Neuromuscular Adaptations to Reduced Use

Lori Ploutz-Snyder, Ph.D.
Disuse Models

- Outcomes are dependent on specifics of disuse model and species used.

<table>
<thead>
<tr>
<th>Animal Models</th>
<th>Human Models</th>
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</thead>
<tbody>
<tr>
<td>Immobilization</td>
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<tr>
<td>Hindlimb Unweighting</td>
<td>Limb Suspension</td>
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<tr>
<td>Spinal Transection</td>
<td>Spinal Cord Injury</td>
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<tr>
<td>Pharmacological Blockade</td>
<td>Bedrest</td>
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<tr>
<td>Spaceflight</td>
<td>Spaceflight</td>
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<tr>
<td>Nerve Compression</td>
<td>Cancer Cachexia (Atrophy)</td>
</tr>
<tr>
<td>Hibernation</td>
<td>Kwashiorkor (Atrophy)</td>
</tr>
</tbody>
</table>
Certain dormant species display no muscle atrophy, despite months of disuse

- *Ursus americanus*
  - Minimal atrophy following 4-months disuse

- *Cyclorana alboguttata*
  - No loss of muscle mass, in vitro force production or swimming performance following 9-months aestivation

- *Cynomys leucurus*
  - Maintenance of slow MHC isoforms

Hudson & Franklin, J Exp Biol, 2002
Hudson & Franklin, J Comp Physiol, 2002
Rourke et al, 2006
Between species differences is related to mass-specific metabolic rate

- Low metabolic rate (normalized to muscle mass) = Less Atrophy
  - $R^2 = 0.76$

- Hypotheses:
  - 1) Lower metabolic rate species are less active… thus disuse is a smaller stimulus
  - 2) Low-metabolic rate species would have lesser reactive oxygen species (ROS) insult
So what about that tiny frog???

- Pre-dormancy & Dormancy: Metabolic rate is drastically reduced
  - Thus, the demands placed on the muscular defense (antioxidants) and repair (de novo protein synthesis) systems are alleviated, and the rate of atrophy are reduced accordingly.
Human Muscle Unloaded With ULLS

Sensitivity: 97.7%
Specificity: 96.5%

(Cook et al. Aviat. Space Env Med 2005)
3 sets of ULLS studies

- Early 1990’s - more muscle required to lift same absolute load following 30 day ULLS
- 2005-06 - Neural vs. muscle morphologic changes with ULLS
- 2006-08 - Low load exercise countermeasure
Muscle Strength Decreases More Than Mass

Combined data from: Adams et al., Berg et al., Hather et al., and Ploutz-Snyder et al.
Neural & Contractile Control of Force

Muscle Strength Decreases More Than Muscle Size

Combined data from: Adams et al., Berg et al., Hather et al., and Ploutz-Snyder et al.
Neural vs. Morphologic Factors

- What neural factors are altered?
- What muscle factors are altered?
- What is the relative contribution of each?
Perturbations

• Neural
  – Mental imagery
• Muscular
  – Ischemia
Immobilization Decreases Cortical Excitability

Kaneko, Murakami et al., Clin Neurophys, 2003
Motor Imagery Activates Same Neural Structures as Motor Performance

Red Pixels: Significant fMRI signal increases during both actual MP and MI

Porro, Francescato et al., *J. Neurosci*, 1996
Motor Imagery Training
↑ Strength & EEG Activity

Ranganathan, Siemionow et al., *Neuropsych.*, 2004
Chronic Ischemia in Rats:
↑ HSP-72, ↓ Myostatin & ↑ Myofiber CSA

50% Atrophy Attenuation Following Surgically-Induced Bed Rest

18 subjects
- 6 men & 12 women
- 18-29 years

- ULLS + No Intervention (n=6)
- ULLS + Ischemia (n=6)
  - 3x/wk
- ULLS + Motor Imagery (n=6)
  - 4x/wk
Spinal Excitability ↑ w/ Motor Imagery

Muscle Strength

Muscle Atrophy

Magnetic Resonance Imaging

PRE-ULLS

POST-ULLS
Muscle Atrophy

Soleus M. Gastrocnemius L. Gastrocnemius

Decrease in Atrophy (% CSA)

Muscle Atrophy (% Decrease in CSA)

Control Groups
Applied Ischemia Group

Large Variability In Atrophy With Unloading

Muscle Action Potential Duration

Slowed Muscle Fiber Conduction Velocity  (Keenan, Farina et al., Exp Brain Research, 2006)

Soleus CMAP Duration (Percent Change)

Control Groups

Applied Ischemia Group

Physiologic Interpretation

- Maintenance of potentiated force, despite ↓ doublet force
  - Common Interpretation: Phosphorylation of Myosin Light Chains increasing Ca^{2+} sensitivity?
  - Shift towards Type II muscle fiber type composition?
Central Activation

Neural vs Muscle Changes

Limitations

• **Sample Size**
  – 2\textsuperscript{nd} largest to date, but still relatively small

• **Unaccounted for variables**
  – Skeletal Muscle Pennation Angle
  – Skeletal Muscle Fiber Type
  – Cortical Excitability
  – Motor Unit Discharge Rate
Exercise Countermeasure

- Ischemia alone maintained only CMAP duration
- Ischemia + low load exercise
- Japanese kaatsu
- Potential for rehab or situations where heavy loading is undesirable.
Countermeasures to unloading

• High-load resistance training has maintained muscle mass and strength during unloading.

• Low-load resistance training with a blood flow restriction (LLBFR) has been shown to increase muscle mass and strength.
  (Shinohara et al. 1998, Takarada et al. 2000, Burgomaster et al. 2003)
Recent Interest in Tourniquet Training

- Kaatsu - Japanese
  - Japan Kaatsu Training Society
  - *International Journal of Kaatsu Training* - their own journal, unclear review process.
  - Inventor/Owner=Yoshiaki Sato, Department of Ischemic Circulatory Physiology
  - Body building websites
    - Testosterone Nation
    - Giant
    - Cutting Edge Muscle
加圧トレーニング

腕や太ももの付け根に近いところをバンドで締めて圧迫し、軽い運動をするだけで筋肉が増える（専門家の指導が必要）
### Unbelievable or Amazing?

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Main Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moritani</td>
<td>1992</td>
<td>Increase motor unit spike amplitude and frequency</td>
</tr>
<tr>
<td>Yoshida</td>
<td>1997</td>
<td>Limited ATP synthesis</td>
</tr>
<tr>
<td>Shinohara</td>
<td>1998</td>
<td>26% increase in KE strength after 4 weeks</td>
</tr>
<tr>
<td>Takarada</td>
<td>2000</td>
<td>GH increased 290x</td>
</tr>
<tr>
<td>Takarada</td>
<td>2000</td>
<td>20% increase in CSA and 18% increase in strength in 16 weeks</td>
</tr>
<tr>
<td>Takarada</td>
<td>2002</td>
<td>14% increase in CSA, 15% increase in strength in 8 weeks</td>
</tr>
<tr>
<td>Takarada</td>
<td>2004</td>
<td>16% increase in CSA and 9% increase in strength in 8 weeks</td>
</tr>
<tr>
<td>Abe*</td>
<td>2005</td>
<td>9% increase in CSA in 2 weeks</td>
</tr>
<tr>
<td>Takano*</td>
<td>2005</td>
<td>GH increase 80x</td>
</tr>
<tr>
<td>Abe*</td>
<td>2005</td>
<td>5% increase in CSA and 10% increase in strength in 8 days</td>
</tr>
<tr>
<td>Ishii*</td>
<td>2005</td>
<td>3% increase in CSA after 8 weeks of circuit training</td>
</tr>
<tr>
<td>Sato*</td>
<td>2005</td>
<td>GH increase 25x</td>
</tr>
<tr>
<td>Tanimoto*</td>
<td>2005</td>
<td>GH increase 17x</td>
</tr>
<tr>
<td>Yasuda*</td>
<td>2005</td>
<td>8% increase in CSA and 14% increase in strength in 2 weeks</td>
</tr>
<tr>
<td>Abe*</td>
<td>2005</td>
<td>3% increase in CSA and 17% increase in strength in 7 days</td>
</tr>
<tr>
<td>Abe*</td>
<td>2005</td>
<td>8% increase in CSA and 6% increase in strength in 3 weeks</td>
</tr>
</tbody>
</table>
Tissue Blood Flow at Rest and During Dynamic Exercise

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Blood flow (ml/min^-1)</th>
<th>Flow rate (ml/100g^-1/min^-1)</th>
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<th>Flow rate (ml/100g^-1/min^-1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS</td>
<td>825</td>
<td>55</td>
<td>1125</td>
<td>75</td>
</tr>
<tr>
<td>Heart</td>
<td>260</td>
<td>87</td>
<td>900</td>
<td>300</td>
</tr>
<tr>
<td>Muscle</td>
<td>1200</td>
<td>25</td>
<td>18000</td>
<td>60-100</td>
</tr>
<tr>
<td>Viscera</td>
<td>2400</td>
<td>65</td>
<td>500</td>
<td>14</td>
</tr>
<tr>
<td>Skin</td>
<td>500</td>
<td>24</td>
<td>500</td>
<td>24</td>
</tr>
</tbody>
</table>

Brooks, Fahey and Baldwin 2005
Low Load With Blood Flow Restriction \( \text{LL}_{\text{BFR}} \)
Growth Hormone Response to Acute $\text{LL}_{\text{BFR}}$ Exercise

GH increased 290 times baseline!!

Takarada et al. J Appl Physiol, 2000
Growth Hormone Response to Acute LL$_{BFR}$ Exercise

~8-fold increase but not 290!
Possible mechanisms of hypertrophy via LL$_{BFR}$

- **Greater reliance on anaerobic metabolism**  

- **Increased angiogenesis during hypoxia**  

- **Altered motor unit recruitment patterns**  

- **Increased levels of growth hormone**  

- **Mechanical signaling of muscle cell**
Methods

16 subjects aged 18-50 yrs

- 8 subjects performed unilateral lower limb suspension (ULLS)
- 8 subjects performed ULLS and LL_{BFR} exercise on the KE 3 times per week (ULLS + Exercise)
**LL_{BFR} Exercise**

- Performed 3x per week

- 3 sets of KE to volitional failure
  - 20% MVC
  - 2-sec con, 2-sec ecc
  - 90 sec rest between sets

- 6 x 83 cm tourniquet cuff around proximal thigh
  - Inflated to 1.3 x SBP for the duration of exercise session

- 100% subject compliance
Average of Control Period | Post ULLS
--- | ---
ULLS PF | ↓ 1.22%
ULLS KE | ↓ 7.37%
ULLS + Ex PF | *↓ 5.72%
ULLS + Ex KE | ↓ 9.11%

Time x Group x Muscle interaction \( p = 0.045 \)
\(^*p < 0.05\) Control Period vs Post ULLS
\(^#p < 0.05\) ULLS vs ULLS + Exercise
CSA along the KE

* Time x Slice Interaction $p=.018$
RESULTS: KE 1-RM

*\( p = .002 \) ULLS vs ULLS + Exercise
RESULTS: KE Endurance

Average of Control Period | Post ULLS

ULLS | ULLS + Exercise

Average of Control Period vs Post ULLS

* p<0.05 ULLS vs ULLS + Exercise
# p<0.05 Control period vs Post ULLS

Endurance (# of Repetitions)

0 10 20 30 40 50

24% 28%
Conclusion

- Performing $L_{BFR}^{LE}$ KE exercise during 30d of unloading can maintain muscle size and strength of the KE and even improve muscular endurance.