

### Intro to Skeletal Muscle Physiology

- In order for contraction of skeletal muscle to occur, electrical signals (action potentials) from motor neurons must be transformed into chemical signals (neurotransmitters)
- Takes place at the neuromuscular junction
- These chemical signals then stimulate electrical signals in sarcolemma of the muscle fiber - if the chemical stimulation is strong enough.
- The electrical signal in the muscle fiber (action potential) then activate a series of events that lead to the shortening of the skeletal muscle fiber

### Intro to Skeletal Muscle Physiology

- Predominant theory of skeletal muscle contraction—Well supported by research
- Sliding filament model of contraction—Interactions between the thin and thick filaments of the sarcomere produce the contraction (shortening) of a skeletal muscle cell
- In relaxed state, thin and thick filaments overlap slightly
- During contraction, thin filaments slide toward the m-line past the thick filaments actin and myosin overlap more
- Occurs when myosin heads bind to actin and pull cross bridges and power stroke

### Muscle Action Potential

- Brief overview of action potential (AP)—AP dependent on voltage gated  $\text{Na}^+$  and  $\text{K}^+$  channel interactions
- Normal resting membrane voltage
- There is a difference in charges inside the cell vs outside—Inside charge is negative compared to outside (outside value is 0)
- $\text{Na}^+$  at high concentration outside the cell vs inside •  $\text{K}^+$  at high concentration inside the cell vs outside

### Events in Generation of an Action Potential

- Depolarization phase - generation and propagation of an action potential (AP)
- End plate potential spreads to adjacent membrane areas
- Voltage-gated  $\text{Na}^+$  channels open— $\text{Na}^+$  influx decreases membrane voltage (makes less negative) toward critical voltage called threshold
- Membrane voltage in which AP will begin
- If threshold reached, AP initiated
- Rapid increase in amount of open voltage gated sodium channels
- Rapid  $\text{Na}^+$  influx into the cell leads to fast positive change in voltage of the intracellular side of membrane
- $\text{Na}^+$  flows into the cell, down its electrochemical gradient
- Once initiated, is unstoppable muscle fiber contraction

### Excitation-Contraction (E-C) Coupling

- Events that transmit AP along sarcolemma lead to sliding of myofilaments
- AP brief; ends before contraction
- However, causes rise in intracellular  $\text{Ca}^{2+}$  contraction
- Latent period
- Time when E-C coupling events occur
- Time between AP initiation and beginning of contraction

### Neuromuscular Junction

- Situated midway along length of muscle fiber
- Axon terminal and muscle fiber separated by gel-filled space called synaptic cleft
- Synaptic vesicles of axon terminal contain neurotransmitter acetylcholine (ACh)
- Junctional folds of sarcolemma contain ACh receptors
- nAChR (nicotinic acetylcholine receptor)
- NMJ includes axon terminals, synaptic cleft, junctional folds

### Chemical and Electrical Gradients of Muscle

- Chemical gradients of skeletal muscle at rest—Comparison intracellular [X] vs. extracellular [X] (Sarcoplasmic vs. interstitial)
- Intracellular  $[\text{Ca}^{2+}]$  very low • Intracellular  $[\text{Na}^+]$  very low
- Intracellular  $[\text{K}^+]$  high
- At rest, the average skeletal muscle cell internal membrane voltage (charge at the surface of the intracellular portion of the plasma membrane) is  $-95\text{mV}$  with respect to a  $0\text{mV}$  outside membrane voltage
- The charge at the surface of the extracellular side of the membrane is almost always  $0\text{mV}$

### Chemical and Electrical Gradients of Muscle

- Generic graphic for a skeletal muscle cell
- Compares membrane voltage and concentrations of important ions inside vs. outside

concentrations are also applicable to most neurons

### Events at the Neuromuscular Junction

- Nerve impulse arrives at axon terminal ACh released into synaptic cleft
- ACh diffuses across cleft (from high concentration to low) and binds with ACh receptors on sarcolemma
- Electrical events generation of action potential

### Generation of an Action Potential

- Resting sarcolemma polarized
- Voltage across membrane different
- Action potential in sarcolemma caused by changes in electrical charges
- Occurs in three steps
- End plate potential
- Depolarization
- Repolarization

### Events in Generation of an Action Potential

- AP spreads across sarcolemma • Voltage-gated  $\text{Na}^+$  channels open in adjacent sarcolemma portions causing them to depolarize to threshold
- Spreads across sarcolemma very quickly

### Events of Excitation-Contraction (E-C) Coupling

- AP propagated along the sarcolemma and into T-tubules
- AP travels down into the T-tubules where it activates DHP receptors
- DHP receptors
  - These voltage-sensitive proteins allow a small amount of calcium to flow into the sarcoplasm but also mechanically stimulate the Ryanodine receptors on the SR
- The Ryanodine receptors are the calcium “flood gates” of the SR
  - When stimulated by the DHP receptors, the ryanodine receptors allow  $Ca^{2+}$  release from SR into the sarcoplasm
  - This increases sarcoplasmic calcium concentration supplying the majority of  $Ca^{2+}$  necessary for contraction of skeletal muscle

### Physiology of Skeletal Muscle Fibers

- For skeletal muscle to contract
  - Activation (at neuromuscular junction)
- Must be nervous system stimulation
- Must generate action potential in sarcolemma
  - Excitation-contraction coupling
- Action potential propagated along sarcolemma
- Intracellular  $Ca^{2+}$  levels must rise briefly leading to the onset of contraction

### The Nerve Stimulus and Events at the NMJ

- Skeletal muscles stimulated by somatic motor neurons
  - Under voluntary control
  - Axons of motor neurons travel from central nervous system via nerves (bundles of mostly neuron axons) to skeletal muscle
  - Each axon may form several branches as it enters whole muscle
  - Each axon ending forms a neuromuscular junction with single muscle fiber

### Destruction of Acetylcholine

- ACh effects quickly terminated by enzyme acetylcholinesterase in synaptic cleft
  - Breaks down ACh to acetate and choline
  - Prevents continued muscle fiber contraction in absence of additional stimulation

### Gen of an Action Potential Across the Sarcolemma

- End plate potential (local depolarization)
  - ACh binding opens chemically (ligand) gated ion channels
  - Simultaneous diffusion of  $Na^{+}$  (inward) and  $K^{+}$  (outward)
  - More  $Na^{+}$  diffuses in, so interior of sarcolemma becomes less negative
  - Local depolarization = end plate potential

### Events in Generation of an Action Potential

- Repolarization – restoring electrical conditions of RMP
  - Voltage-gated  $K^{+}$  channels begin to open
  - $K^{+}$  efflux (outflow) begins to outpace  $Na^{+}$  influx
  - rapidly restores resting polarity (makes negative again)
  - $Na^{+}$  are closing, eventually decreasing  $Na^{+}$  influx
  - Another muscle fiber depolarization AP cannot be stimulated
  - in refractory period until repolarization complete
  - Eventually,  $K^{+}$  channels close (lowers  $K^{+}$  efflux)
  - Chemical and electrical conditions of resting state restored by  $Na^{+}$ - $K^{+}$  pump and  $K^{+}$  leaking out of the cell through  $K^{+}$  leak channels

### Channels Involved in Initiating Muscle Contraction

- Nerve impulse (AP) reaches axon terminal voltage-gated calcium channels open ACh released to synaptic cleft
- ACh binds to its receptors on sarcolemma opens ligand-gated  $Na^{+}$  and  $K^{+}$  channels end plate potential
- Opens voltage-gated  $Na^{+}$  channels AP propagation

### Channels Involved in Initiating Muscle Contraction (cont)

- Voltage-sensitive proteins in T tubules (DHP receptors) change shape and activate the Ryanodine receptors SR releases  $Ca^{2+}$  to cytosol