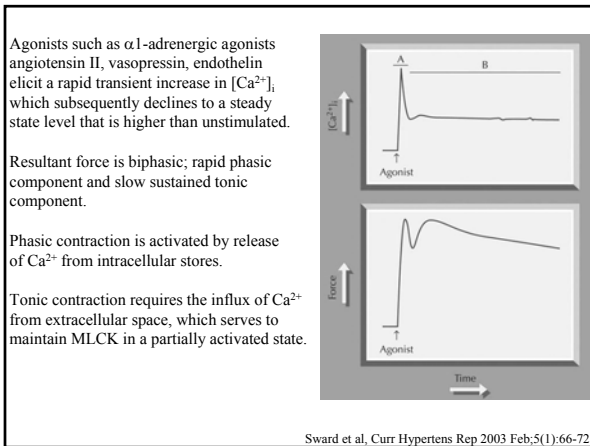
Basics of muscle contraction

- Control of intracellular Ca^{2+} - principal mechanism that initiates contraction and relaxation in smooth and striated muscle
- Regulatory pathways:
 - striated muscle- Ca^{2+} activates contraction by binding to thin filament associated protein, troponin
 - smooth muscle- Ca^{2+} binds to calmodulin, which then associates with the catalytic subunit of myosin light chain kinase- phosphorylates serine 19 on the regulatory light chain of myosin. Phosphorylation of Ser19 allows the myosin ATPase to be activated by actin and the muscle to contract.

Basics of muscle contraction

- Calcium regulation is vital
- In smooth muscle, the cytosolic free Ca^{2+} concentration is $\sim 0.1 \mu\text{M}$ in basal state; $\sim 10,000$ times lower than that present in the extracellular space (mM)
- Activation of cells induces an increase in cytosolic concentration up to $\sim 1-10 \mu\text{M}$.
- Ca^{2+} diffuses in cell much more slowly than predicted from its small volume; Ca^{2+} atom migrate $0.1-0.5 \mu\text{m}$, lasting only $\sim 50 \mu\text{s}$ before being bound.
- Ca^{2+} used by different vasoactive agents comes from extracellular and/or intracellular space.
- Intracellular Ca^{2+} is localized in the mitochondria and SR
- Location is most important

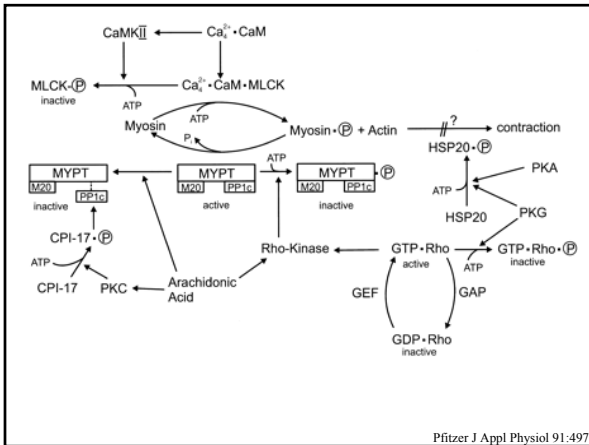




- The degree of interaction is determined by the net level of phosphorylation of the 20 kDa regulatory light chains of myosin II (rMLC).
- MLC is regulated by MLC kinase (MLCK) and MLC phosphatase (MLCP or PP1M).
- The extent of the rMLC phosphorylation and the amplitude of force production depends on the balance of the activities of MLCK and MLCP.
- Under certain conditions, force is also regulated independent of the changes in rMLC phosphorylation levels perhaps by thin filament associated proteins (caldesmon and calponin), which can be phosphorylated by MAP kinase and/or other kinases.
- Thin filament associated proteins might modulate the effect of rMLC phosphorylation, which is alone sufficient to initiate and maintain contraction.
- MLCP is a trimer comprising a 130 kD regulatory myosin binding subunit (MBS), a 37 kD catalytic subunit (PP1c), and a 20 kD protein of uncertain function (M20).

Signals that decrease Ca^{2+} sensitivity

- Well-established that cAMP and cGMP decreases Ca^{2+} sensitivity of contraction in both intact and permeabilized smooth muscle.
- In vitro, PKA phosphorylates MLCK at two sites; site A decreases affinity of MLCK for Ca^{2+} /calmodulin complex.
- However, agents that elevate PKA have negligible effects on phosphorylation of site A and Ca^{2+} activation of MLCK; suggests that cAMP/PKA desensitizes smooth muscle by an alternate mechanism.
- Phosphorylation of MLCK by PKG has no effect on activity.
- Endogenous nitric oxide and related nitrovasodilators regulate blood pressure by activation of soluble guanylate cyclase, elevation of cGMP, activation of cGMP dependent kinase (cGKI α or PKG). cGMP-mediated vascular smooth muscle cell relaxation is characterized by a reduction in intracellular calcium concentration and activation of PP1M, which reduces the sensitivity of the contractile apparatus to intracellular calcium.
- The mechanism by which cGMP increases PP1M activity and myosin light chain dephosphorylation was elucidated in a series of experiments published by Surks et al.



Ion channels in smooth muscle

