Animal Models of Musculoskeletal Pain

Kathleen A. Sluka, PT, PhD
Associate Professor
Physical Therapy and Rehabilitation Science Graduate Program
Neuroscience Graduate Program
Pain Research Program
University of Iowa
Iowa City, IA 52242
Goals

• Animal models of musculoskeletal pain
  – Pain-like behaviors
  – Neuronal changes

• Animal models of back pain
  – Pain-like behaviors
  – Neuronal changes
  – Potential mediators
Pain Generators in Low Back

- Muscle
- Facet Joint
- Ligaments
- Intervertebral disc
- Nerve root
Animal Models of Musculoskeletal Pain

- **Inflammatory** (Mense-muscle, Schaible and Schmidt-joint)
  - Injection of carrageenan and/or kaolin
  - Produces acute and chronic inflammation
  - Produces mechanical and heat hyperalgesia for 8 weeks

- **Non-inflammatory** (Sluka-muscle)
  - Two injections of acid into the muscle
  - No peripheral tissue damage
  - Produced mechanical hyperalgesia for up to 4 weeks
Models

Saline/Carrageenan

Mechanical and heat stimuli

Acidic Saline Model

- No heat hyperalgesia (Sluka et al., 2001)
- No motor deficits (Sluka et al., 2001)
- Minimal to no tissue damage (Sluka et al., 2001)
- pH decreases to a maximum of 6.0 (with 4.0) (Sluka et al., 2001)
- Ipsilateral lidocaine or unilateral dorsal rhizotomy has no effect on the contralateral hyperalgesia (Sluka et al., 2001)
- Hyperalgesia reduced by intrathecal opioids, NMDA and AMPA/KA antagonists (Sluka et al., 2002, JPET 302: 1146-1150; Skyba et al., Pain, 98: 69-78, 2002)
Animal Models of Low Back Pain

- Does injury to the disc produce pain?
- Does disc degeneration produce pain?
- Does herniation of the disc produce pain?
Neuronal changes after deep tissue injury

- Sensitization of peripheral nerves
  - Increased response to movement
  - Increased spontaneous activity

- Sensitization of central neurons
  - Increased response to joint movement
  - Increased response to cutaneous stimulation
  - Increased size of receptive field

Innervation of Intervertebral Disc

Freemont et al., 1997, Lancet 350: 178-181

Aoki et al., The Spine Journal 4: 275-280, 2004
Innervation Patterns for Back
see Aoki et al., Life Sciences 74: 2627-2642

Innervation of:

L5-L6 IVD: T13-L6
L5-L6 facet: L1-L5
Muscle L5 level: L1-L6
Skin L5 level: L1-L2
SI Joint: L3-S3
Summary

– Innervated by DRG from multiple segments
– Increased innervation in painful discs and innervation of new areas
– Injury to disc causes mechanical hyperalgesia
– Nucleus Pulposis applied to nerve causes mechanical hyperalgesia
– Nucleus Pulposis + Compression increases hyperalgesia
– Injury to nerve causes hyperalgesia
References

• Ohtori et al., J Pain, 5:385-391
• Kawakami et al., in Press
• Onda et al., 2005, Spine 30: 188-193
• DeLeo JA
Pathomechanism of radicular pain

- Epidural space
- Nucleus pulposus
- Anulus fibrosus
- Nerve root
- DRG

Inflammation leads to:
- Chemicals: PLA₂, NO, etc.
- Cytokines: PLA₂, NO, etc.

Axons in DRG lead to hyperalgesia, pain

Kawakami
Inflammatory Cytokines

- Herniated discs release inflammatory cytokines: IL-1β, IL-6, TNF, prostaglandins

- Increase mechanical sensitivity of the receptive field by IL-1β and TNF after application to sacral roots

- Blockade of TNF reduces low back pain in humans
  - Tobinick et al., Swiss Medical Weekly, 2003, 133: 170-177
Summary

• Low back pain
  – Inflammatory component
  – Cytokines and prostaglandins likely are key factors that result in local and radicular pain

• Future studies aimed at deciphering mechanisms that produce low back pain, and distinguish this from radicular pain
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