Inflammation: Friend or Foe?

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Outline

1. Why this topic?
2. Muscle regeneration
3. Inflammatory Process
4. Impact of NSAIDs
5. Impact of Ice, heat, ultrasound

Why?
Why??

• High number of PT’s directly recommend NSAIDs¹
  — Studies suggest knowledge is inadequate
• <1/2 of PT’s believed that NSAIDs should be withheld during first few days after injury
  — Inflammation has BENEFICIAL effects
  — Lack of knowledge regarding the effect of inflammation on tissue healing
• Regenerative Medicine is growing
  — Regenerative Rehabilitation???
Muscle Regeneration

- Myofibers are Postmitotic
  - Muscle cells themselves cannot divide
- Satellite cells (adult muscle stem cells) are responsible for regeneration
  - No satellite cells, no regeneration
- Can get increase in muscle fiber size (hypertrophy) without satellite cells

Muscle Regeneration

- After injury, satellite cells are activated and become myoblasts
  - Extensive proliferation during first few days of injury
- At 3 to 7 days, proliferation stops and myoblasts differentiate and fuse to the myofibers then form myotubes
- After day 7, myotubes grow to form new mature myofibers
**Muscle Regeneration**

- The inflammatory process plays a KEY role in satellite cell function

**Inflammatory Process**

- Damage to blood vessels and tissue starts the inflammatory process
  - Mast cells are released
    - STIMULATE proliferation of SATELLITE cells
    - Inflammatory cells coordinate muscle healing
  - Early inflammatory mediators stimulate vasodilation and increase vascular permeability
    - Allows for infiltration of inflammatory cells into the tissue
Inflammatory Process

- Neutrophils show up first (first 72 hours)
  - Break down cell debris to clean the injured zone
  - Can induce secondary damage to the intact living tissue
  - Depends on severity of injury
  - Release cytokines
    - Stimulates inflammatory cell recruitment
    - Stimulates myoblasts
- M1 Macrophages also appear during the first 72 hours
  - Break down muscle cell debris
  - Release pro-inflammatory factors
    - Stimulates inflammatory cell recruitment
    - Stimulates myoblasts

Inflammatory Process

- ~48 hours after muscle injury, macrophages change from M1 phenotype to M2 phenotype
  - Release anti-inflammatory molecules and growth factors
  - Stops myoblast proliferation
  - Stimulates myoblast differentiation, fusion, and myofiber growth
  - This change is essential in muscle regeneration as well as resolving inflammation
  - Depleting macrophages during acute injury phase leads to defective muscle healing, persistent necrotic tissue, and increased fat accumulation (mice)

Inflammatory Process

- Pro-inflammatory lipid mediators start to become replaced by anti-inflammatory mediators
  - Also essential to muscle regeneration and resolution of inflammation
  - COX-2 essential to this process
    - It promotes inflammation in the early stages and helps with the resolution in later stages
    - COX-2 is blocked by NSAIIDs
Impact of NSAIDs

• Acute inhibition of COX-2 in mice has shown:
  – Diminished proliferation, differentiation, and fusion of satellite cells
  – Impaired skeletal muscle growth, delayed skeletal muscle repair, and increased fibrosis

Impact of NSAIDs

• Acute inhibition of COX-2 in humans has shown:
  – No significant improvement in outcomes when NSAIDs added to physical therapy treatment following acute hamstring injury at days 1, 3, and 7 (meclofenamate and diclofenac)
    • VAS rating, thigh circumference (swelling), isokinetic muscle performance testing
    • Placebo group had significantly less pain at day 7 in more severe injuries

Impact of NSAIDs

• Acute inhibition of COX-2 in humans has shown:
  – Suppression of satellite cells in the vastus lateralis following eccentric exercise after 8 days (Indomethacin)
    • 200 maximal eccentric contractions in to an isokinetic dynamometer
  – No significant difference in MVC
  – No difference in muscle soreness
    • Pressure with a probe
  – Increase in inflammatory cells at day 8 in the indomethacin leg
    • Not statistically significant (p = 0.9)
Impact of NSAIDS

- Acute inhibition of COX-2 in humans has shown:
  - Suppression of satellite cells in the vastus lateralis following a 36 km run induced injury at day 8 (Indomethacin)
  - Increase in satellite cells in placebo group
  - No increase in NSAID group

Impact of NSAIDS

- Immobilization of a limb for 2 weeks in elderly patients followed by 6 weeks of retraining showed:
  - NSAID consumption did not affect muscle mass and strength (Ibuprofen 1200 mg)
  - Did not significantly affect circulating levels of inflammatory markers

What about ice???

- Exercise stimulates intramuscular inflammation and increases satellite cell activity\(^2\)
  - Increased amount of neutrophils, macrophages, and increased gene expression of cytokines and neurotrophins
  - Response was no different between cold water immersion or active recovery groups
  - “Cryotherapy does not substantially alter local or systemic inflammatory responses to exercise induced muscle damage”
  - Many studies that demonstrate decrease in inflammation were performed in mice (muscles are more superficial)
What about ice???

- Muscle mass increases significantly following training in both active recovery and cold water immersion³
  - Significantly less of an increase in cold water vs. active recovery
- Leg press strength, knee extension strength, and maximal isometric torque gains were significantly higher in active recovery group
- Significant gain in satellite cell count after exercise in active recovery group only

What about Heat???

- One time application of 42°C hot pack 5 minutes after crush injury to extensor digitorum in mice for 20 minutes:
  - Facilitated migration of macrophages⁴
  - Facilitated proliferation and differentiation of satellite cells
  - Muscle cross sectional area larger at 14 and 28 days in the heat group vs. non heat group

What about Heat???

- Heating of myoblasts in vitro showed⁵:
  - Significant upregulation of myofibrillogenesis genes
  - Increased differentiation of myoblasts
- Heating the lower extremities in humans has shown⁶:
  - Promotion of key angiogenic mediators in skeletal muscle
What about Ultrasound?

- Low intensity pulsed ultrasound following muscle injury in mice was found to (daily 3 minute sessions, 1 Mhz, 0.4 W/cm², 1:5 pulsed mode, for 7 days):\(^5\)
  - Decrease number of neutrophils and macrophages within first day
  - Decrease total macrophages and M1 macrophages after 2 days
  - Increase number of M2 macrophages after 2 days
  - Helps to resolve inflammatory process?
  - Decrease total number of macrophages after days 3-7
  - Don’t know how this affected muscle regeneration

What should we do???
Questions?????

References


