Endogenous Peripheral Opioid Analgesia Systems

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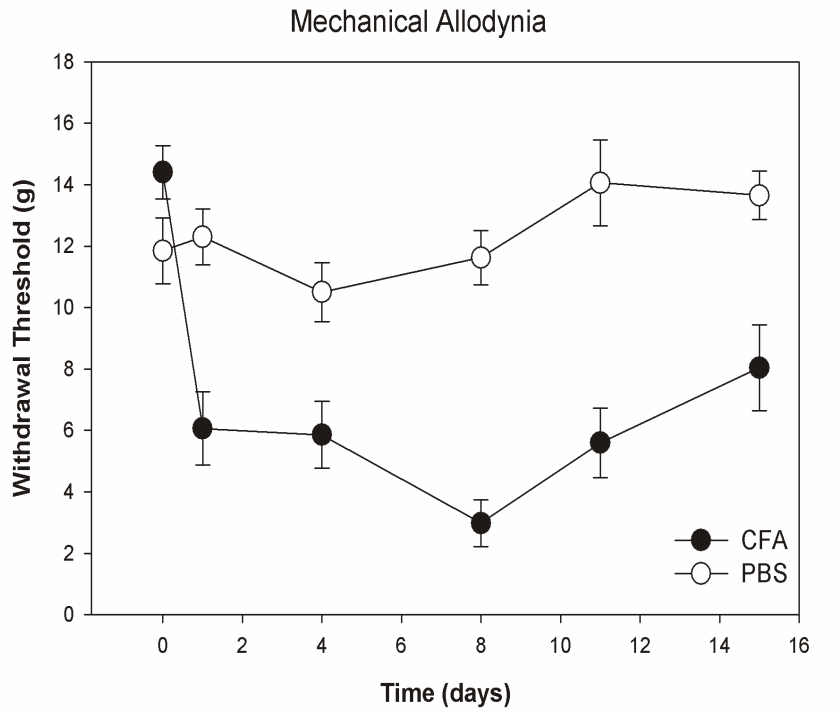
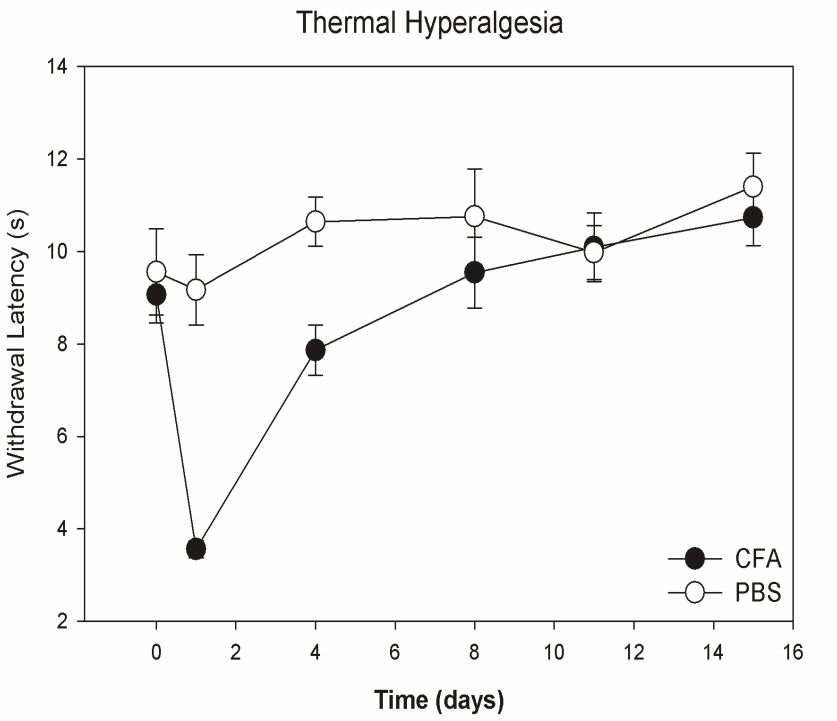
CFA Model of Cutaneous Inflammatory Pain

- Complete Freund's Adjuvant injected into plantar surface of hind paw
- Calor, dolor, rubor, and tumor

Behavior

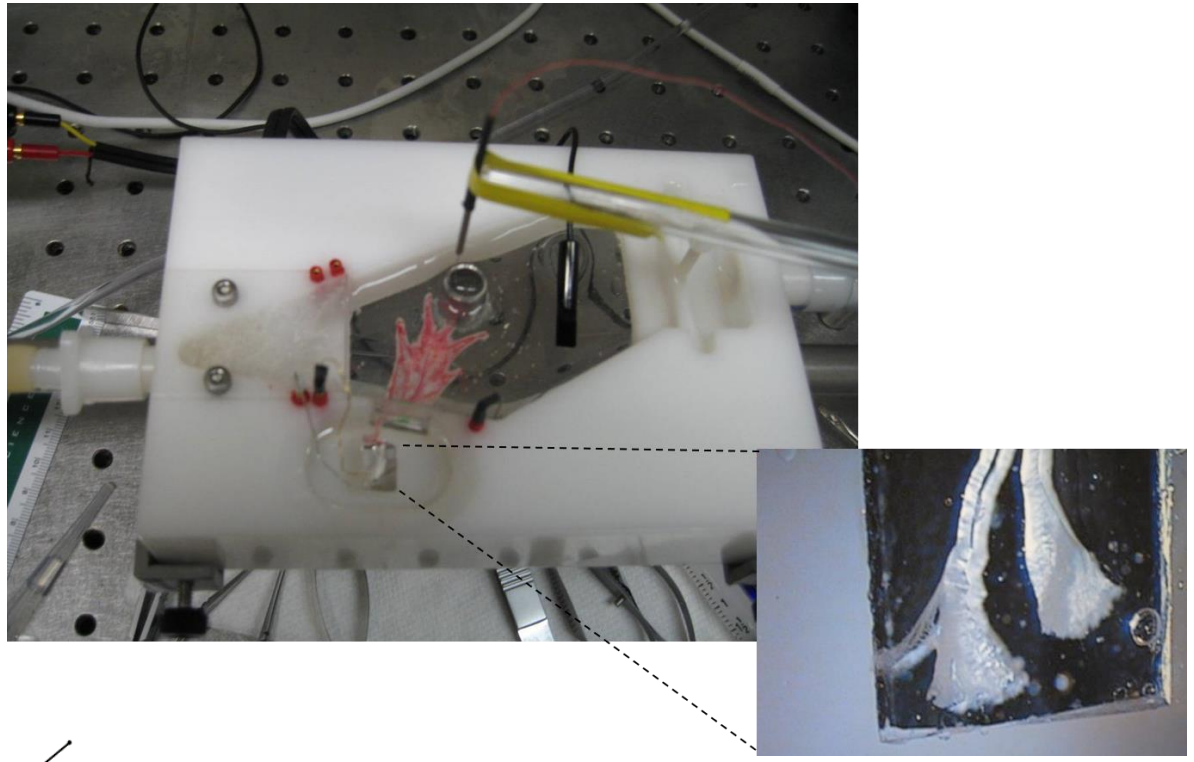


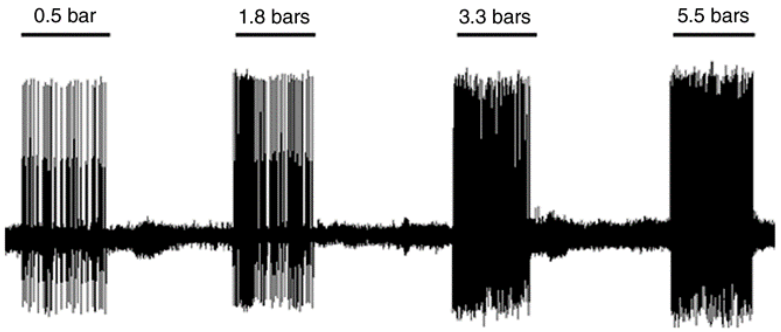


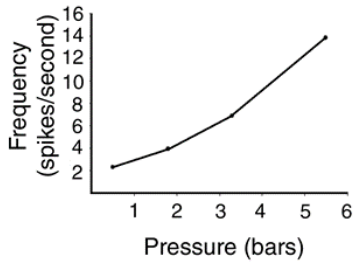
CFA Model of Cutaneous Inflammatory Pain

- 18 hours after injection, skin-nerve removed for *in vitro* recording
- record electrical activity of single afferent fibers

Electrophysiology



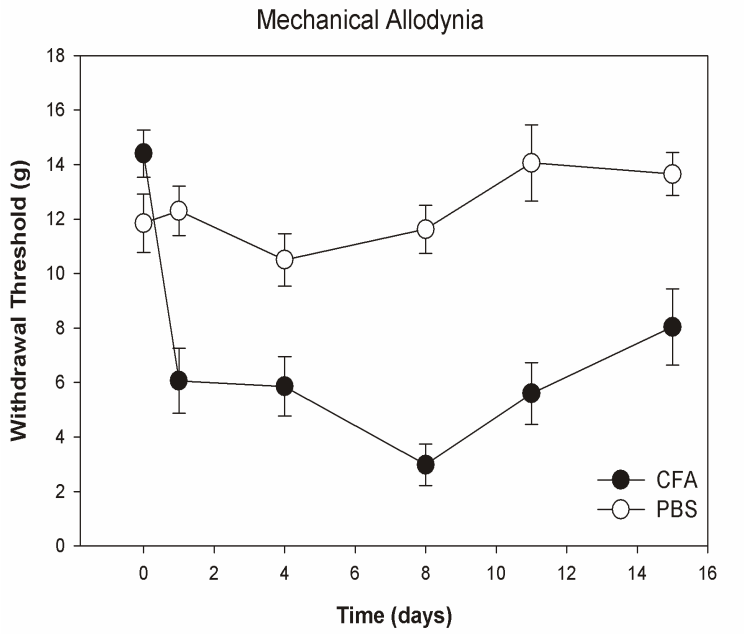


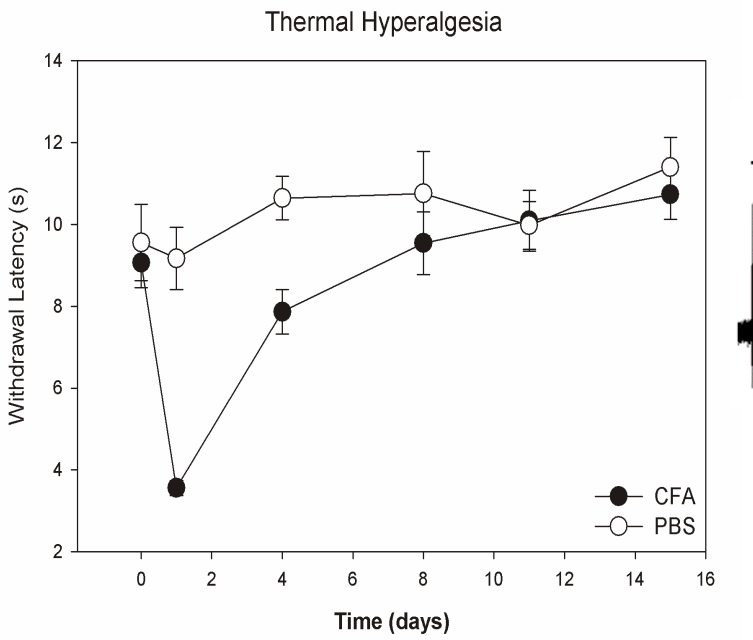


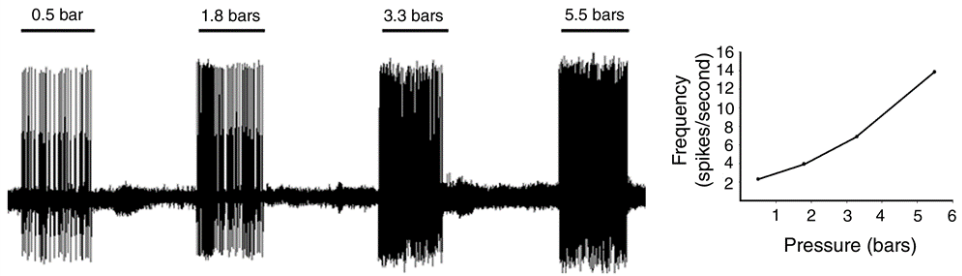
CFA Model of Cutaneous Inflammatory Pain

Afferent Fibers (nociceptors) Innervating Inflamed Skin

- Spontaneous activity increased
- Mechanical thresholds reduced
- Responses to noxious mechanical stimuli increased
- Heat thresholds not changed
- Responses to noxious heat increased

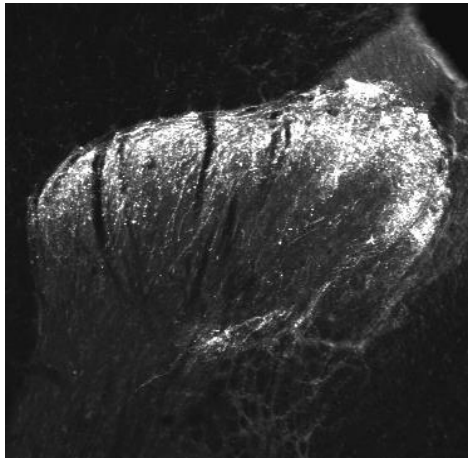


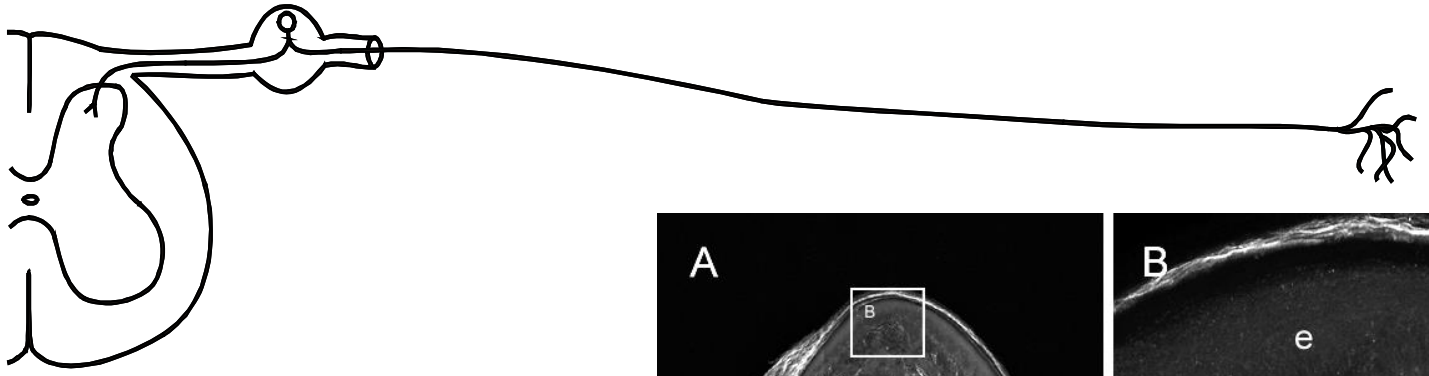


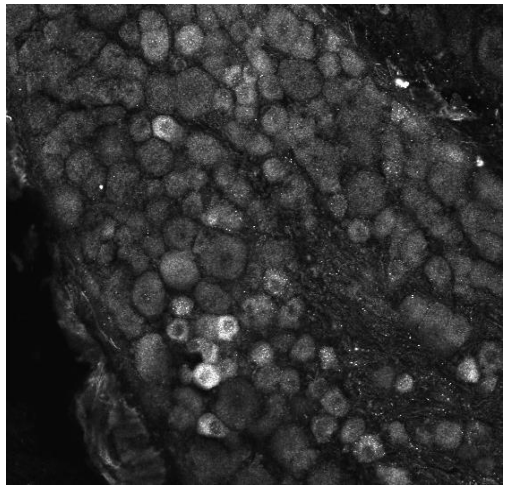


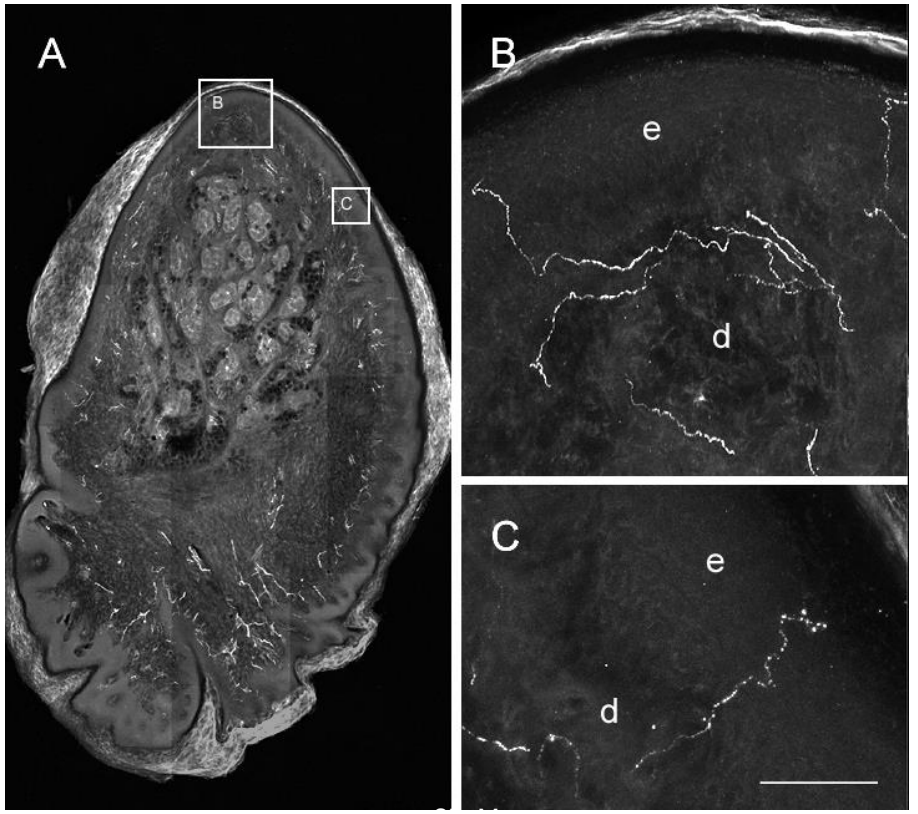
Opioid Receptors Are Expressed by Sensory Neurons

Delta opioid receptors (DOR) in normal tissue



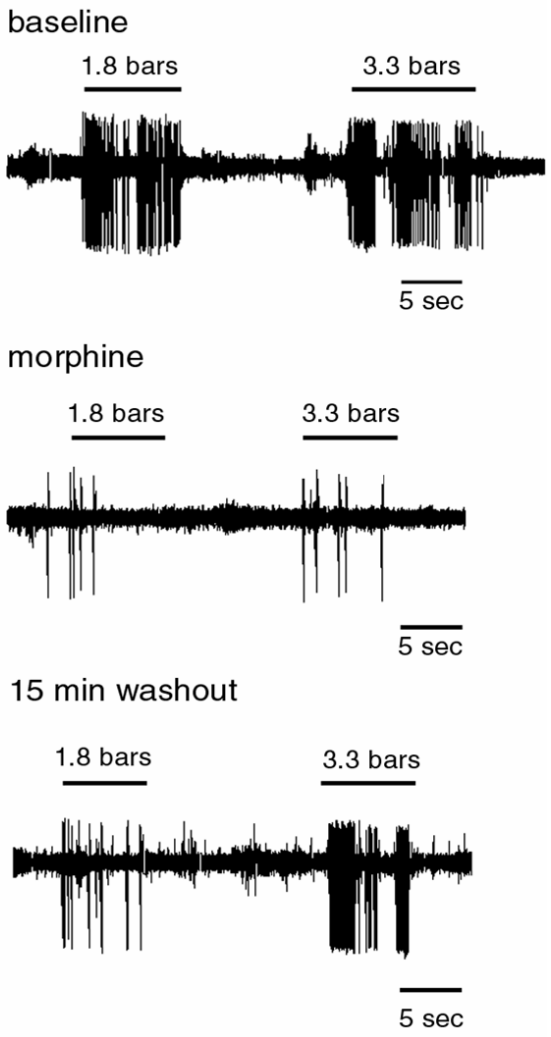




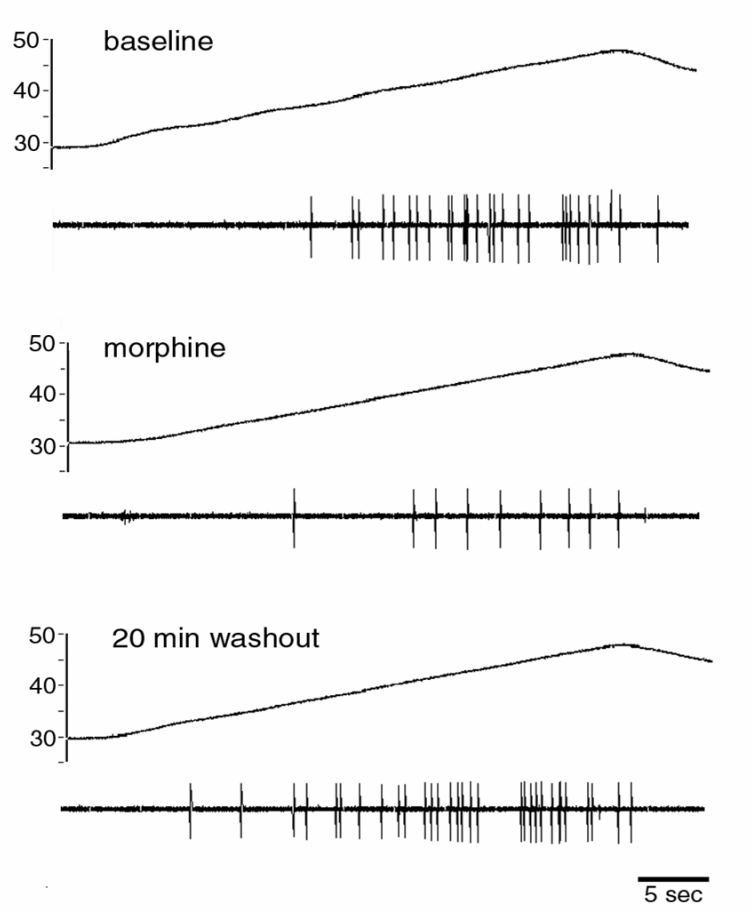


Wenk and Honda 1999

Effects of Morphine Sulfate: inflamed skin (18 hr)



Mechanical

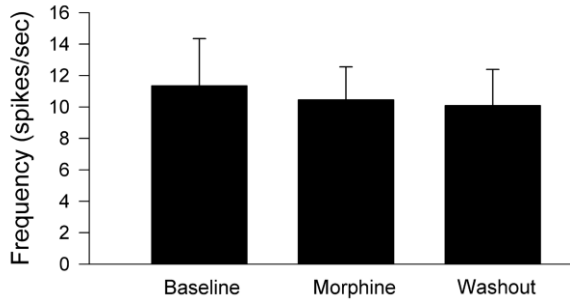


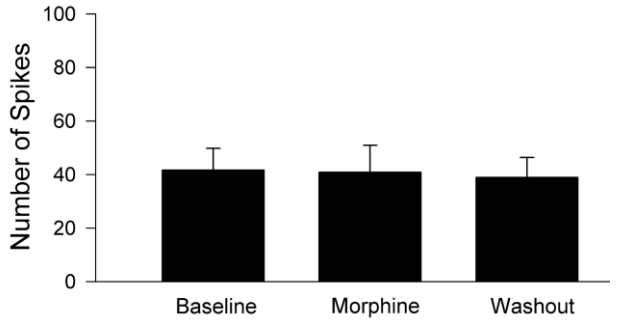
Heat

Wenk et al., J. Neurophysiol 2006

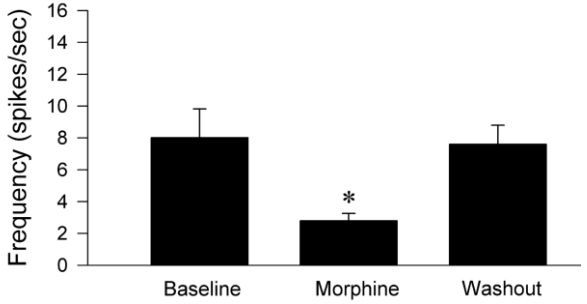
Effects of Morphine Sulfate: population

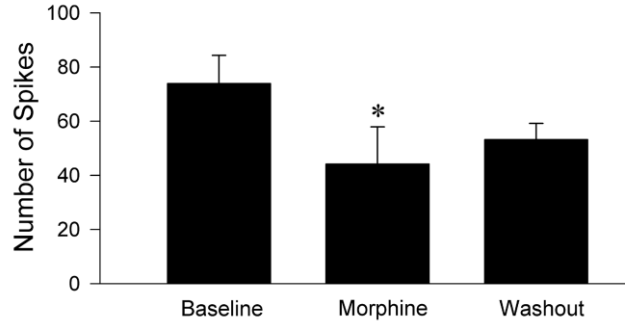
Normal



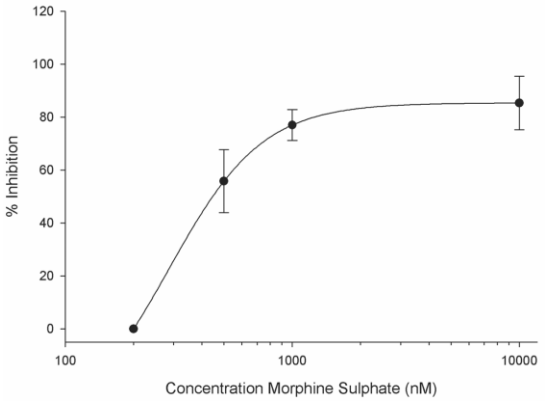


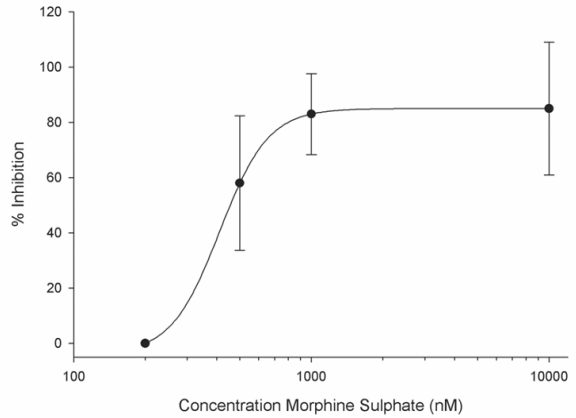
Inflamed





Inflamed



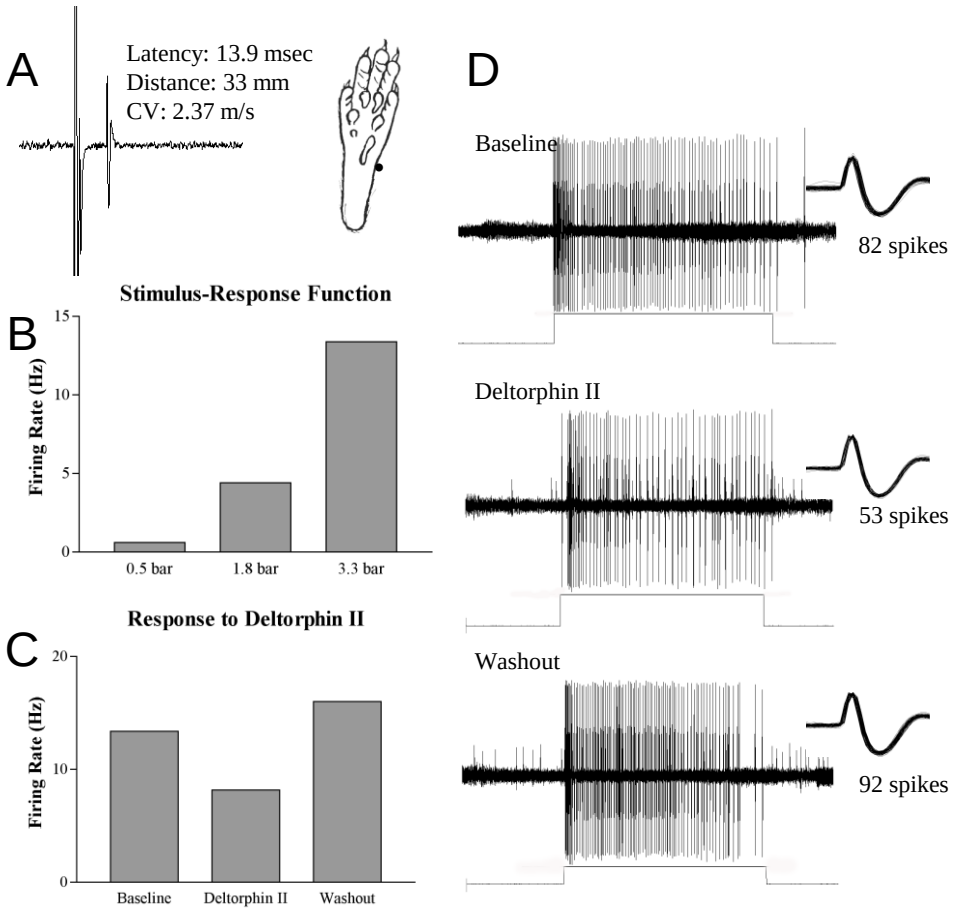


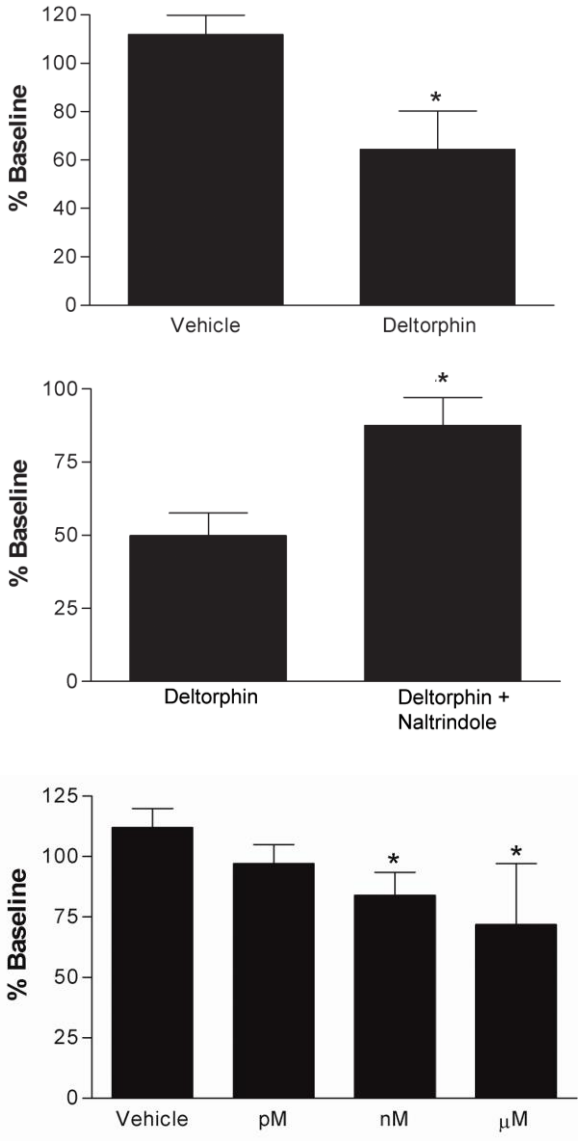
Mechanical

Heat

Wenk et al., J. Neurophysiol 2006

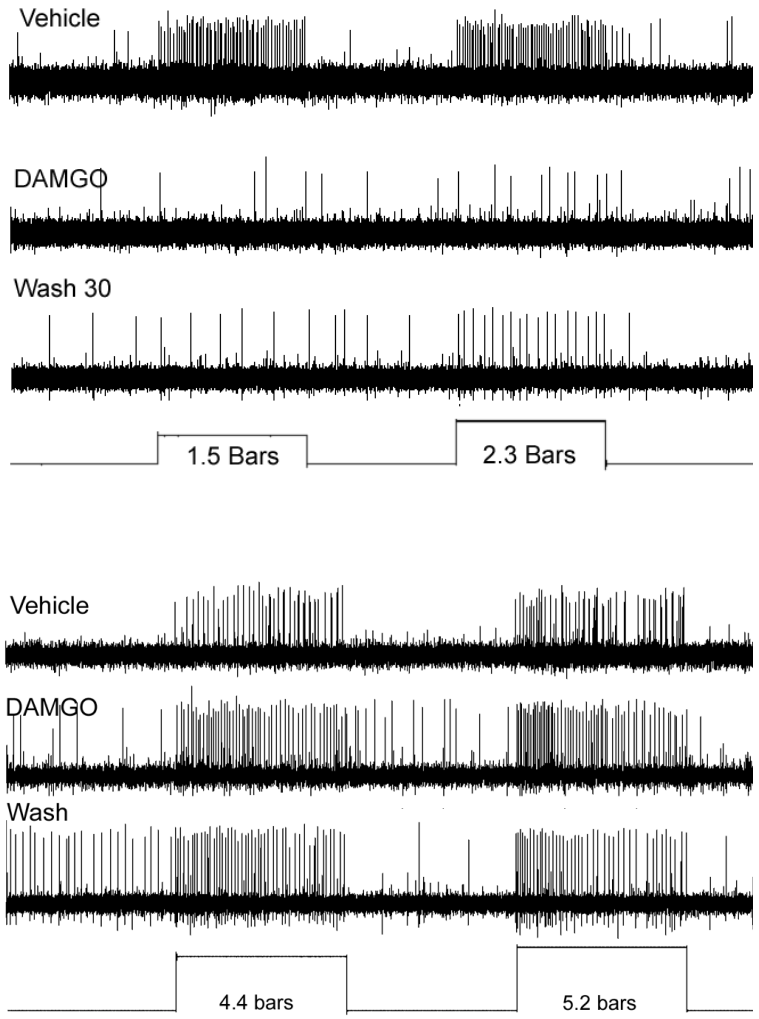
Delta Opioid Receptor (DOR): deltorphin II (18 hrs CFA)

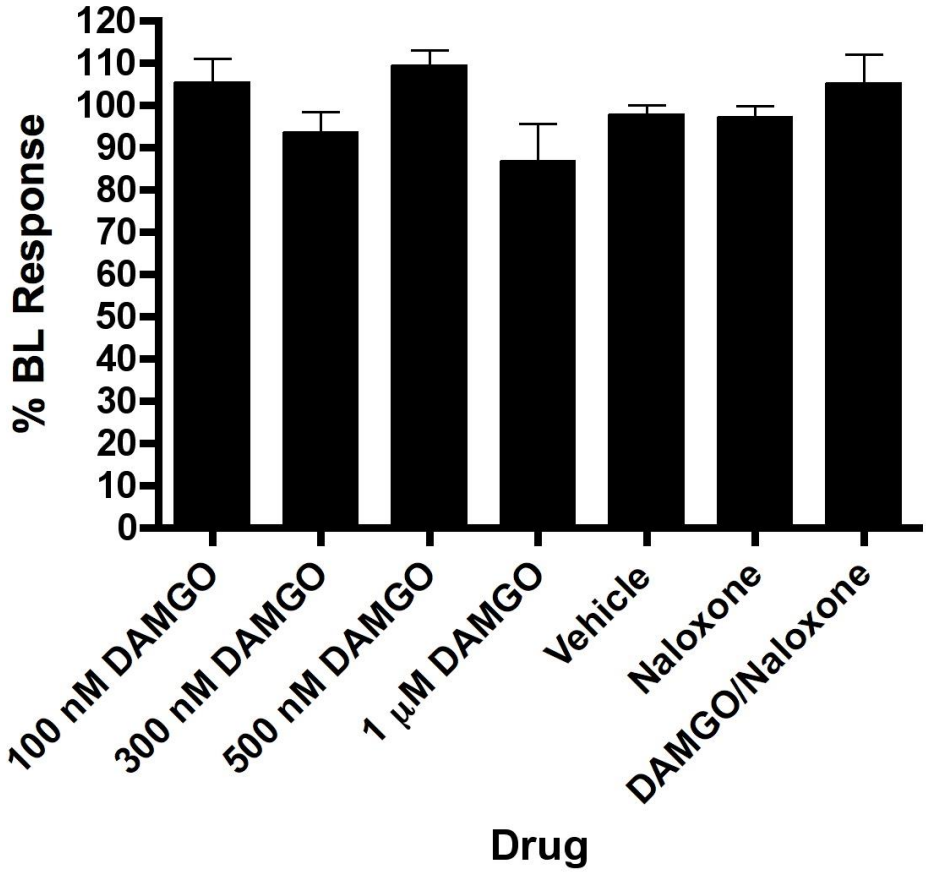




Brederson and Honda. 2016

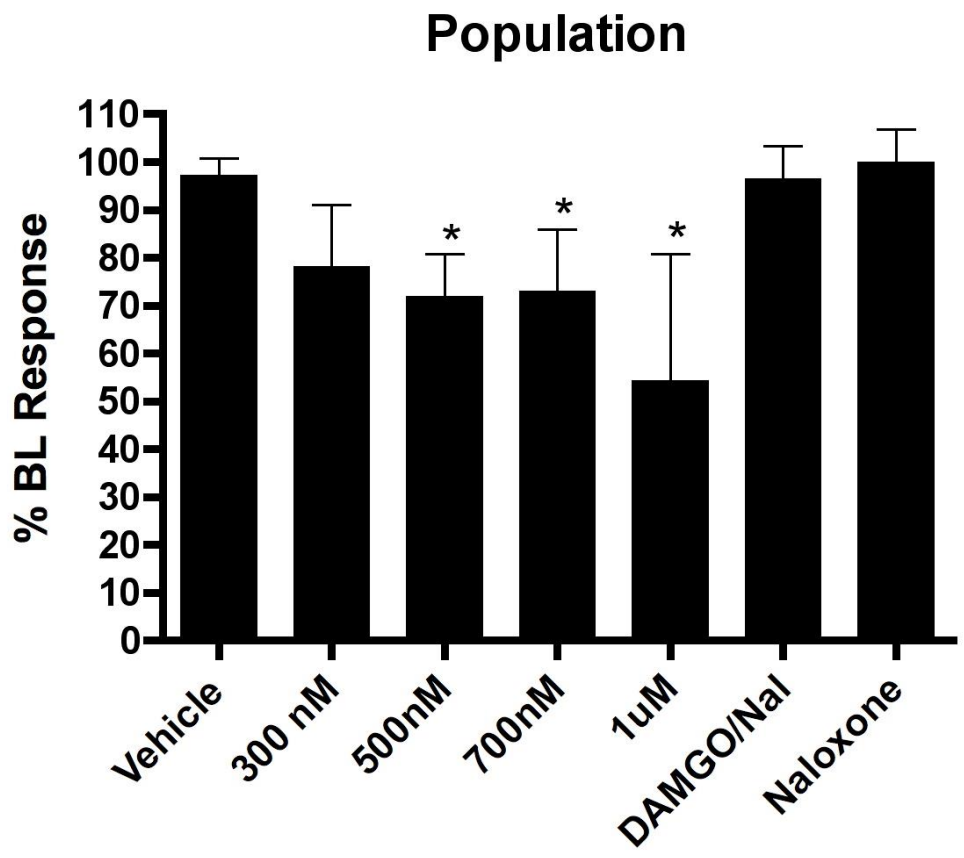
Mu Opioid Receptor (MOR): DAMGO (18 hrs CFA)

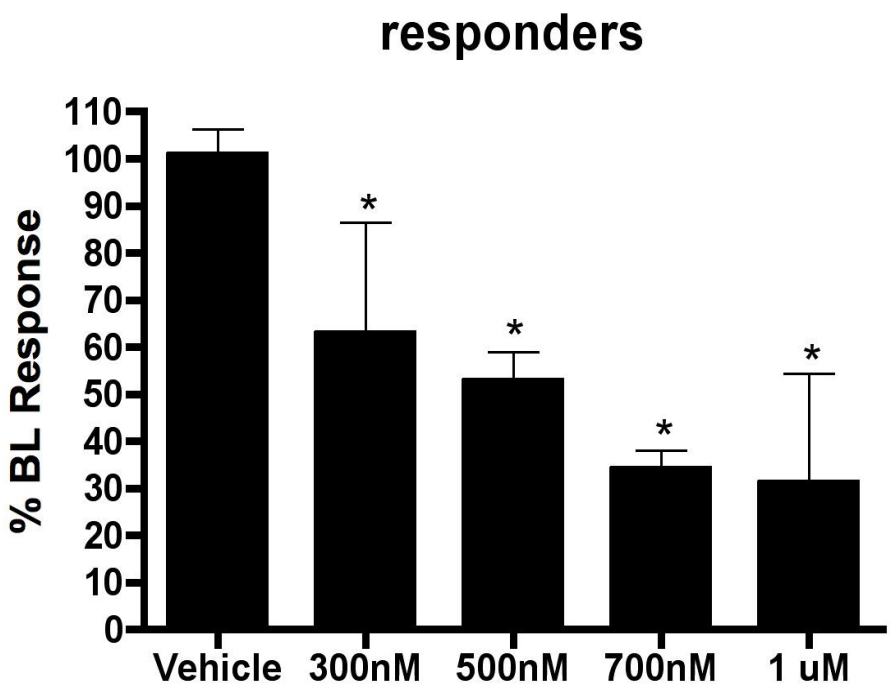




Satterfield et al., 2009

*Mu Opioid Receptor (MOR): DAMGO (**72 hrs CFA**)*

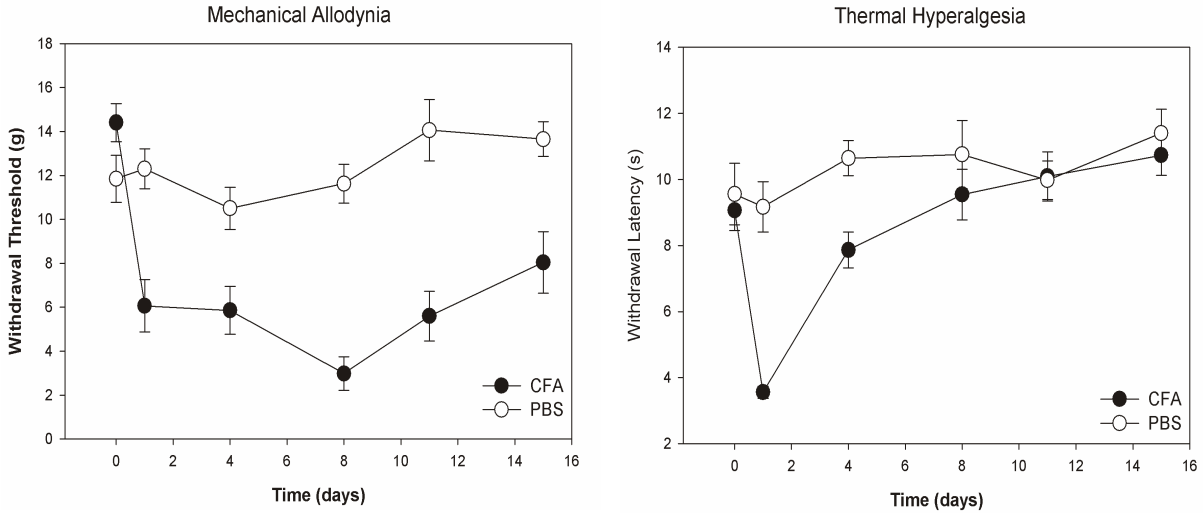




Satterfield et al., 2009

Summary: Opioid Receptors in Inflamed Skin

- Opioids are ineffective in healthy skin
- 18 hours after inflammatory insult:
  - Morphine is effective
  - DOR are functional
  - MOR are not functional
- 72 hours after inflammatory insult:
  - Morphine is effective
  - DOR uncertain function
  - MOR functional



Increased Efficacy of ORs: Possible Mechanisms

Increased receptor availability

- Receptor synthesis
- Receptor trafficking
- Receptor insertion

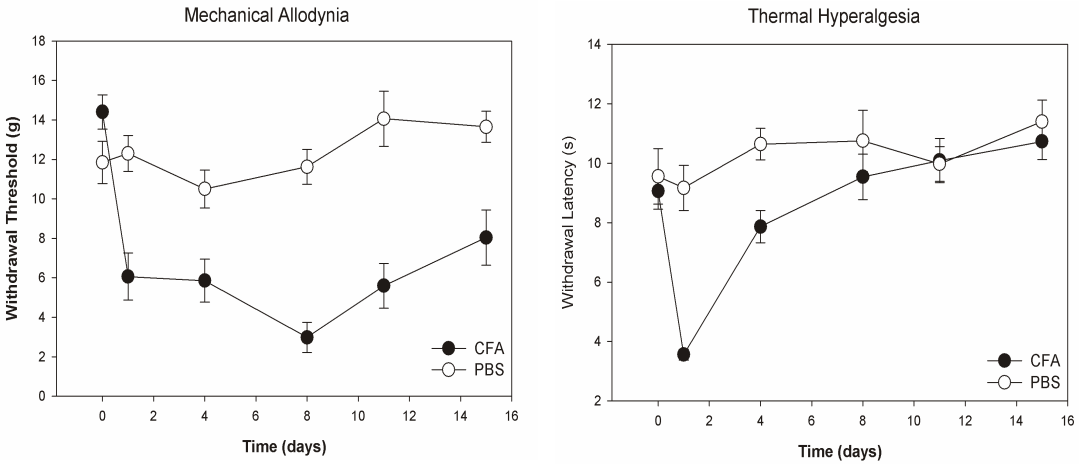
Increased access of ligand to receptors

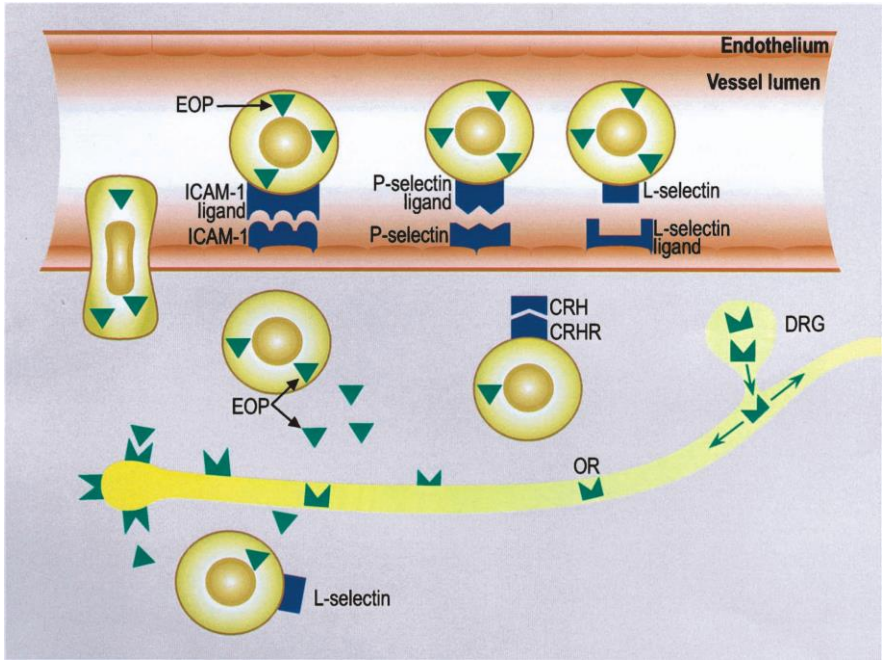
- Disruption of perineurium
- Infiltrating opioid containing leukocytes

Receptor modulation

- impart “functional competence”

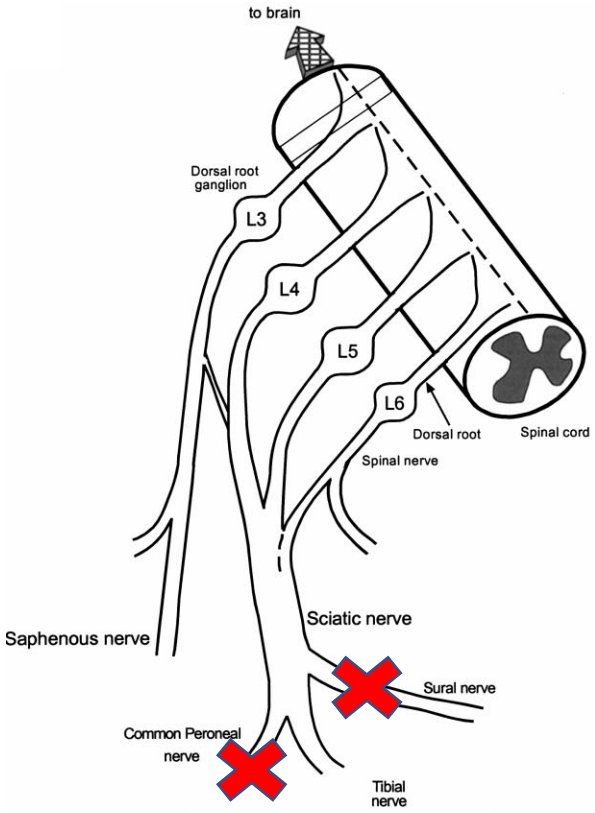
  PKC involvement ? Immune signals?

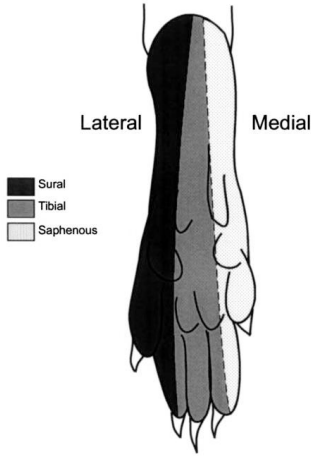


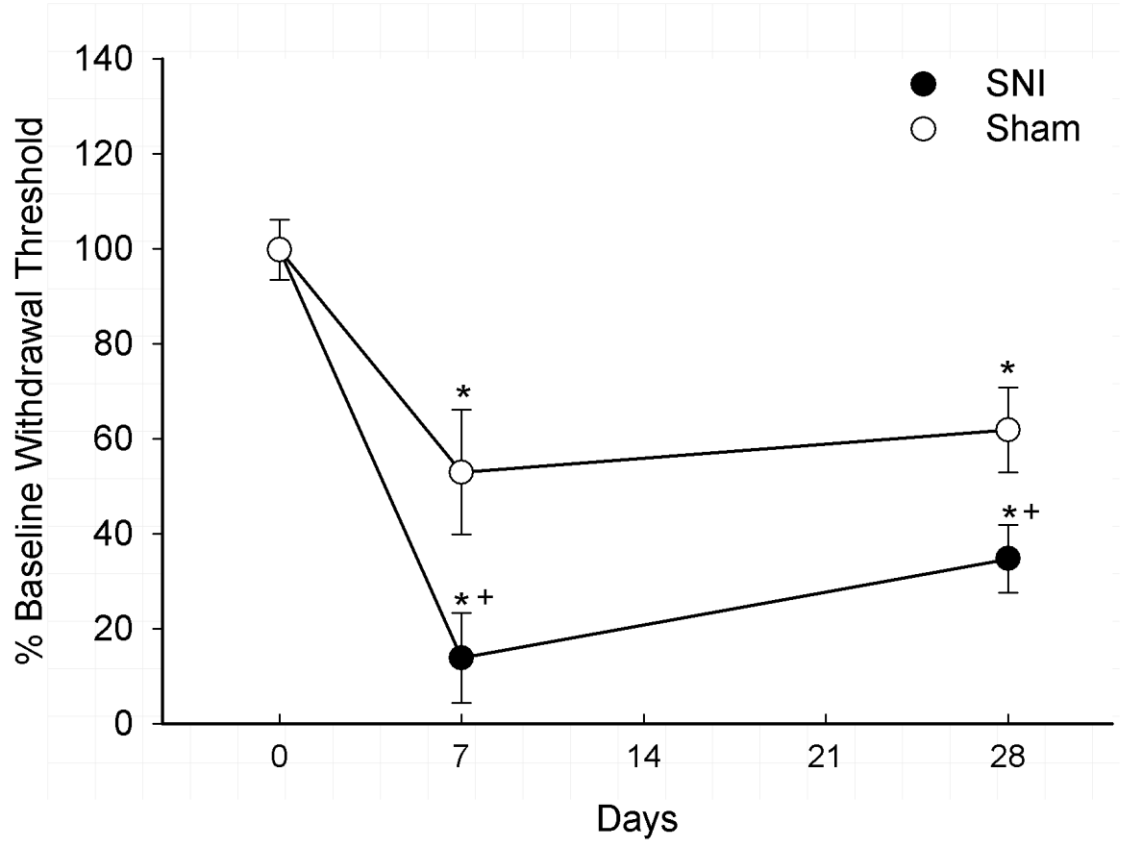


Machelska et al., (2002) J. Neuroscience 13:5588–5596

Spared Nerve (tibial) Injury: model of neuropathic pain



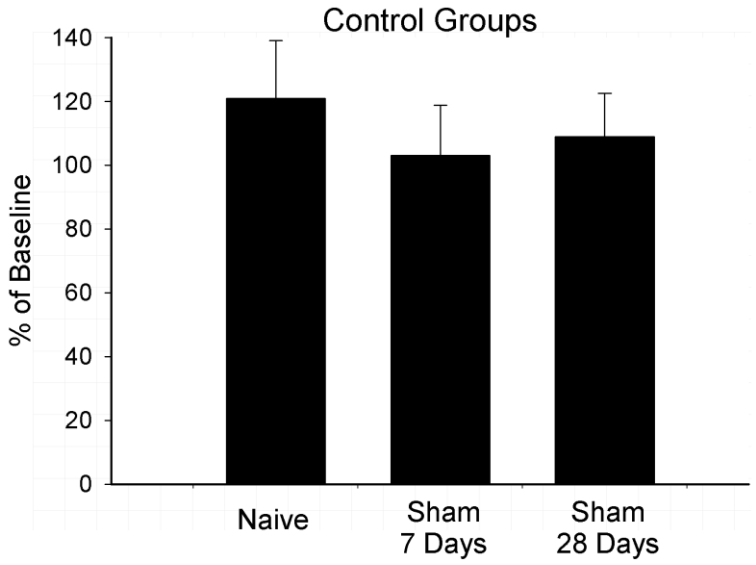


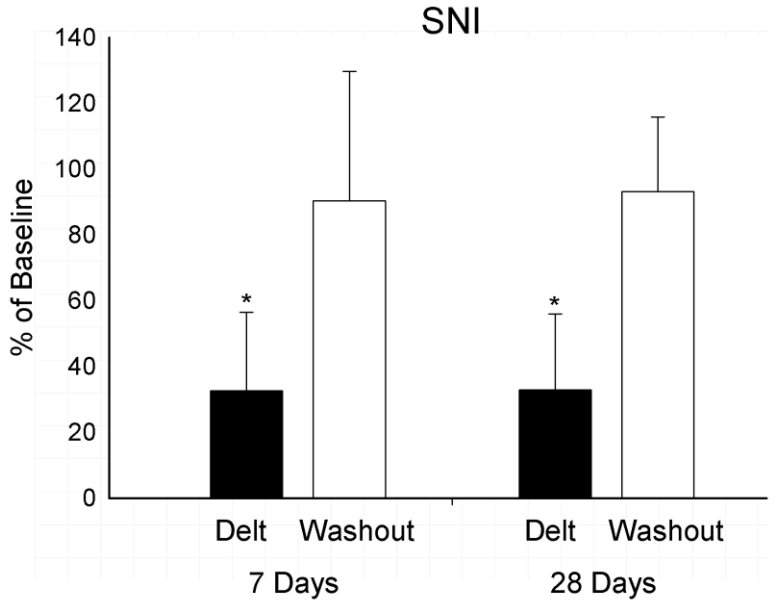


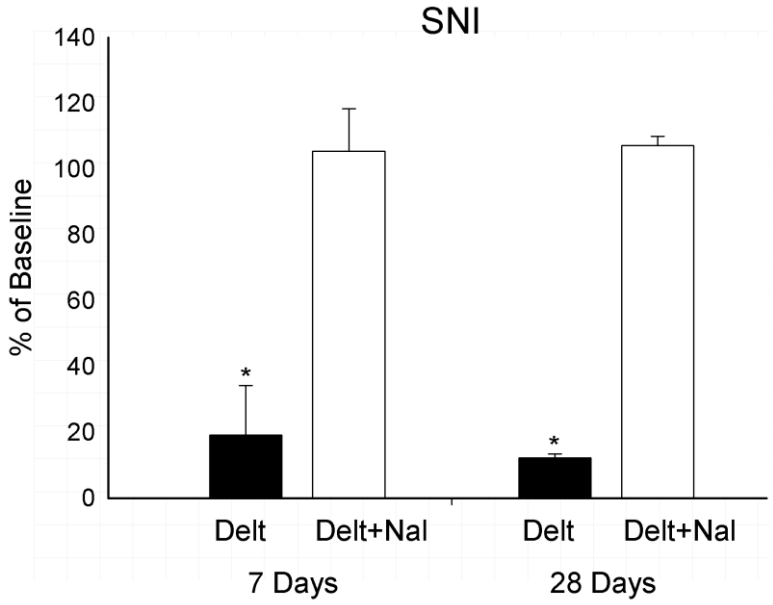
Decosterd and Woolf 2000

Joukal et al, 2019

Electrophysiology: Mechanical Responsiveness







Joukal et al, 2019

Acknowledgements

Honda Lab

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T32 DA07097 (JDB)
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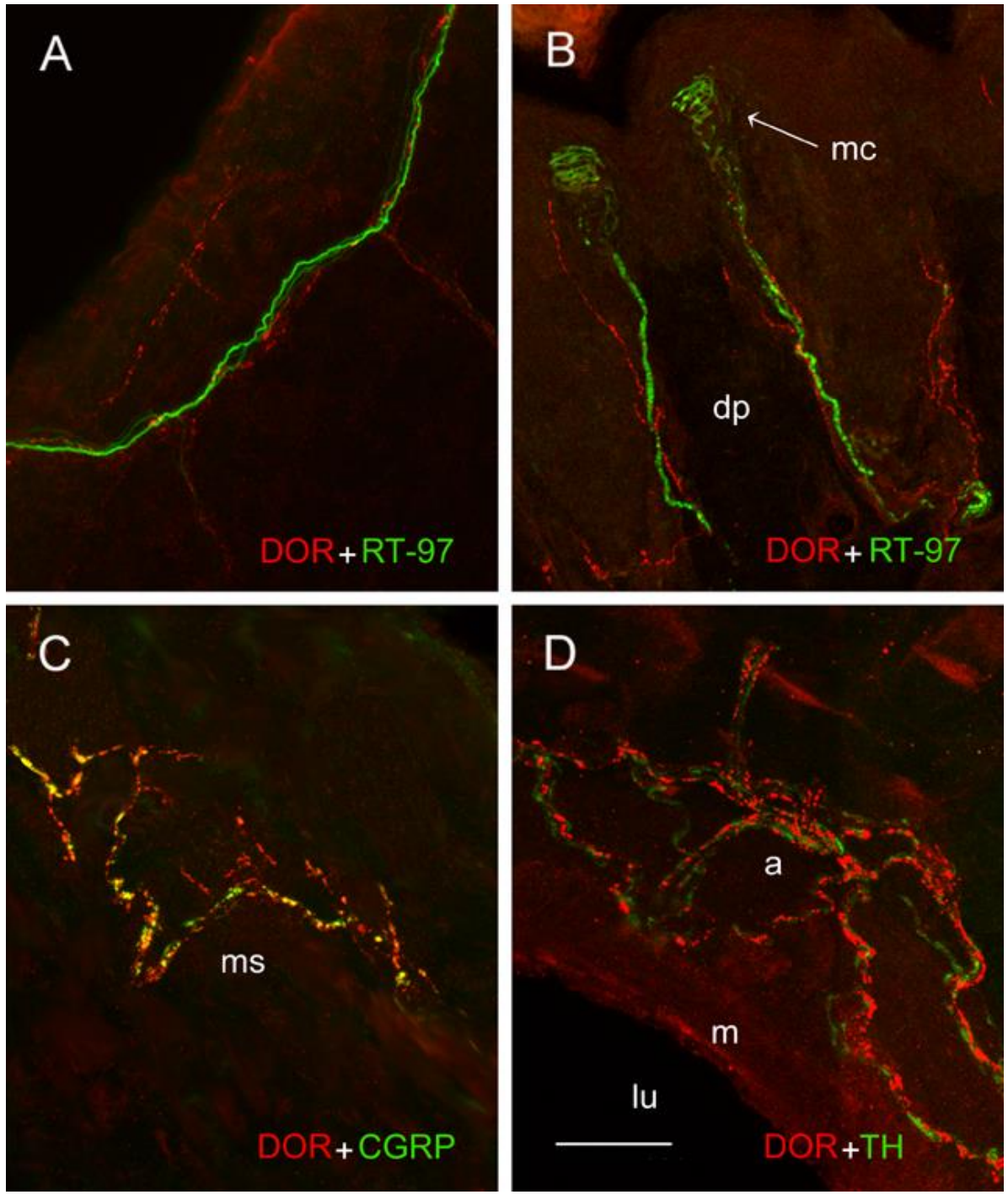


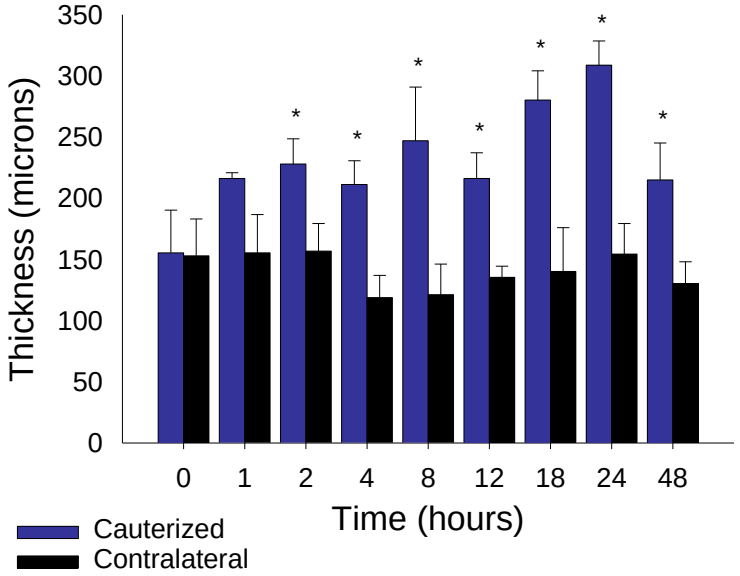
DOR-ir Peripheral Tissues

DOR-ir and RT-97-ir did not colocalize

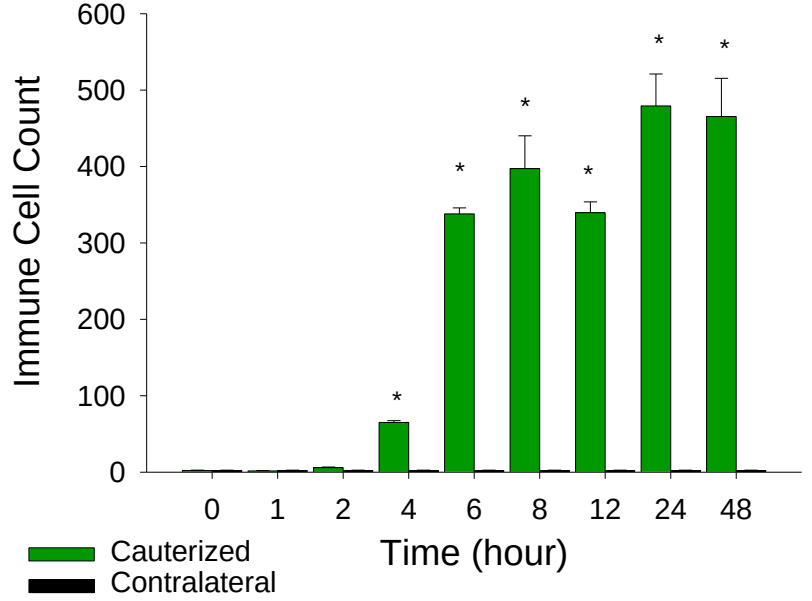
80% of DOR-ir fibers displayed CGRP-ir

DOR-ir and TH-ir did not colocalize

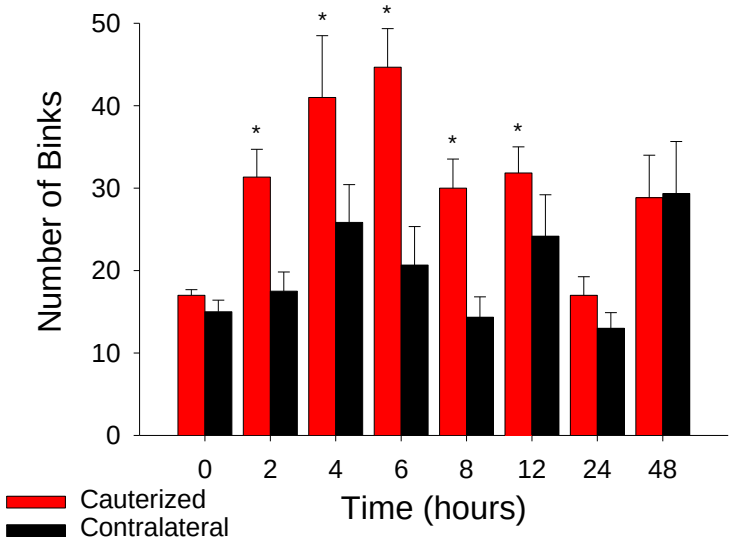
Stromal Edema

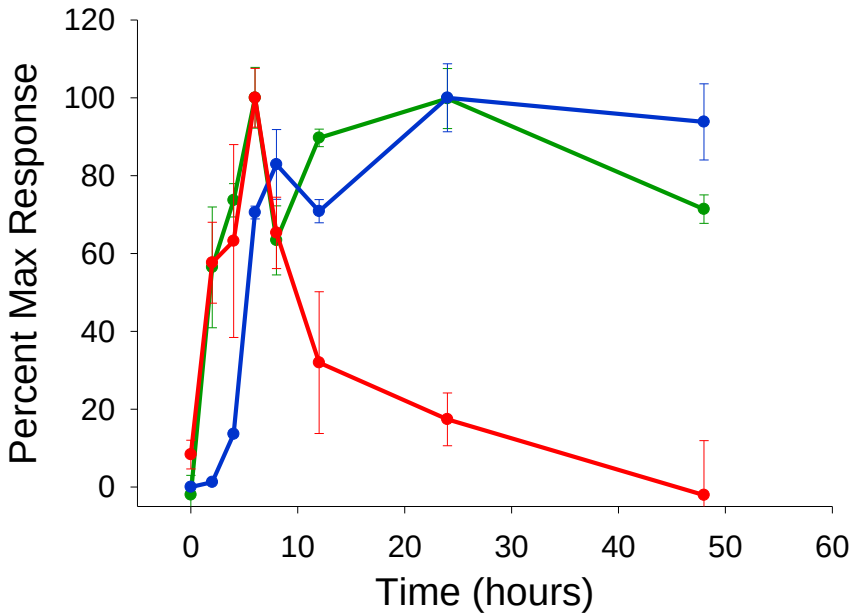


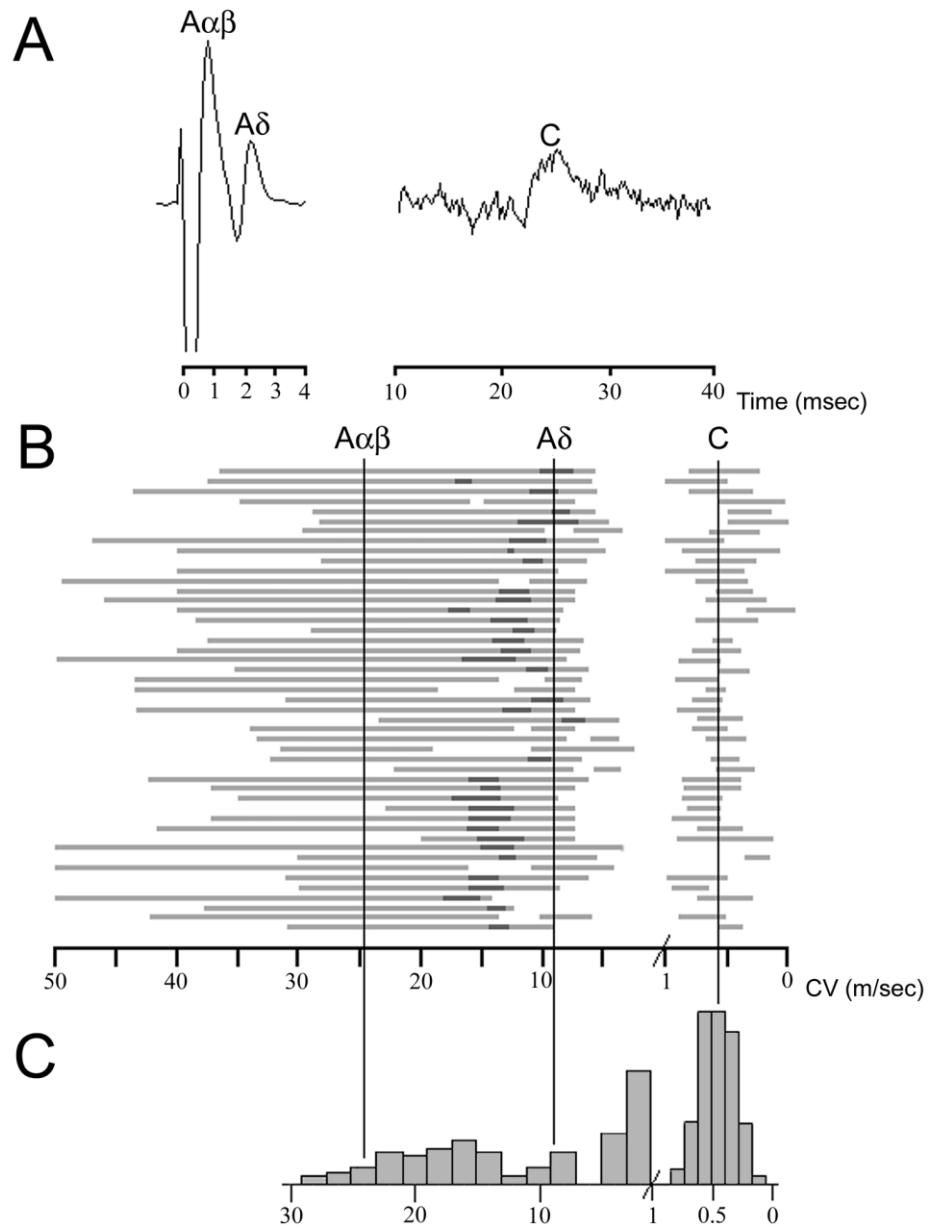
Immune Cell Count



Capsaicin Response






A
Aαβ
Aδ
C
0 1 2 3 4
10 20 30 40
Time (msec)
B
Aαβ
Aδ
C
50 40 30 20 10 1 0
CV (m/sec)
C
30 20 10 1 0.5 0