1. [20 points] From the statements below regarding smooth muscle choose the most correct statement AND briefly explain why each of the incorrect statements is incorrect.
   A. Phosphorylation of ATP bound to myosin light chains depends on the binding of $Ca^{2+}$ to calmodulin; this binding is potentiated by myosin light chain kinase.
   B. The formation of crossbridges that can continue to cycle requires that myosin phosphatase be activated by an elevated intracellular concentration of $Ca^{2+}$.
   C. The velocity of unloaded shortening ($V_0$) is proportional to the percentage of crossbridges with phosphorylated light chains.
   D. In response to a sustained (in time) stimulation most crossbridges become, and remain, phosphorylated.

A. Phosphorylation of ATP bound to myosin light chains depends on the binding of $Ca^{2+}$ to calmodulin; this binding is potentiated by myosin light chain kinase.

"Phosphorylation of ATP bound to myosin light chains depends on the binding of $Ca^{2+}$ to calmodulin" but the binding of $Ca^{2+}$ to calmodulin ***is not potentiated*** by MLCK: $Ca^{2+}$ binds to calmodulin, this binding ***activates*** the myosin light chain kinase (MLCK).

B. The formation of crossbridges that can continue to cycle requires that myosin phosphatase be activated by an elevated intracellular concentration of $Ca^{2+}$.

Phosphorylated cross-bridges, without the need of an increase of intracellular concentration of $Ca^{2+}$, continue to cycle as long as the cross-bridges remain phosphorylated. The cycle ends when myoplasmic $Ca^{2+}$ concentration falls.

C. The velocity of unloaded shortening ($V_0$) is proportional to the percentage of crossbridges with phosphorylated light chains.

D. In response to a sustained (in time) stimulation most crossbridges become, and remain, phosphorylated.

When a stimulation is prolonged (in time), the $Ca^{2+}$ and phosphorylation levels fall from an initial peak, to sub-maximal levels indicating that most cross-bridges do not become nor remain phosphorylated (video 3 - slide 4).

2. [20 points] From the statements below regarding $Ca^{2+}$ handling in smooth muscle choose the one that is most correct AND briefly explain why each of the incorrect statements are incorrect.
   A. $Ca^{2+}$ is released from the sarcoplasmic reticulum in response to an action potential coupled from the sarcolemma to the sarcoplasmic reticulum by the caveoli.
   B. In response to a ligand binding to a receptor on the sarcolemma an ATP - powered pump drives extracellular $Ca^{2+}$ across the sarcolemma and into the myofilament space.
   C. An increase in the concentration of intracellular $Ca^{2+}$ reduces the activity of myosin light chain kinase.
   D. To enable relaxation, $Ca^{2+}$ can be removed from the myofilament space by re-accumulation into the sarcoplasmic reticulum and by extrusion across the sarcolemma; both of these require energy.

A. $Ca^{2+}$ is released from the sarcoplasmic reticulum in response to an action potential coupled from the sarcolemma to the sarcoplasmic reticulum by the caveoli.

The release of $Ca^{2+}$ from the sarcoplasmic reticulum into the myoplasm is not the response to an action potential coupled from the sarcolemma to the SR by the calveoli.

(The trigger for the release of $Ca^{2+}$ from the SR is the binding of a ligand to a sarcolemma receptor (G-protein) which allows the conversion of PIP2 into the second messenger InsP3 which opens InsP3-gated $Ca^{2+}$ channels in the SR, releasing $Ca^{2+}$ from the SR (Video 3, slide 6)).

B. In response to a ligand binding to a receptor on the sarcolemma an ATP - powered pump drives extracellular $Ca^{2+}$ across the sarcolemma and into the myofilament space.

When a ligand binds to a receptor, on the sarcolemma, receptor activated channels, and not powered pumps, allow entry of extracellular $Ca^{2+}$ across the sarcolemma into the myofilament space.

C. An increase in the concentration of intracellular $Ca^{2+}$ reduces the activity of myosin light chain kinase.

An increase of the concentration of intracellular $Ca^{2+}$ increases not decreases the activity of MLCK by the binding of *more* $Ca^{2+}$ to calmodulin, thus *more* $Ca^{2+}$-calmodulin complexes *activate* MLCK increasing its activity.

D. To enable relaxation, $Ca^{2+}$ can be removed from the myofilament space by re-accumulation into the sarcoplasmic reticulum and by extrusion across the sarcolemma; both of these require energy.

3. [20 points] Indicate which of the following statements regarding smooth muscle is ***not*** correct AND briefly explain why it is incorrect.
   A. Activator $Ca^{2+}$ (for contraction) can enter the myofilament space across the sarcolemma in response to a stimulus that does not alter the sarcolemma's membrane potential.
   B. Crossbridges in the "latch" state go through (finish, if they are attached) their cycle more slowly than crossbridges that are phosphorylated.
   C. Single-unit smooth muscle is more densely innervated than is multi-unit smooth muscle.
   D. $Ca^{2+}$ in the myofilament space can be extruded across the sarcolemma *via* a secondary active transport mechanism.

A. Activator $Ca^{2+}$ (for contraction) can enter the myofilament space across the sarcolemma in response to a stimulus that does not alter the sarcolemma's membrane potential.
B. Crossbridges in the "latch" state go through (finish, if they are attached) their cycle more slowly than crossbridges that are phosphorylated.
C. Single-unit smooth muscle is more densely innervated than is multi-unit smooth muscle.

Multi-unit smooth muscle is more densely innervated. This is explained by their activity pattern: in the single-unit muscle, each muscle cell is connected to adjacent cells by gap junctions, which allow action potential propagation occurring in one cell to propagate to other cells, *in a multi-unit smooth muscle*, cells are not connected and require more inputs from the neuron.

D. $Ca^{2+}$ in the myofilament space can be extruded across the sarcolemma *via* a secondary active transport mechanism.