Massage as an Intervention for Muscle Atrophy

Esther Dupont-Versteegden, PhD
College of Health Sciences, University of Kentucky

Outline

• Massage as an anabolic intervention: mechanotherapy
• Mechanotherapy and aging
• Cellular responses to mechanotherapy
  – Single cell sequencing
• Conclusions
Massage as a Mechanotherapy

- Examples of health promoting effects:
  - Alleviation of pain
  - Recovery after exercise
  - Increase in joint flexibility
  - Lessening of anxiety and depression
  - Promotion of tissue regeneration
  - Improving circulation
  - Enhancing immunity
  - NOTE: atrophy not on this list

Investigating Mechanotherapy Using Cyclic Compressive Loading (CCL)

- Hind limb muscles: right leg only
- Different highly controlled load levels
- 0.5 Hz
- Real time force feedback through strain gauge

Massage as an ‘immunomodulator’ in unperturbed muscle

* **Massage**: control (0N), low load (LL, 1.4N) and medium load (ML, 4.5N)
  - 30 min/session
  - 4 consecutive days

* **Microarray**: 634 genes were differentially expressed with CCL

• Human muscle
  • Massage after exercise-induced damage:
    – Potentiated mitochondrial biogenesis pathway
    – Attenuated production of inflammatory cytokines
    – Activated Focal Adhesion Kinase (FAK) pathway

Anabolic signaling in skeletal muscle

Use of massage as an enhancer of muscle growth
  • Massage may be useful as an intervention in:
    – Elderly with impaired muscle regrowth after atrophy
    – Patients in ICU/hospital who are not able to mobilize
    – Subjects who are otherwise mobility impaired, e.g., after orthopedic surgery
Hind limb suspension: Model for disuse muscle atrophy and muscle recovery

- Hind limb suspension (HS)
  - Tail suspension
  - Atrophy in selected hind limb muscles (soleus, gastrocnemius, plantaris)
  - Animal model for space flight and bed rest
- Reloading (RE)
  - Normal cage ambulation
- Animal model: F344/BN
  - 10 (or 30) months of age

Experimental protocol regrowth: Adult (10 months, F344/BN)

Miller et al., J Physiol 2018
Protein synthesis is elevated with massage in rats during recovery from atrophy

Massage enhances the muscle growth response during regrowth after atrophy

Massage induces DNA synthesis and satellite cell number in regrowing muscle
Satellite cells increased after one bout of massage

Cross-over effect of massage

Aging and Massage

- Decrease in muscle size with aging (sarcopenia) and inhibited regrowth response
- Extracellular matrix changes with age
- Anabolic resistance to mechanical loading?
Muscle regrowth not affected by massage in aged

**Myoblast Protein Synthesis**

<table>
<thead>
<tr>
<th>Time</th>
<th>Control</th>
<th>RE</th>
<th>REM</th>
</tr>
</thead>
<tbody>
<tr>
<td>WB14</td>
<td>0.04</td>
<td>0.05</td>
<td>0.04</td>
</tr>
<tr>
<td>30 mo</td>
<td>0.03</td>
<td>0.02</td>
<td>0.03</td>
</tr>
</tbody>
</table>

**Myoblast Protein Degradation**

<table>
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<tr>
<th>Time</th>
<th>Control</th>
<th>RE</th>
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</tr>
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<tbody>
<tr>
<td>WB14</td>
<td>0.02</td>
<td>0.03</td>
<td>0.02</td>
</tr>
<tr>
<td>30 mo</td>
<td>0.01</td>
<td>0.02</td>
<td>0.01</td>
</tr>
</tbody>
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Lawrence et al., Geroscience, 2020

Muscle stiffness is higher in aged muscle

**Passive Stiffness (Stress/Strain)**

<table>
<thead>
<tr>
<th>Time</th>
<th>10 mo</th>
<th>30 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrocnemius Muscle</td>
<td>0.01</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Hettinger et al., Journals Gerontology, 2021

Damage in aged muscle with higher massage load

Hettinger et al., Journals Gerontology, 2021
Mechanotransduction

Mechanosignaling lower in aged with massage

<table>
<thead>
<tr>
<th></th>
<th>10 months</th>
<th>30 months</th>
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<tbody>
<tr>
<td></td>
<td>CON (n=7)</td>
<td>CCL (n=8)</td>
</tr>
<tr>
<td>ITG4A</td>
<td>3.9 ± 0.3</td>
<td>2.7 ± 0.3</td>
</tr>
<tr>
<td>ITG8B1</td>
<td>30.9 ± 1.7</td>
<td>26.7 ± 3.1</td>
</tr>
<tr>
<td>ITG8B2</td>
<td>20.7 ± 5.8</td>
<td>41.9 ± 6.4*</td>
</tr>
<tr>
<td>ITG8B5</td>
<td>11.6 ± 3.0</td>
<td>5.7 ± 1.5</td>
</tr>
</tbody>
</table>

Van Pelt et al., J Appl Physiol, 2019

Experimental Design

Hettinger et al., FUNCTION, in press
Graph-based cell population classification identifies 17 populations across groups

Mechanotherapy inhibits pro-inflammatory and recovers phagocytosing macrophages

Muscle from females responds differently to massage