

don't rub me the wrong way- WHAT THE MESSAGE ON MASSAGE?

Chris Waters-Banker, MSc, ATC
Doctoral Candidate- ABD



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OUTLINE

- Inflammatory response
 - Neutrophils, Macrophages, and Cytokines
- Current treatment of muscle injury
 - RICE and NSAID use
- Mechanotransduction and manual therapy
 - Influencing microenvironments to promote healing
- Massage
 - Basic Science



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LEARNING OBJECTIVES

Following this workshop participants will be able to:

- Describe the important time points, and key players associated with the inflammatory process
- Describe the effects of early administration of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) following muscle injury
- Describe the concept of mechanotransduction and its application through manual therapies



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INFLAMMATORY RESPONSE

- Treatment of any injury requires a sound understanding of the inflammatory response
 - Incredibly diverse
 - Involves numerous players
 - Temporal in nature



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IMMUNE SYSTEM IN ACTION

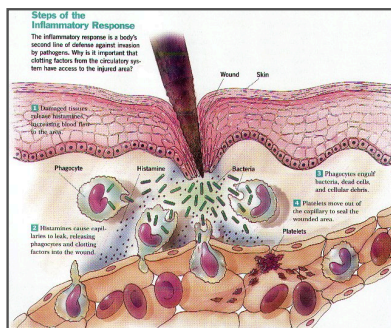


Image from: <http://vdmh.weebly.com>

INFLAMMATORY RESPONSE [KEY PLAYERS]

- Neutrophils: first to arrive
 - Main Job: Break down of tissue through respiratory burst
- Macrophages: second to arrive
 - M1: Pro-inflammatory
 - Main Job: Phagocytose necrotic tissue and debris
 - M2: Anti-inflammatory (resident macrophages)
 - Main Job: Aid in repair and regeneration
- Cytokines
 - Both pro- and anti-inflammatory
 - Main job: induce action of cells



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IMMUNE SYSTEM IN ACTION

- P and E-Selectin activation allows for the adhesion of leukocytes, such as neutrophils, to the vascular wall. These leukocytes will make their way into the tissue via diapedesis

Butterfield et al. JAT 2006

INFLAMMATORY CELL RECRUITMENT

- Disruption of phospholipid bilayer of the cell membrane releases Arachidonic Acid (AA).
- AA is not only a chemoattractant for neutrophils, but as little as 5 μM is a potent stimulator of respiratory burst as well.

INFLAMMATORY CELL RECRUITMENT

Tidball and Villalta. American Journal of Physiology, 2010

PHENOTYPE TRANSITION

Fig. 5. Generalized diagram of the interactions between macrophages and muscle cells during the proliferative stage and differentiation stages of myogenesis in injured muscle. "Th1" and "Th2" represent cells that produce Th1 or Th2 cytokines, that include helper T-cells or macrophages. "M1" and "M2" represent macrophage populations. Solid lines indicate activating effects on target cells. Dotted lines represent deactivating effects.

Tidball and Villalta. American Journal of Physiology, 2010

CURRENT TREATMENT [MUSCLE INJURIES]

- Muscle strains are one of the most common, and repetitive injuries, not only in the athletic population, but the working population as well.
- How are we treating these injuries? And why?
 - Rest
 - Ice
 - Compression
 - Elevation
 - NSAIDs

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ROLE OF NSAIDS

- Non-Steroidal Anti-Inflammatory Drugs are the most common utilized drug in the treatment of inflammatory conditions
- Operate as non-selective Cyclo-oxygenase-1 (COX1)/Cyclo-oxygenase-2 (COX2) or Selective COX1 or COX2 inhibitors.
- These drugs inhibit the action of the enzyme COX1 or COX2 from converting arachidonic acid into Prostaglandin

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ROLE OF NSAIDS

- Disruption of the phospholipid bilayer of cell membranes, promotes the production of arachidonic acid
- Non-Selective versus Selective COX-Inhibitors inhibits action of COX enzymes

Kuby Immunology, 5th Edition

ROLE OF NSAIDS [AFFERENT NERVES]

Mense, Current Pain and Headache Reports, 2003

RECAP

- NSAIDS targeting COX-2 (COX-2 inhibitors):
 - Stop the synthesis of arachidonic acid to prostaglandin-E2 (PGE2)
 - Afferent nerves have specific receptors for PGE2, and are excited with high levels of PGE2 in the extracellular space
 - Excitatory signals travel up the nerve fiber to the soma located in the dorsal horn of the spinal cord
 - Intensity of the signal is interpreted as pain

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THE PROBLEM

- Unfortunately NSAIDS have been shown to significantly affect the regeneration of muscle after injury
- Prostaglandins:
 - Contribute to various stages of myogenesis
 - Synthesized by regenerating muscle
 - Involved in myoblast proliferation, differentiation, and fusion
- In other words: they play a very important role in muscle growth.
- AND they are potent chemoattractants for inflammatory cells!!

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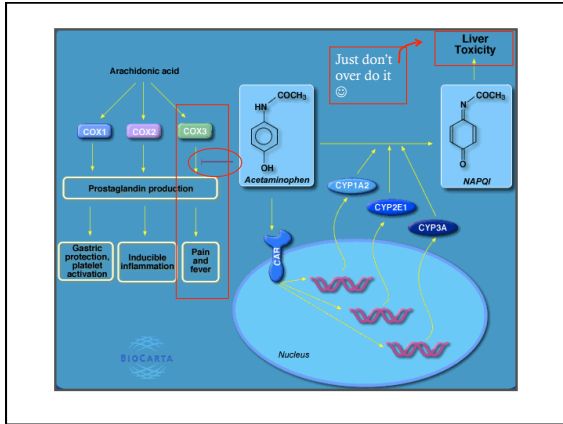
NSAIDS AND MUSCLE REGENERATION

- Bondensen et al. The COX-2 Pathway is Essential During Early Stages of Skeletal Muscle Regeneration. *Am J Physiol Cell Physiol.* 287; 2: C475-83. 2004
- Cross-sectional area of regenerating myofibers is decreased significantly (20-33%) by COX-2 inhibitor
 - Decrease is seen up to 3 weeks post injury
- COX-2 inhibitors appear to not effect the cross-sectional area of un-injured fibers.
 - Suggesting no role of Prostaglandins on regular maintenance
- COX-2 appears to play a BIG role in EARLY regeneration of muscle following injury

SO WHAT CAN WE DO

- COX-3 is a third isoform of the cyclo-oxygenase group that is largely associated with the spinal cord in terms of:
 - Pain
 - Fever
- COX-3 does not play a role in inflammation

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MECHANOTRANSDUCTION

- Mechanotransduction is the transformation of a mechanical stimulus into a chemical signal.
- Mechanical deformation of a tissue, or cell itself, results in a signaling cascade of events

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MECHANOTRANSDUCTION

Trotter and Purslow. Journal of morphology, 1992

- Muscle fiber and Cytoskeleton are very interconnected, influencing one another.

Image from: www.ccbm.jhu.edu

IMPORTANCE

- Massage is an ancient manual therapy technique dating back to as early as 2598 BC (Goan GC, 1994)
- Massage is sought after for the relief of:
 - Spasm (Herman 2012, Myklebust 2007)
 - Pain (Herman 2012, Myklebust 2007)
 - Swelling (Herman 2012, Myklebust 2007)
 - Disease Prevention (Hawk 2012)
 - Improved Immune Function (Hawk 2012)
 - Relaxation (Herman 2012, Myklebust 2007)

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IMPORTANCE

- Americans make more than 160 million visits to alternative medicine practitioners annually to seek relief of musculoskeletal weakness and pain
 - Spending an upwards of 11.9 billion dollars
 - Majority of which is OUT OF POCKET
 - \$62 mean for each visit to a massage therapist

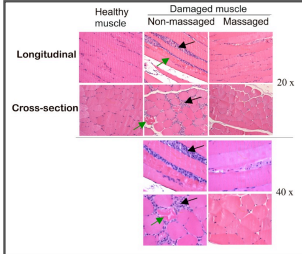
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IMPORTANCE

- Massage is one of the first manual therapies to be integrates alongside conventional medicine in hospitals around the US (Herman 2012, Myklebust 2007)
- Although it has recently gained a considerable presence in the health care system, the evidence in support for massage has remained mostly anecdotal.

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GROWING EVIDENCE [CELL INFILTRATION]



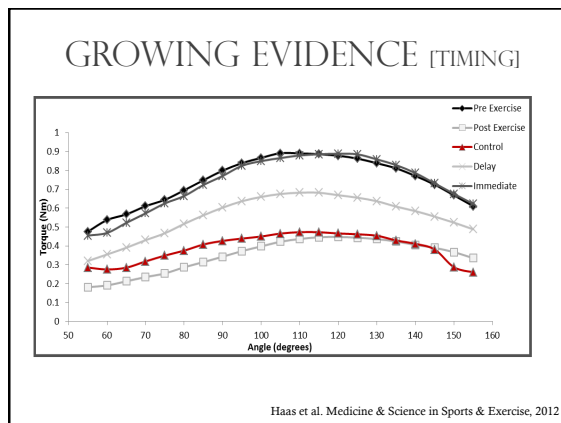
Healthy muscle Damaged muscle
Non-massaged Massaged

Longitudinal
Cross-section

20 x
40 x

- Results showed an attenuation of the inflammatory response following massage administered to rabbit tibialis anterior muscle.
 - Immediately post eccentric exercise
 - 30 minutes
 - 4 consecutive days

Butterfield et al. Medicine & Science in Sports & Exercise, 2008

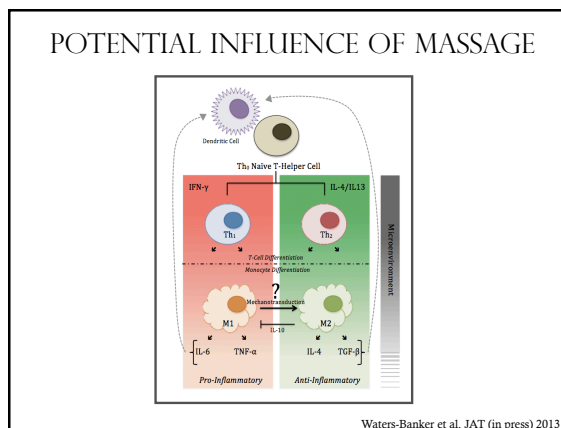


IMPORTANCE [HUMAN WORK]

- Human biopsies exercised/massaged quadriceps showed an attenuation of pro-inflammatory cytokines (Crane 2012)
 - TNF- α , IL-6

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MASSAGE

- The question remains: What influence does massage have on the local tissue?
- And what influence does massage have on the inflammatory response?
- Food for thought: Can the proper mechanical compression of muscle tissue influence potentially beneficial immunomodulatory effects that promote macrophage phenotype change, and early transition into the repair and regeneration phase?
 - Application of load, and technique

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THINGS TO THINK ABOUT [MESSAGE: CLINICAL APPLICATION]

- Numerous indications and contraindications exist
 - Evidence to support?
- Environment: Acute or chronic?
 - Inflammation, damage, pain or...
 - Long standing injury
- What is the goal of the treatment?
 - Attenuate/modulate inflammation or...
 - Induce inflammation?

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FINAL THOUGHTS

- The inflammatory response exists for a reason
- The goal is not to abolish it, but rather **attenuate/optimize** it in hopes to restrict uninhibited secondary hypoxic events
- Manual therapies, such as massage, may provide practitioners the opportunity to create an optimal environment for healing, promoting a quicker recovery of structure and function, absent of pharmaceuticals

THANK YOU!

- **My committee @**
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