Vertebrate Physiology

ECOL 437 (aka MCB 437, VetSci 437)
University of Arizona
Fall 2005

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Term Paper Tips:
- Physiology and science should be subject, not researchers and experiments
- Hanging your paper on a question or a problem helps give direction and focus
- More physiology
- Subheadings often helpful
- More sophisticated Future Directions, including gaps in current knowledge, flaws in current studies, proposed detailed experiments, think outside the box
- Synthesize, not serial book reports
- Abstract, role is summary of entire paper, not an intro to the intro
- Avoid Prounouns (its, these, this, ... which, there are)
- Passive voice to be avoided (e.g., Avoid passive voice)
- Leading and following zeros (0.5, .5, .50)
- Page numbers
- Citation format (J. of Physiology, instructions to authors, [full journal names])
- Turn in old, graded work with each new version
- Peer editing (read quickly, then read for content and writing, lots of comments)
Excitation-Contraction Coupling, from the beginning...

1. AP from CNS arrives at neuromuscular junction.

2. ACh released into synapse.

3. ACh binds to nicotinic receptors on motor endplate.

4. Ion channels for K+ and Na+ open; greater Na+ influx leads to depolarization and AP in muscle plasma membrane

EPP = Endplate Potential (~Excitatory Post-Synaptic Potential or EPSP)

Excitation-Contraction Coupling, the middle I...

5. Change in membrane potential (AP) reaches deep into the muscle cell via transverse tubules (T-tubules; one per Z-disk)

Excitation-Contraction Coupling, the middle II...

6. T-tubules have voltage sensitive proteins called dihydropyridine receptors

7. Dihydropyridine receptors in the T-tubules are mechanically linked with ryanodine receptors (RR) on the sarcoplasmic reticulum (SR)

The ends of the SR adjacent to the T-tubule are called terminal cisternae (w/ calsequestrin)

8. Calcium stored in the SR. Released into the cytosol via the ryanodine receptor channel when the RR is mechanically triggered by the voltage sensitive dihydropyridine receptor.

Excitation-Contraction Coupling, the last bit...

9. Calcium triggers release of more calcium from some ryanodine receptors that are not linked to dihydropyridine receptors

   Called calcium-induced calcium release

10. Calcium binds to troponin leading to actomyosin complex...

11. After repolarization, calcium actively (requires ATP) moved back into SR where much of it is bound to calsequestrin

12. Muscle relaxes as long as ATP is present to allow actomyosin complex to dissociate
Review of EC Coupling and Muscle Contraction

Time course of excitation-contraction events

- **Latent period about 2ms**

**Force-Velocity Curve**

- **Greatest force during isometric contraction**
- **Greatest velocity when muscle is unloaded**

**Muscles can produce power**

- **Muscle fiber types vary in their mechanical properties**

- **Power = force * velocity**
- **Maximum power output is found at intermediate force and velocity (~40%)**

**Different Muscle Fiber-Types**

<table>
<thead>
<tr>
<th>Property</th>
<th>Slow oxidative (type I)</th>
<th>Fast oxidative (type IIa)</th>
<th>Fast glycolytic (type IIb)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fiber diameter</td>
<td>।</td>
<td>।</td>
<td>।</td>
</tr>
<tr>
<td>Force per cross-sectional area</td>
<td>।</td>
<td>।</td>
<td>।</td>
</tr>
<tr>
<td>Rate of contraction (V_{max})</td>
<td>।</td>
<td>।</td>
<td>।</td>
</tr>
<tr>
<td>Myosin ATPase activity</td>
<td>।</td>
<td>।</td>
<td>।</td>
</tr>
<tr>
<td>Resistance to fatigue</td>
<td>।</td>
<td>।</td>
<td>।</td>
</tr>
<tr>
<td>Number of mitochondria</td>
<td>।</td>
<td>।</td>
<td>।</td>
</tr>
<tr>
<td>Capacity for oxidative phosphorylation</td>
<td>।</td>
<td>।</td>
<td>।</td>
</tr>
<tr>
<td>Enzymes for anaerobic glycolysis</td>
<td>।</td>
<td>।</td>
<td>।</td>
</tr>
</tbody>
</table>

**Histochemistry**

- **FOG** (fast-twitch oxidative glycolytic; dark mATPase and dark SDH)
- **SO** (slow-oxidative; light mATPase, dark SDH)
- **FG** (fast-twitch glycolytic; dark mATPase, light SDH)
The electric eel - *Electrophorus electricus*

The eel generates electric charge in a battery of biological electrochemical cells, each cell providing about 0.15 V and an overall potential difference of ~700 V. Note that the eel's head is the cathode (+) and its tail the anode (-). The cells extend over the length of the eel.

Thanks to Professor Don Stevens, Zoology, for the picture and expert advice.

Control of Muscle Force

- Two primary factors can be adjusted to increase whole muscle force:
  - the force developed by each contracting fiber (summation)
  - the number of muscle fibers contracting within a muscle (recruitment)

Summation

Increase force by decreasing time between individual action potentials (increase rate of stimulation)

Motor Unit

Motor unit = motor neuron and all of the muscle fibers it innervates

AP in motor neuron causes all innervated fibers to contract simultaneously
Recruitment

Each muscle consists of many intermingled motor units

Motor Neurons

Increase force by adding more motor units

Muscle fibers

Isometric Contraction

iso = same
metric = length

Randall et al., 2002

Isotonic Contraction

iso = same
tonic = tension

Purely isotonic contraction

Randall et al., 2002

Muscles and Movement
Gail Koshland, 2004

Activating muscles

STRUCTURES OF THE NERVOUS SYSTEM:
- cerebral cortex
- frontal, parietal, temporal, occipital lobes
- basal ganglia
- cerebellum
- brain stem
- spinal cord
- peripheral nerves

motoneuron in the spinal cord
A motor unit = the motoneuron + the muscle fibers that it innervates

Motoneuron pool = all motoneurons that innervate a single muscle

= 200 motoneurons

Motoneuron size = motor unit size

Size Principle

Increasing firing frequency of recruited motor units

Small units, producing small amounts of force, are recruited first. Firing rate of these units increase as new units are recruited.

Large units, producing large amounts of force, are recruited later and also increase firing rate with more excitation.

Contraction of increasing force (gms)
**Cellular Energetics**

- **Actin + Myosin**
  - Crossbridge movement
- **ATP**
  - ADP + P_i
- **PCr + ADP** → Cr + ATP
- **Non-oxidative energy source**
  - Glucose → 2 Lactate + 2 ATP
- **Oxidative energy source**
  - Glucose + O_2 → CO_2 + H_2O + 36 ATP

**Energy systems differ in their rate of and capacity for producing ATP**

**Fatigue**

- **Fatigue can result from many factors including:**
  - Decreased motivation
  - Failure of neuromuscular transmission
  - Accumulation of metabolic end-products
  - Dehydration

- **Cause of fatigue depends on intensity & duration of exercise**

**Fatigue**

- Continuous exercise at moderate speeds results in net accumulation of P_i
  - PCr + ADP + H^+ → Cr + ATP
  - ATP + H_2O → ADP + P_i + H^+ + energy

Exercise also produces net accumulation of lactic acid

**Correlation vs. Causation**

**Wilson et al., 1988**

**Muscle Biopsy**

- Prepare homogenate & perform enzymatic analysis of homogenate (e.g., creatine phosphate, ATP, P_i, lactate, glucose, glycogen)
  - Pros: low cost per assay
  - Cons: many samples required for time course

**31P-Magnetic Resonance Spectroscopy**

- Intact muscle (e.g., creatine phosphate, ATP, P_i, pH)
  - Pros: multiple time points for each preparation
  - Cons: high cost per preparation

**pH** can be determined from position of P_i peak
31P-Magnetic Resonance Spectroscopy

Rat muscle

P_i

ATP

PCr

Time

Kushmerick & Meyer, 1985

Postulated Mechanisms of P_i Effect on Force

- Reduced cross-bridge force development
- Reduced Ca^{2+} release from sarcoplasmic reticulum
- Reduced Ca^{2+} sensitivity of myofilaments

Decreased pH (e.g., lactic acid) does not seem to have much effect on contractility - but may cause pain!

Cooke & Pate, 1985; Allen & Westerblad, 2001; Westerblad et al. 2002

How did he get so BIG??

Muscle growth, repair and regeneration

Cindy Rankin
Dept of Physiology
(guest lecture 07 October 2004, ECOL 437, Vertebrate Physiology)
Muscle Growth in a Dish

Factors influencing growth

- Genetics
- Location
- Tension
- Innervation
- Environment

Factors cont.

- Environment:
  - Myogenic Regulatory Factors
    - Myo D, Myf5, Myogenin
  - Growth Factors
    - Insulin-like Growth Factor I (IGF-I)
    - Fibroblast Growth Factor (FGF)
    - Transforming Growth Factor (TGF-β)
    - Myostatin (MSTN)

“Double-Muscling”

myostatin deficient

How to add Mass/Strength?

- Increase numbers of fibers:
  - Hyperplasia
- Increase size of existing fibers:
  - Hypertrophy
Satellite Cell

- Adds nuclear material
- Stimulated to proliferate
- Fuses with existing fiber
- Fuses with other SC’s to regenerate

Factors affecting SC activity

- Damage
- Exercise

Process of repair

Process of Repair

- Degeneration
  - Necrosis
  - Inflammation
    - Neutrophils
    - Macrophages
- Regeneration
  - Satellite Cells
Factors affecting SC activity

- Damage
- Exercise
- Drugs (Androgenic Steroids)
- Loss of innervation
- Stretch
- Local anesthetics

Smooth Muscle

- Lacks sarcomeres, isn’t striated
- Walls of hollow organs – visceral functions
  (GI tract, urinary bladder, uterus, blood vessels)
- Heterogenous
- Innervated by autonomic NS
- Each fiber is individual cell with one nucleus
- No T-tubules
- Organized into bundles of actin and myosin anchored to dense bodies or to the plasma membrane
- Can be single-unit or multi-unit – Neurogenic (walls of blood vessels, iris)
- Myogenic and electronically linked via gap junctions
  (peristaltic waves in GI tract)

Smooth Muscle

- Autonomic NT released from varicosities along axon, not at motor endplate, affecting many cells
- Poorly developed SR, calcium mostly across plasma membrane
- Several ways to regulate calcium concentration (no troponin)
  - One is via calcium-calmodulin complex that then binds to caldesmon, removing caldesmon from blocking actin binding sites
- Some smooth muscle responds to stretch (vessels, GI)
- Processes all very slow and require little energy

Skeletal muscle

Cardiac muscle

**TABLE 17.3** Characteristics of the three major types of muscles in vertebrates (Part 1)

<table>
<thead>
<tr>
<th></th>
<th>Skeletal</th>
<th>Multis/unit smooth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structure</td>
<td>Large, cylindrical, multinucleate fibers</td>
<td>Small, spindle-shaped, uninucleate cells</td>
</tr>
<tr>
<td>Visible striations</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Mechanism of contraction</td>
<td>Thick myosin and thin actin filaments slide by each other</td>
<td>Thick myosin and thin actin filaments slide by each other</td>
</tr>
<tr>
<td>Crossbridge action regulated by Ca²⁺ ions</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Innervation</td>
<td>Somatic nervous system initiates contractions</td>
<td>Autonomic nervous system initiates contractions</td>
</tr>
<tr>
<td>Spontaneous production of action potentials by pacemakers</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

Behavior Initiation

Animal Behavior, Neurobiology

Complex

Bring together nervous, endocrine, muscular systems, etc.

Responsive to situation(s)

Parallel Processing

Reflexes / Learned / Plasticity

Complicated Neuronal Circuitry

Simple Reflexes - basis of neuronal circuitry

Reflex Arc, Stereotypic Behavior

e.g., stretch reflex (patellar tendon)

- Tonic tension in muscle
- Important for maintenance of posture via negative feedback
- Only 2 neurons required
- Monosynaptic reflex

Simple Reflexes

Stretch receptor = muscle spindle organ

- Contains intrafusal fibers (as opposed to extrafusal)
- Sensitive to stretch (stretch \(\rightarrow\) APs)
- Need to be reset for new muscle length
- Gamma-efferent neurons innervate spindle

Table 17.3 Characteristics of the three major types of muscles in vertebrates (Part 3)

<table>
<thead>
<tr>
<th>Skeletal</th>
<th>Multinucleated smooth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hormones influence function</td>
<td>No</td>
</tr>
<tr>
<td>Gap junctions present</td>
<td>No</td>
</tr>
<tr>
<td>Transverse tubules</td>
<td>Yes</td>
</tr>
<tr>
<td>Sarcolemma</td>
<td>Abundant</td>
</tr>
<tr>
<td>Source of Ca(^{2+}) ions for regulation</td>
<td>Sarcolemmal reticulum</td>
</tr>
<tr>
<td>Troponin and tropomyosin</td>
<td>Both present</td>
</tr>
<tr>
<td>Ca regulation</td>
<td>Ca and troponin; tropomyosin–troponin complex moves to expose myosin-binding sites on actin</td>
</tr>
<tr>
<td>Speed of contraction (reflecting myosin ATPase activity)</td>
<td>Varies from fast to slow depending on fiber type</td>
</tr>
</tbody>
</table>


Table 17.3 Characteristics of the three major types of muscles in vertebrates (Part 2)

<table>
<thead>
<tr>
<th>Single-unit smooth</th>
<th>Cardiac</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structure</td>
<td>Small, spindle-shaped, multinucleate cells</td>
</tr>
<tr>
<td>Visible striations</td>
<td>No</td>
</tr>
<tr>
<td>Mechanism of contraction</td>
<td>Thick myosin and thin actin filaments slide by each other</td>
</tr>
<tr>
<td>Cross-bridge action regulated by Ca(^{2+}) ions</td>
<td>Yes</td>
</tr>
<tr>
<td>Innervation</td>
<td>Autonomic nervous system modulates contractions</td>
</tr>
<tr>
<td>Spontaneous production of action potentials by pacemakers</td>
<td>Yes</td>
</tr>
</tbody>
</table>


Simple Reflexes – basis of neuronal circuitry

Reflex Arc, Stereotypic Behavior

e.g., stretch reflex (patellar tendon)

- Tonic tension in muscle
- Important for maintenance of posture via negative feedback
- Only 2 neurons required
- Monosynaptic reflex

Stretch receptor activates 1a afferent neuron

Alpha-motor neuron activates quadriceps

Stretch receptor activates 1a afferent neuron

Alpha-motor neuron activates quadriceps

Table 17.3 Characteristics of the three major types of muscles in vertebrates (Part 4)

<table>
<thead>
<tr>
<th>Single-unit smooth</th>
<th>Cardiac</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hormones influence function</td>
<td>Yes</td>
</tr>
<tr>
<td>Gap junctions present</td>
<td>Yes</td>
</tr>
<tr>
<td>Transverse tubules</td>
<td>No</td>
</tr>
<tr>
<td>Sarcolemma</td>
<td>Exocellular fluid and sarcoplasmic reticulum</td>
</tr>
<tr>
<td>Source of Ca(^{2+}) ions for regulation</td>
<td>Tropomyosin only</td>
</tr>
<tr>
<td>Troponin and tropomyosin</td>
<td>Ca and tropomyosin; tropomyosin–troponin complex moves to expose myosin-binding sites on actin</td>
</tr>
<tr>
<td>Speed of contraction (reflecting myosin ATPase activity)</td>
<td>Very slow</td>
</tr>
</tbody>
</table>

1. 1a-afferent neuron
2. Alpha-motor neuron
3. Gamma-motor neuron

c. Contracted muscle without ‘reset’ muscle spindle

Simple Reflexes +
Other neurons become involved as well:
- 1a-afferents inhibit the antagonist muscle (Knee flexor ~ hamstring)
- Conscious decision to bend leg etc.

- Limb

Hill et al. 2004 Fig 18.4

Hill et al. 2004 Fig 18.7
Buerens & Krujit found that herring gulls:
- prefer the larger of two eggs of the same colour
- prefer the speckled egg over an unspeckled egg of the same colour
- prefer natural, coloured (brown speckled) eggs over brown unspeckled eggs
- prefer green speckled eggs over green unspeckled eggs
- prefer green eggs over brown eggs

Law of Nerve-Specific Energy

Action Potentials and Graded Potentials don't convey specific information.

Rather, the geographic connections, summation of different inputs, and modulation are important for correct response.

Peripheral vs. Central Control

**CPG = central pattern generator**

- neuronal network producing repetitive output

Walking, swimming, flying, breathing

Toad walking with no afferents
- awkward
- flaccid muscles

Sensory feedback
Higher centers can override

Some patterns at level of spinal cord if stimulate initially (cats on treadmill)

Central Pattern Generators in Cat Spinal Cord

Hill et al. 2004 Fig 18.14
Basal Ganglia (plans & initiates movement)  
Parkinson’s Disease (akinesia, too much inhibition of motor function, mediated by dopamine)  
Huntington’s Disease (chorea, not enough inhibition of motor function)  
Hill et al. 2004, Fig 18.19

Endocrine Control of Bird Song  
- During breeding season some vocal centers enlarge (increase number of neurons)  
- Response to testosterone (T) and day length  
- Treatment of young females with estrogen primes them to sing in response to elevated T later in life  
Randall et al. 2002

Extra