Homework Assignment - Module 3

1. [20 points] Choose the statement about the mammalian skeletal muscle neuromuscular junction that is the most correct **AND** briefly explain why the remaining choices are not correct.
    1. Binding of acetylcholine (ACh) to receptors on the muscle cell membrane causes a decrease in membrane sodium conductance (g_{Na}).
    2. When an action potential reaches the motor nerve terminal bouton (swelling; this is the end of the motor nerve axon branch) the change in nerve membrane potential allows the entry of chloride ion (Cl^-) into the terminal bouton, which in turn allows the release of acetylcholine (ACh) from the nerve terminal bouton.
    3. A drug that binds to acetylcholine (ACh) receptors on the muscle membrane but whose binding does not affect muscle membrane ion permeability can uncouple excitation-contraction coupling.
    4. Increased entry of Ca^{2+} into the muscle cell following binding of acetylcholine (ACh) to ACh receptors on the muscle membrane initiates a muscle membrane action potential.

    1. Binding of acetylcholine (ACh) to receptors on the muscle cell membrane causes a decrease in membrane sodium conductance (g_{Na}).

       The binding of ACh to nicotinic receptors on motor end plate, increases their permeability to Na^+: more Na^+ moves into the muscle fiber. There is a current between depolarized end plate and adjacent muscle plasma membrane: the sodium conductance *increases* instead of decreasing.

    2. When an action potential reaches the motor nerve terminal bouton (swelling; this is the end of the motor nerve axon branch) the change in nerve membrane potential allows the entry of chloride ion (Cl^-) into the terminal bouton, which in turn allows the release of acetylcholine (ACh) from the nerve terminal bouton.

       When an action potential reaches in a motor neuron at the axon terminal, the cell membrane is depolarized (increased flow of Na+ into the cell), opening voltage-gated Ca^{++} channels. *Calcium and not chloride ions,* into the axon terminal, bind to proteins enabling acetylcholine (ACh) vesicles to fuse with the pre-synaptic axon terminal membrane releasing ACh into the extracellular cleft between the axon terminal and the motor end plate.

    3. A drug that binds to acetylcholine (ACh) receptors on the muscle membrane but whose binding does not affect muscle membrane ion permeability can uncouple excitation-contraction coupling.

This is correct.

4. Increased entry of Ca^{2+} into the muscle cell following binding of acetylcholine (ACh) to ACh receptors on the muscle membrane initiates a muscle membrane action potential.

Binding of acetylcholine (ACh) to ACh receptors on the muscle membrane initiates a muscle membrane action potential which leads to an increased of Ca^{2+} into the muscle cell.
First, an action potential propagates to an alpha motor neuron axon terminal, depolarizing the axion membrane, opening voltage-gated Ca^{2+} channels.
The calcium ions in the axon terminal, cause ACh vesicles to release ACh into the synaptic cleft, and bind acetylcholine to ACh receptors on the muscle fiber. Binding of ACh opens ion channels, with more Na^{+} moving in compared to K^{+} moving out, produces an end-plate potential (**EPP**). The EPP initiates an action potential over the surface of muscle fiber and propagated into the T-tubules, where it is detected by the DHPR receptor, which induces by opening the RYR, a release of Ca^{++} into the muscle cells.

2. [20 points] Choose the statement about mammalian skeletal muscle that is the most correct **AND** briefly explain why the remaining choices are not correct.
    1. Binding of Ca^{2+} to tropomyosin allows the S-1 heads of crossbridges to attach to their binding sites on the actin thin filament.
    2. In response to an action potential in the T-tubular system Ca^{2+} is actively pumped out of the lateral cisternae (sacs) of the sarcoplasmic reticulum into the myofilament space.
    3. The action potential in the T-tubular system is coupled to the membrane of the sarcoplasmic reticulum by gap junctions between the two membrane systems.
    4. Relaxation requires that Ca^{2+} be removed from the myofilament space by an active, ATP-powered pump in the membrane of the sarcoplasmic reticulum.

1. Binding of Ca^{2+} to tropomyosin allows the S-1 heads of crossbridges to attach to their binding sites on the actin thin filament.

Ca^{2+} binds to troponin-C and not tropomyosin which allows the tropomyosin to move away from the myosin-binding site on the underlying actin molecule, which in turn “allows the S-1 heads of crossbridges to attach to their binding sites on the actin thin filament”.

2. In response to an action potential in the T-tubular system Ca^{2+} is actively pumped out of the lateral cisternae (sacs) of the sarcoplasmic reticulum into the myofilament space.

In response of an action potential in the T-tubular system Ca^{2+} is released from the sarcoplasmic reticulum into the cytosol where it binds to troponin on the thin filament, exposing the binding-sites for myosin.

3. The action potential in the T-tubular system is coupled to the membrane of the sarcoplasmic reticulum by gap junctions between the two membrane systems.

The action potential in the T-tubular system is not coupled to the membrane of the sarcoplasmic reticulum by gap junctions but by a triad junction consisting of central T-tubule, with a terminal cisterna of sarcoplasmic reticulum, on either side.

4. Relaxation requires that Ca^{2+} be removed from the myofilament space by an active, ATP-powered pump in the membrane of the sarcoplasmic reticulum.

2. [20 points] Assume the existence of a drug whose only effect is to prolong the time course of the binding of Ca^{2+} to troponin-C (TnC) in skeletal muscle by a factor of about 3. In comparison to an untreated muscle, a muscle treated with this drug will ... (chose the most correct response) **AND** briefly explain why the remaining choices are not correct.
    1. Have an increased rate of rise of force in an isometric twitch.
    2. Require a lower stimulus repetition rate to achieve a fused tetanus.
    3. Have a larger velocity of unloaded shortening (V_o).
    4. Relax more quickly.

    1. Have an increased rate of rise of force in an isometric twitch.
    An isometric twitch depends mostly on the total number of cross-bridges bound to actin and not how long the binding of Ca^{2+} to troponin-C lasts.
    A single action potential releases enough of Ca^{2+} to saturate troponin-C and therefore *all* the myosin-binding sites on the actin thin filaments are available, the twitch force generated approximates the maximal force for an isometric twitch. A longer duration of the binding of Ca^{2+} to troponin-C will not incur an increased rate of rise of force in an isometric twitch.

    2. Require a lower stimulus repetition rate to achieve a fused tetanus.

3. Have a larger velocity of unloaded shortening (V_o).

   Velocity of unloaded shortening (V_0), depends on the ATPase rate, and approximates the muscle fiber intrinsic force and does not depend on how long the Ca^{2+} binds to troponin-C.

4. Relax more quickly.

   The relaxation begins as Ca^{2+} is pumped back into the sarcoplasmic reticulum by the Ca^{2+}-ATPase pump. The relaxation will be quicker if the calcium ions are transported back, faster into the SR, and it is not related to a longer binding in time of Ca^{2+} to troponin-C.

4. [20 points] With reference to mammalian skeletal muscle, choose the equation that best describes the detachment of the "used" crossbridge from the thin filament following the power stroke **AND** briefly explain/describe the steps in the crossbridge cycle represented by the remaining choices.
   1. $A + M{\bullet}ATP \rightarrow A + M^*{\bullet}ADP{\bullet}P_i$
   2. $A + M^*{\bullet}ADP{\bullet}P_i \rightarrow A{\bullet}M^*{\bullet}ADP{\bullet}P_i$
   3. $A{\bullet}M^*{\bullet}ADP{\bullet}P_i \rightarrow A{\bullet}M + ADP + P_i$
   4. $A{\bullet}M + ATP \rightarrow A + M{\bullet}ATP$

   1. $A + M{\bullet}ATP \rightarrow A + M^*{\bullet}ADP{\bullet}P_i$

      Following the detachment of the "used" crossbridge from the thin filament (dissociation of actin and myosin), the myosin is hydrolyzed by myosin-ATPase, reforming the energized state of myosin and returning the crossbridge to its pre-power stroke position.

   2. $A + M^*{\bullet}ADP{\bullet}P_i \rightarrow A{\bullet}M^*{\bullet}ADP{\bullet}P_i$

      Binding of energized myosin cross-bridge (M) to a thin filament actin molecule (A).

   3. $A{\bullet}M^*{\bullet}ADP{\bullet}P_i \rightarrow A{\bullet}M + ADP + P_i$

      Power stroke step in the cross-bridge cycle

      Energized cross bridge binding to actin triggers produces the power stroke movement (myosin molecule pulls the actin filament towards the center of the sarcomere) and the release of P_i and ADP

   4. $A{\bullet}M + ATP \rightarrow A + M{\bullet}ATP$

5. [20 points] Choose the statement which best describes a role of ATP in skeletal muscle *relaxation* **AND** briefly explain why the remaining choices are not correct.
    1. ATP binds to myosin S-2, which allows bound crossbridges to release from the thin filament.
    2. Chemical energy from the hydrolysis of ATP is transformed into mechanical energy when bound crossbridges rotate from the 90° to the 45° configuration.
    3. Chemical energy from the hydrolysis of ATP is needed to power the pumps in the SR that take up Ca^{2+}.
    4. ATP binds to TnI, allowing tropomyosin to rotate into the groove of the actin helix, thus blocking attachment of crossbridges to the thin filament.

    1. ATP binds to myosin S-2, which allows bound crossbridges to release from the thin filament.

       ATP binds to myosin head S-1 (not S-2 arm), breaking the link between myosin and actin, allowing the next cross-bridge cycle.

    2. Chemical energy from the hydrolysis of ATP is transformed into mechanical energy when bound crossbridges rotate from the 90° to the 45° configuration.

       The binding of myosin to actin brings about the release of products of hydrolysis of ATP, and the bound crossbridges rotate from the 90° to the 45° configuration (ATP hydrolysis happened in the previous step of the cross bridge cycle).

    3. Chemical energy from the hydrolysis of ATP is needed to power the pumps in the SR that take up Ca^{2+}.

    4. ATP binds to TnI, allowing tropomyosin to rotate into the groove of the actin helix, thus blocking attachment of crossbridges to the thin filament.

       Ca^{2+} concentration decreases *as the result of Ca^{2+}-ATPase* transporting Ca^{2+} back into SR, the *removal of Ca^{2+}* from troponin allows the tropomyosin in the blocking position, preventing attachment of cross-bridges to actin in the thin filament.