Application of neurobiological pain mechanisms to an orthopaedic injury

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Outline : 1) Review neurobiological pain mechanisms, 2) Application of pain mechanisms to an animal model, 3) Application of pain mechanisms to a human model, 4) Open discussion

1) Pain mechanisms

– *Nociceptive neuron*: A central (i.e. nociceptive pathway) or peripheral (i.e. nociceptor) neuron of the somatosensory nervous system that is capable of encoding noxious stimuli – IASP

Pain definitions: http://www.iasp-pain.org/Taxonomy

- *Nociceptive pain*: Pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors

Injury and Nociceptors

– Peripheral nociceptors send signal to CNS nociceptive pathway
– CNS modulates signal to result in an output
  • Pain (cortex)
  • Alterations in motor output (motor reflex)
  • Alterations in autonomic function
  • Alterations in mood and affect
– Activation of silent nociceptors
– Sensitization to mechanical, thermal and chemical stimuli

Sensitization

• Occurs after tissue injury and pain
• Neurons become more excitable
  – Nociceptors fire more frequently, respond in exaggerated way to stimuli
  – Non-nociceptors (touch, proprioception) do not sensitize
• Definition: Increased responsiveness of nociceptive neurons to their normal or subthreshold afferent input (IASP)

Peripheral vs. Central Sensitization

• Definition: Increased responsiveness of nociceptive neurons in the [peripheral/central] nervous system to their normal or subthreshold afferent input (IASP)
• Peripheral sensitization can be addressed through peripherally-direct treatments
  – Ex. Ice to reduce inflammation with bursitis
• Central sensitization
  – May be addressed through peripherally-directed treatments if primarily driven by peripheral sensitization
  – Otherwise, treatments need to address factors perpetuating sensitization within the CNS

Definitions

• Acute pain
  – Pain associated with tissue damage or occurs in response to tissue injury
  – Protective- it is there for a reason
• Chronic Pain
  – Pain that outlasts normal tissue healing time (~3 months) or after noxious stimulus is no longer active
  – Otherwise, treatments need to address factors perpetuating sensitization within the CNS

Central sensitization

- Accepted component of many chronic pain conditions
- Commonly studied in basic science and clinical pain research
  - Methods to directly and indirectly assess central excitability in basic science research
  - Methods to indirectly assess central excitability in clinical research

Ex. Temporal Summation

- Increased pain to a repetitive stimuli
- Reflects excitability of central nervous system

Noxious ≠ Painful

- Noxious: Stimulus that is harmful or has the potential to harm; Activates nociceptors
- Pain: An unpleasant sensory and emotional experience associated with actual or potential tissue damage

Definitions

- *Hyperalgesia*
  - Increased pain to a noxious stimuli
- *Primary hyperalgesia*
  - Occurs at the site of tissue injury
  - Reflects changes in primary afferent activity
  - Mediated by changes in PNS
- *Secondary hyperalgesia*
  - Occurs in an area surrounding the injury
  - Reflects changes in central neurons
  - Mediated by changes in CNS
- *Referred Pain*
  - Pain outside the area of injury
  - Within the same dermatome or spinal segmental innervation
- *Allodynia*
  - *Painful response to an innocuous stimuli*

2) Unilateral Intramuscular Injection of Acidic Saline Produce a Bilateral, Long-Lasting Hyperalgesia. Sluka KA, Kalra A, Moore SA. Muscle Nerve, 2001.

- Repeated unilateral acidic injections to gastrocnemius muscle in a rat model
- Hyperalgesia defined by a lower withdrawal threshold (bending force) to pressure of Von Frey Filaments
- Bilateral mechanical hyperalgesia in acidic-injection group compared to saline-injected control group
- Hyperalgesia dependent on sufficient noxious dose and proximity in time
  - pH 4.0 induced greatest hyperalgesia
  - Injection intervals of 2-5 days apart produced hyperalgesia

- Critical threshold and window where reinjury can induce persistent (~4 weeks in rat model) hyperalgesia
- Hyperalgesia not related to tissue damage
  - Histology of gastroc similar between acid and saline injection groups
- Hyperalgesia not maintained by continued input of peripheral nociceptors site of injury
  - Unilateral dorsal rhizotomy (cut dorsal roots of L4-S1) and lidocaine injection had no effect on contralateral mechanical hyperalgesia

- Evidence of central sensitization:
  - Contralateral decrease in withdrawal threshold
  - Elimination of sensory input from site of injury (lidocaine injection) and afferent input from L4-S1 (dorsal rhizotomy)
  - Follow-up paper: Chronic hyperalgesia induced by repeated acid injections in muscle is abolished by the loss of ASIC3, but not ASIC1. Pain, 2003.

• Clinical implications:
- Biomedical model not always sufficient to treat pain
  - Treatment for chronic musculoskeletal disorders target peripheral pain sources
  - Yet chronic pain may be maintained with the central nervous system (sensitized nociceptive pathway)

Biopsychosocial Model
- Alternative to the Biomedical Model
- Takes patient and patient experiences into account
- Recognizes that pain is influenced by psychosocial factors

Psychosocial Factors
• Pain catastrophizing: Thoughts that magnify the threat of pain
- *Pain Catastrophizing Scale*
  - 13-item, 5-point likert scale
  - Score ranges from 0 (low) to 52 (high)
  - Indicate to what degree have catastrophizing thoughts feelings during pain

• Kinesiophobia: Fear of movement-related injury
- *Tampa Scale of Kinesiophobia*
  - 17-item, 4-point likert scale
  - Score ranges from 17 (low) to 68 (high)
  - Indicate level of agreement with statements indicating fear of movement

<u>3) Application of neurobiological pain mechanisms to an orthopaedic injury</u>
<u>- Preliminary Analysis-</u> Chimenti RL, Hall MM, Phisitkul P, Merriwether EN, Yack JH, Sluka KA

Ongoing Clinical Mechanistic Study
- Insertional Achilles tendinopathy
- Imaging often demonstrates tissue damage and radiographic abnormalities
- Conflicting evidence on correlation between tendon/bone pathology and pain

Motivation
- IAT does not respond well to conservative care (Nicholson, 2007; Kader, 2002), and then referred to other peripherally directed treatments
- Approximately 40% of IAT patients will continue to report residual pain more than 2 years after surgery (Maffulli, 2008; McGarvey 2002)
- Quickly emerging field of research supporting that central sensitization contributes to tendinopathy pain (Plinsinga, 2010; Tompra, 2015)

Hypothesis
- Pain mechanisms mediated by the CNS contribute to the persistence of IAT pain

Methods
- Case-control study: preliminary analysis of data on 9 participants with AT

Summary of Findings

• While preliminary findings need to be examined in a larger sample:
  - Some centrally mediated pain mechanisms (Pain catastrophizing, Kinesiophobia) were relieved by an anesthetic injection to the Achilles tendon insertion
  - Other centrally mediated pain mechanisms (PPT, CPM, Temporal summation) were unchanged by an intervention targeting the peripheral pain source
• Pain can limit participation in exercise
  – 6/9 often do not exercise because of pain
• Psychological factors can limit participation in exercise
  – Majority of participants have a slight to moderate degree of pain catastrophizing
  – Majority of participants have some kinesiophobia
  – 1/3 of sample had depression

Clinical implications

- Limitations: Small sample size, preliminary analysis, specific to chronic Achilles tendon pain, need to compare findings to healthy controls
- *In this sample of patients with chronic Achilles tendinopathy*:
  • Interventions targeting PNS may be effective at reducing pain catastrophizing and kinesiophobia
  • Need an intervention targeting both PNS and CNS

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