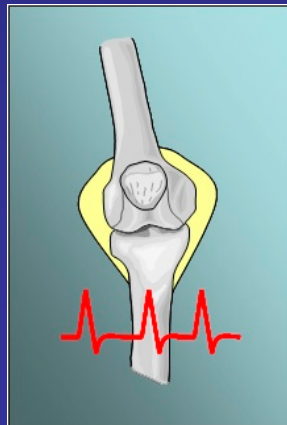


# Activation of Cannabinoid CB<sub>2</sub> Receptors Reveals a Paradoxical Effect on Joint Pain in Normal and Osteoarthritic Rat Knees

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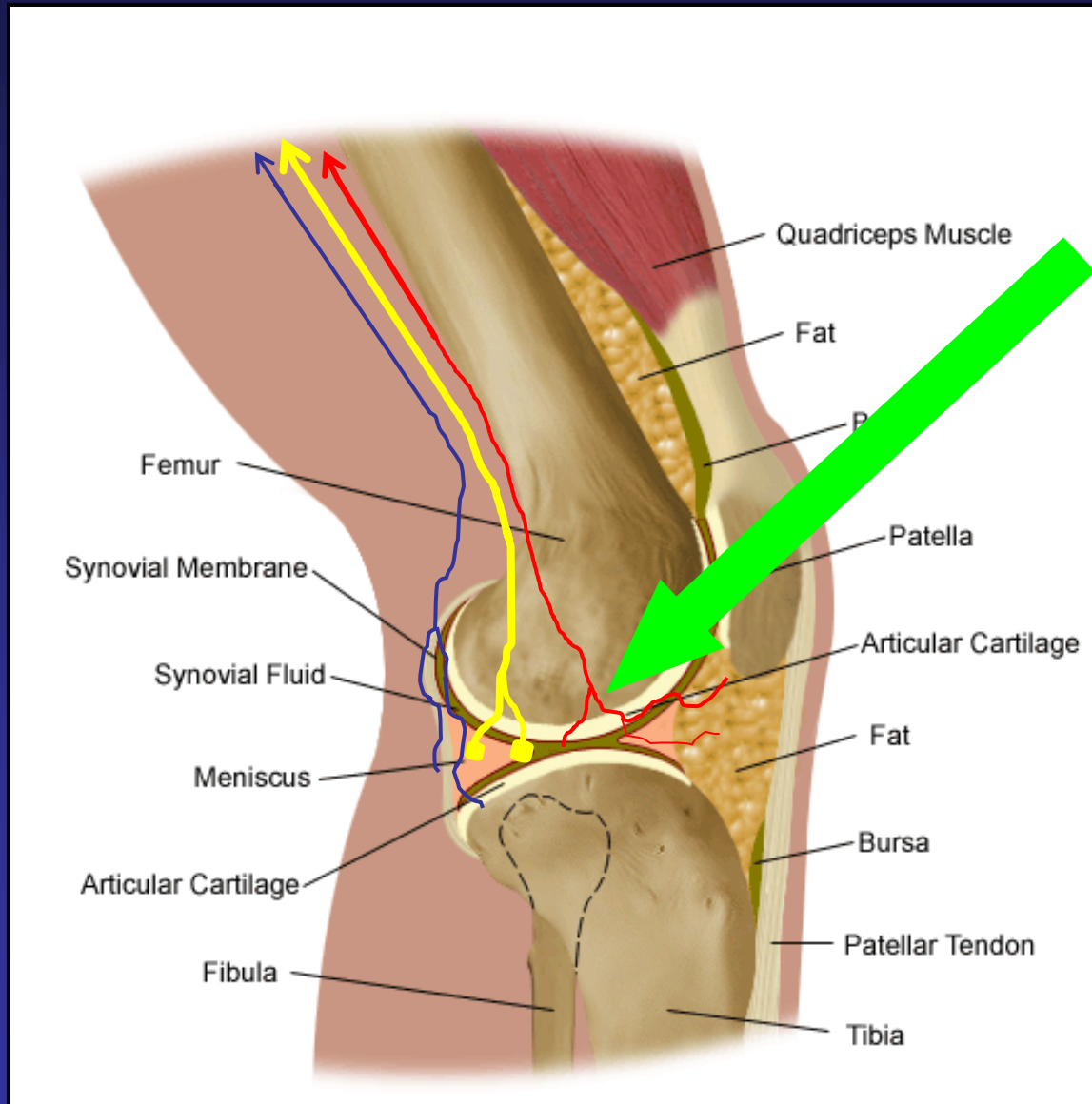
University of Calgary



# Disclosure statement

- Collaboration with Eli Lilly (USA)
- Contract with AstraZeneca (UK)

# Afferent joint nerve fibres



Free nerve endings in the joint respond to mechanical damage or inflammation perceived as pain

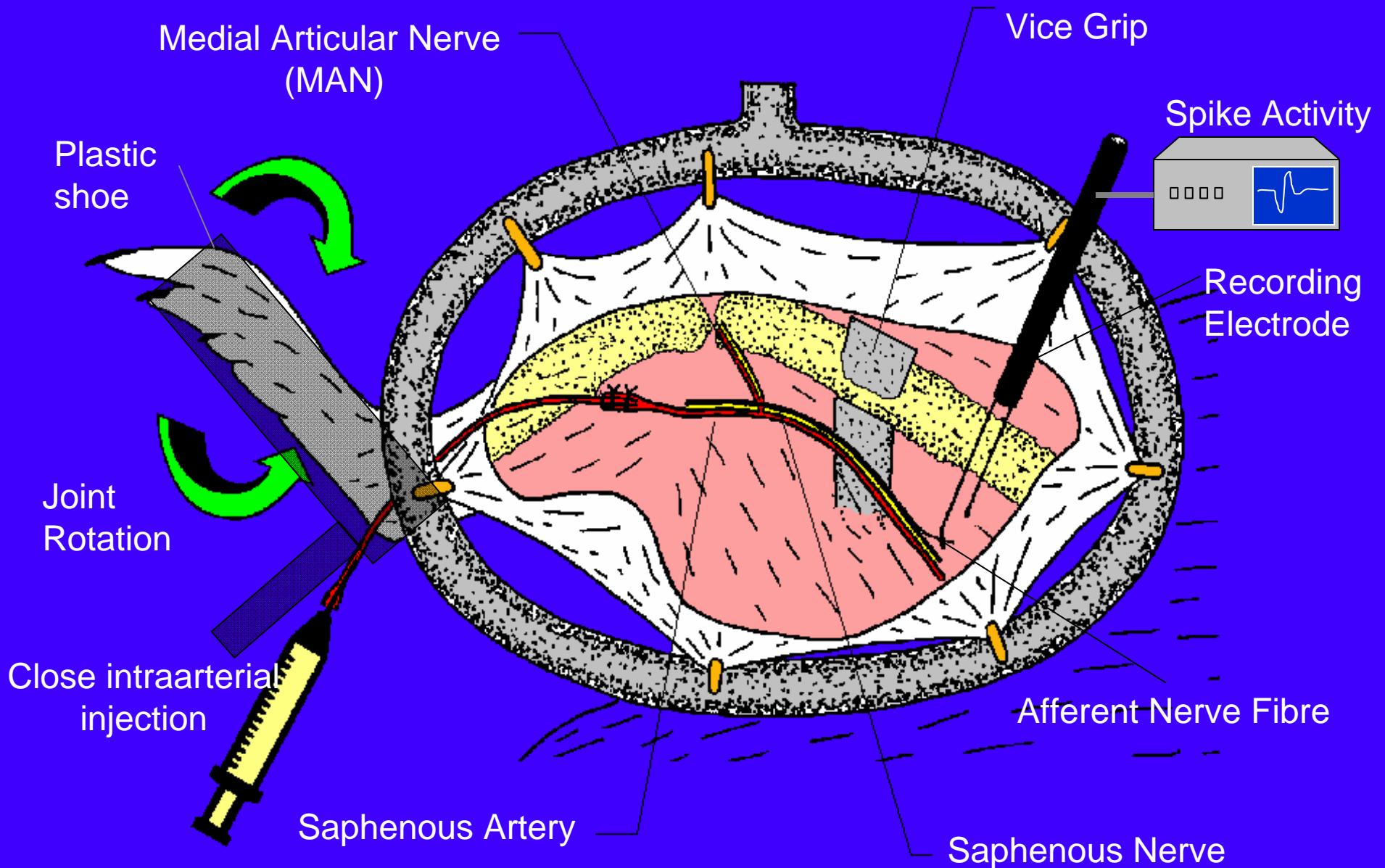
## **A $\delta$ fibres (Group III)**

myelinated, CV 2.5 – 20m/s  
produce fast sharp phasic pain

## **C fibres (Group IV)**

unmyelinated CV > 2.5m/s  
produce dull burning tonic pain  
release of pro-inflammatory mediators

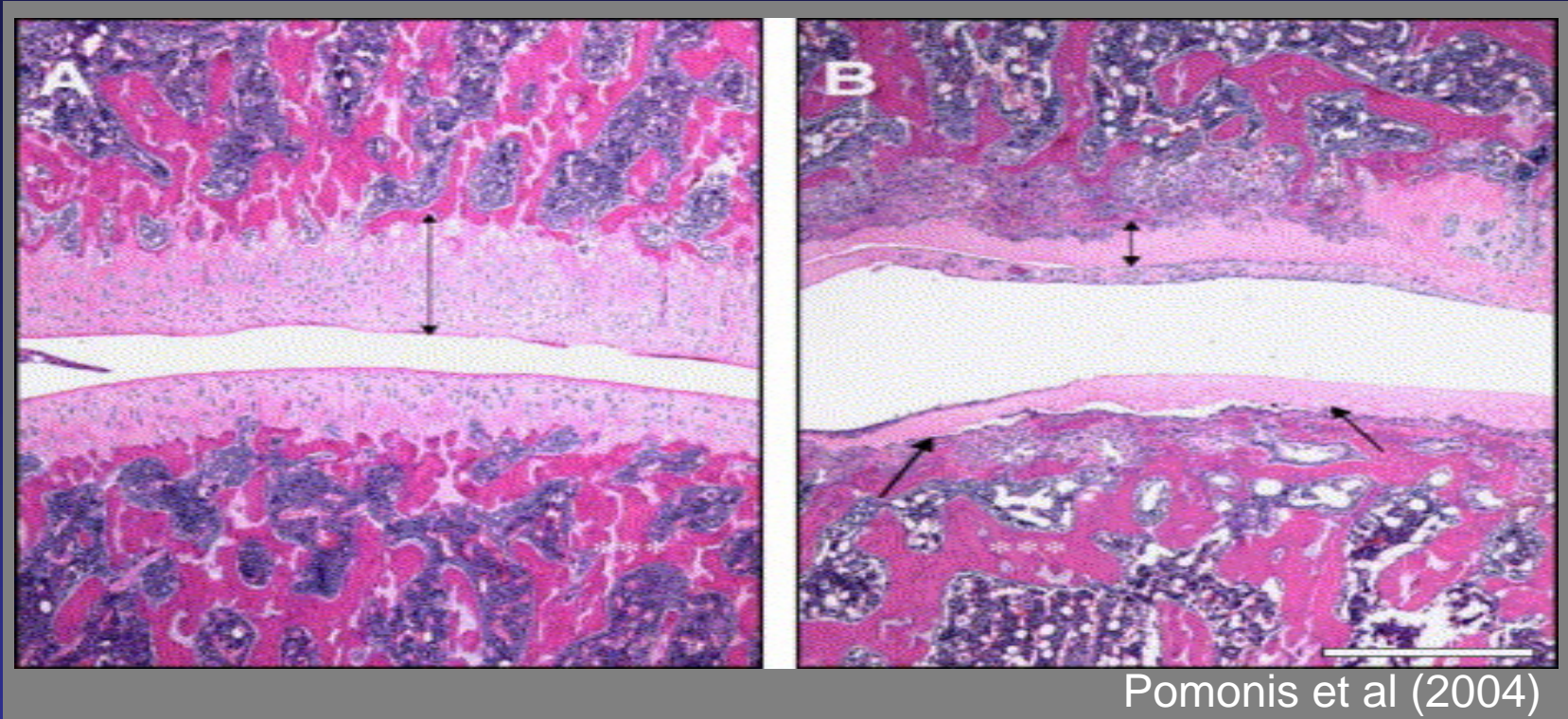
# Afferent Nerve Recording



# Osteoarthritis

- Osteoarthritis is a type of arthritis that is caused by the breakdown and eventual loss of cartilage mainly in weight bearing joints
- One of the most prominent features but least studied symptoms associated with arthritis is chronic pain
- No disease modifying drugs are available and analgesics have side effects

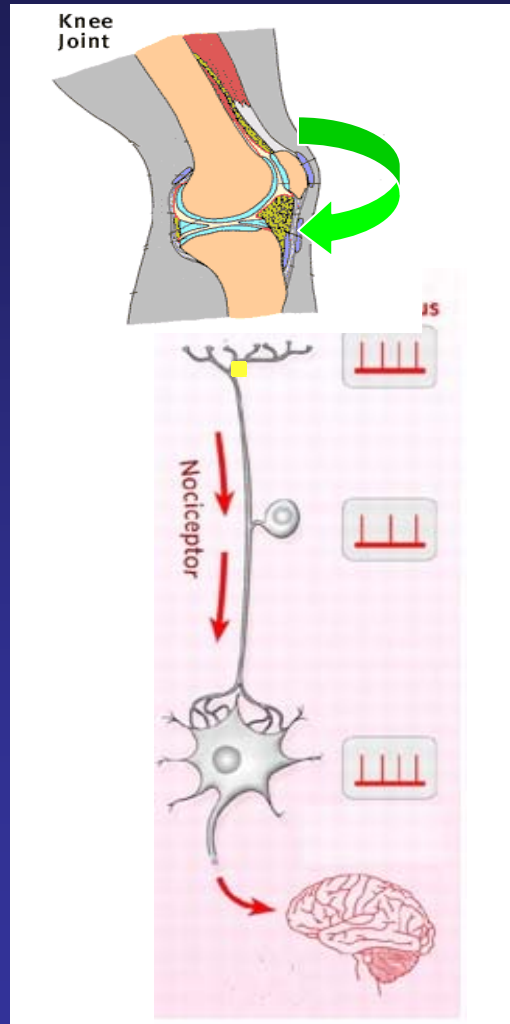
# MIA model of Osteoarthritis



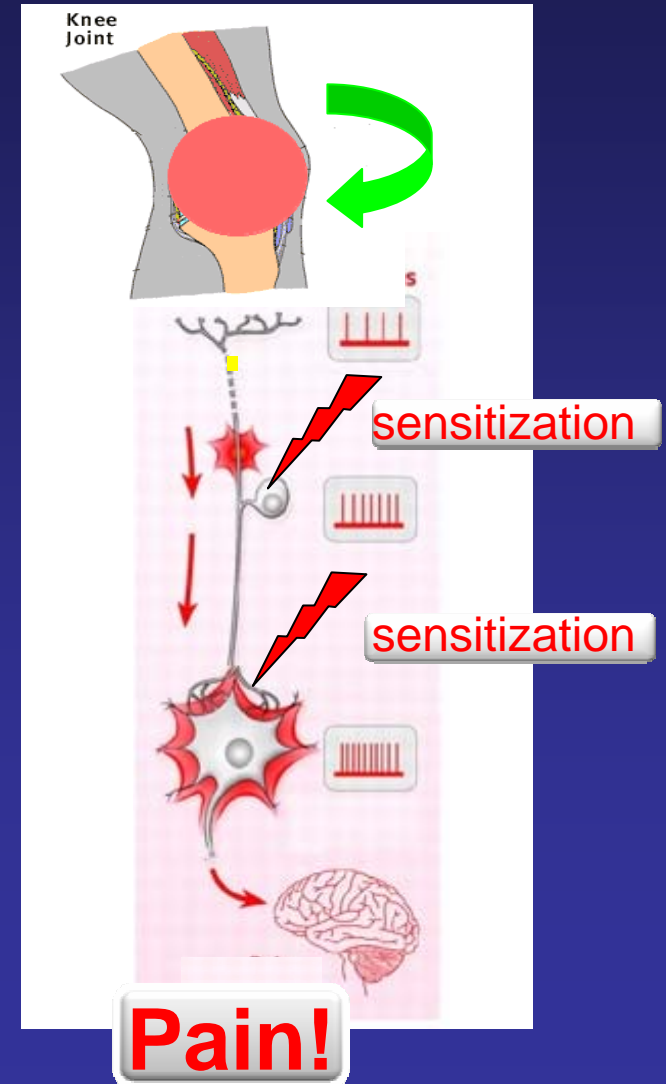
- Injection of sodium monoiodoacetate (MIA) into joint
- MIA inhibits glycolysis > disruption of chondrocyte metabolism > cartilage degeneration (Kalbhen, 1987)
- Nerve recordings 14 days after MIA injection

# Osteoarthritis sensitizes Nerves

Normal knee joint



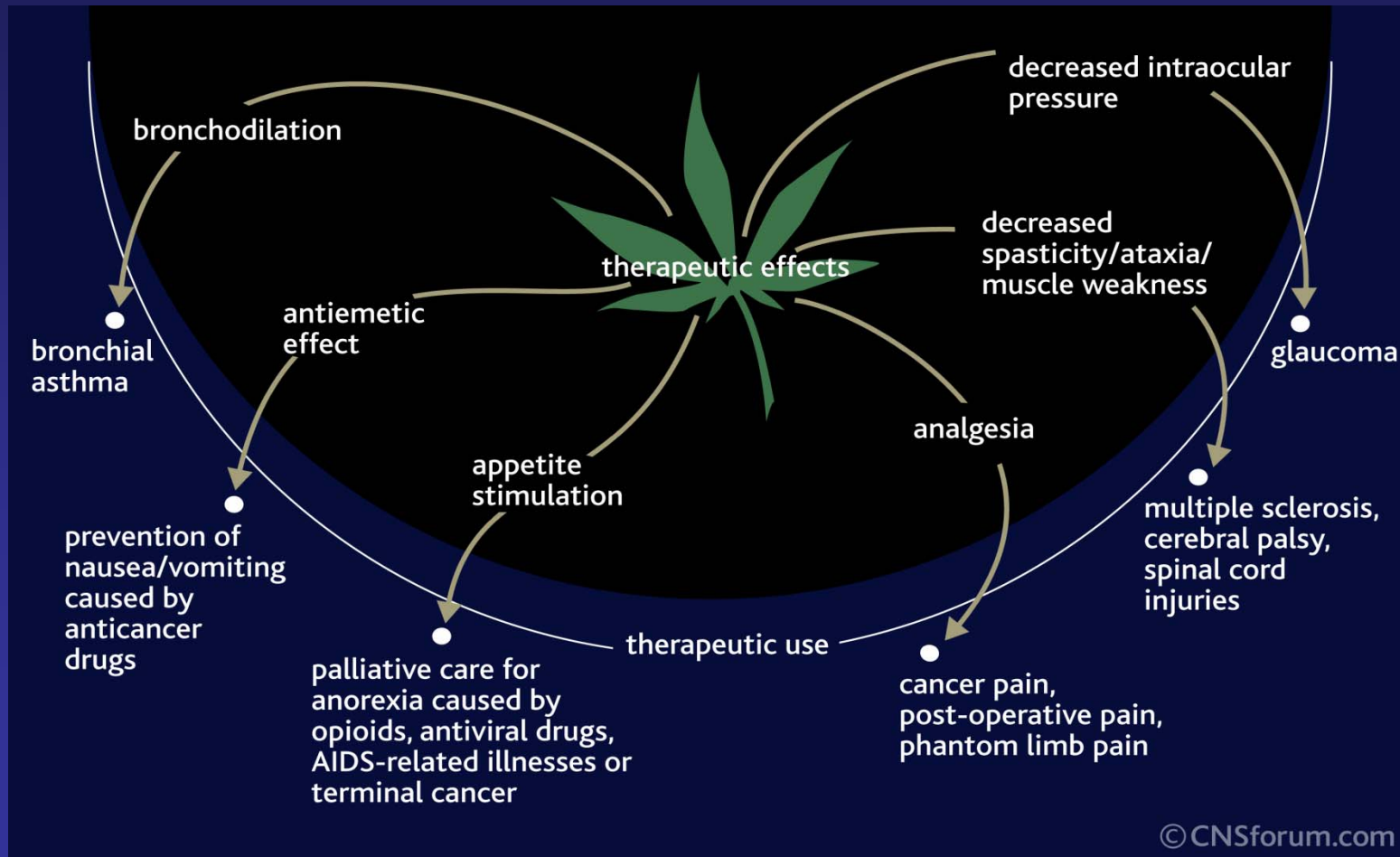
Arthritic knee joint



# Cannabinoids

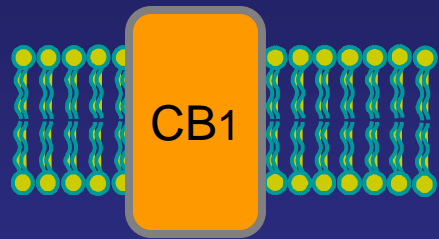


Cannabinoids are the active compounds in the Cannabis plant (*Cannabis sativa*)

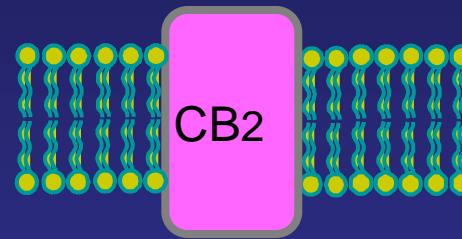


# Cannabinoid (CB) receptors

- Two CB receptor subtypes have been identified:



CNS, peripheral nerve terminals



Immune system

- The CB<sub>1</sub> agonist ACEA reduces nerve activity in a rat model of osteoarthritis

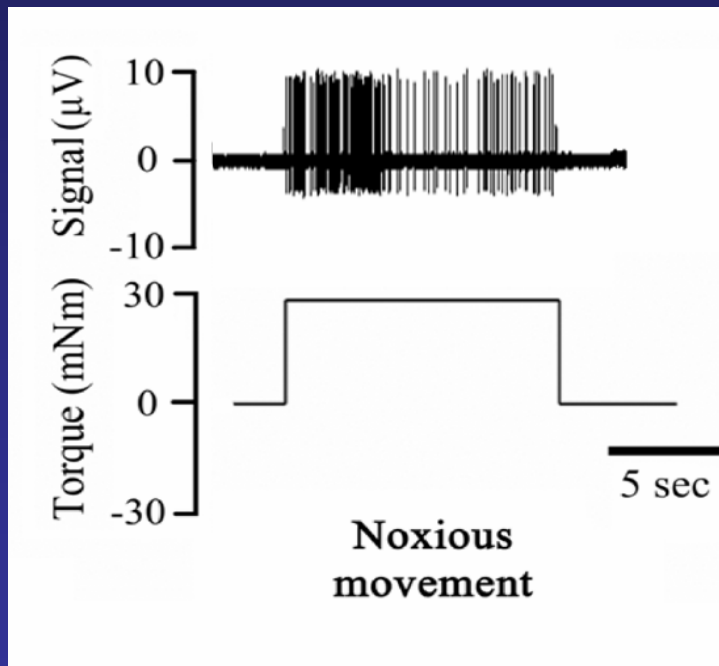
*(Schuelert & McDougall 2008; Arthritis & Rheumatism)*

?

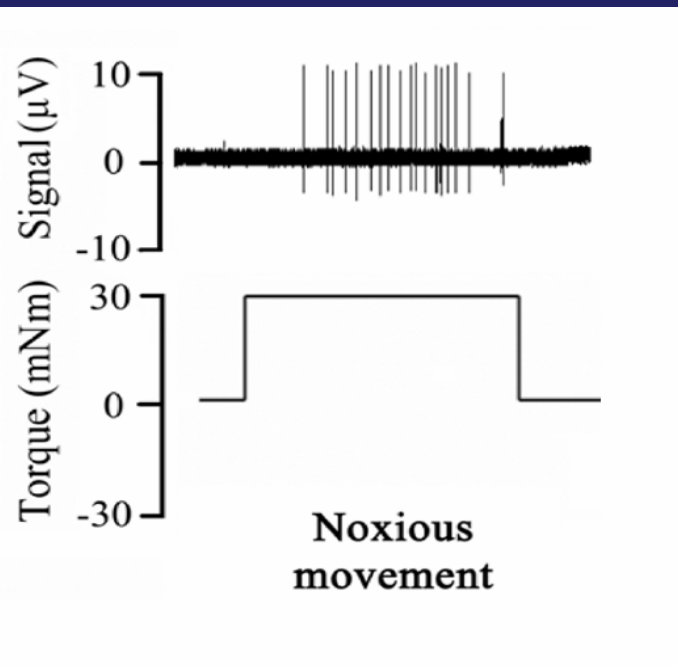
- Does local application of cannabinoid CB<sub>2</sub> agonist GW405833 into the normal rat knee joint reduce joint pain?

# CB2 agonist GW405833 control joint

control

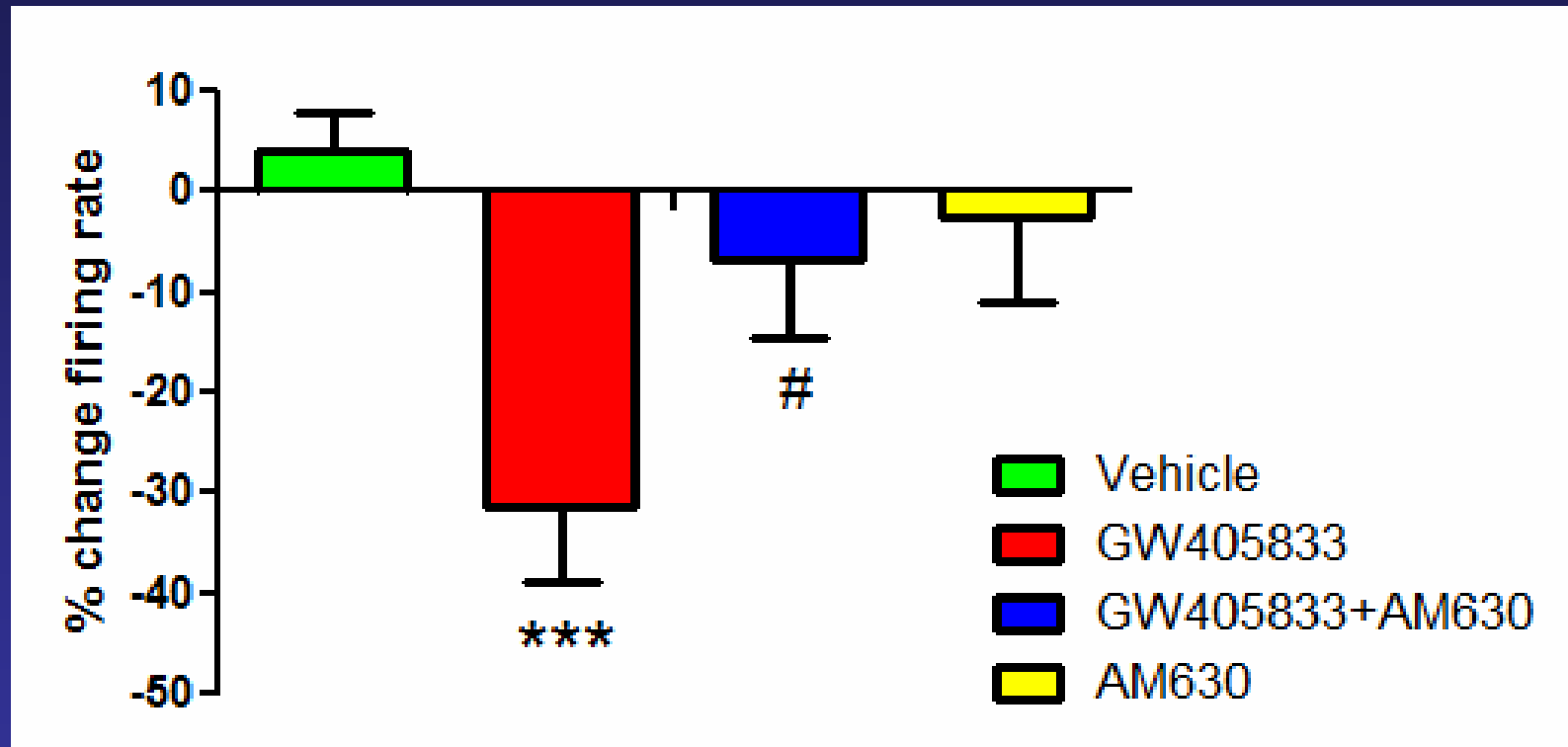


GW405833



GW405833 reduces afferent nerve activity  
in the control joint

# CB2 agonist GW405833 control joint



Desensitizing effect can be blocked by  
co-administration of the CB<sub>2</sub> antagonist AM630

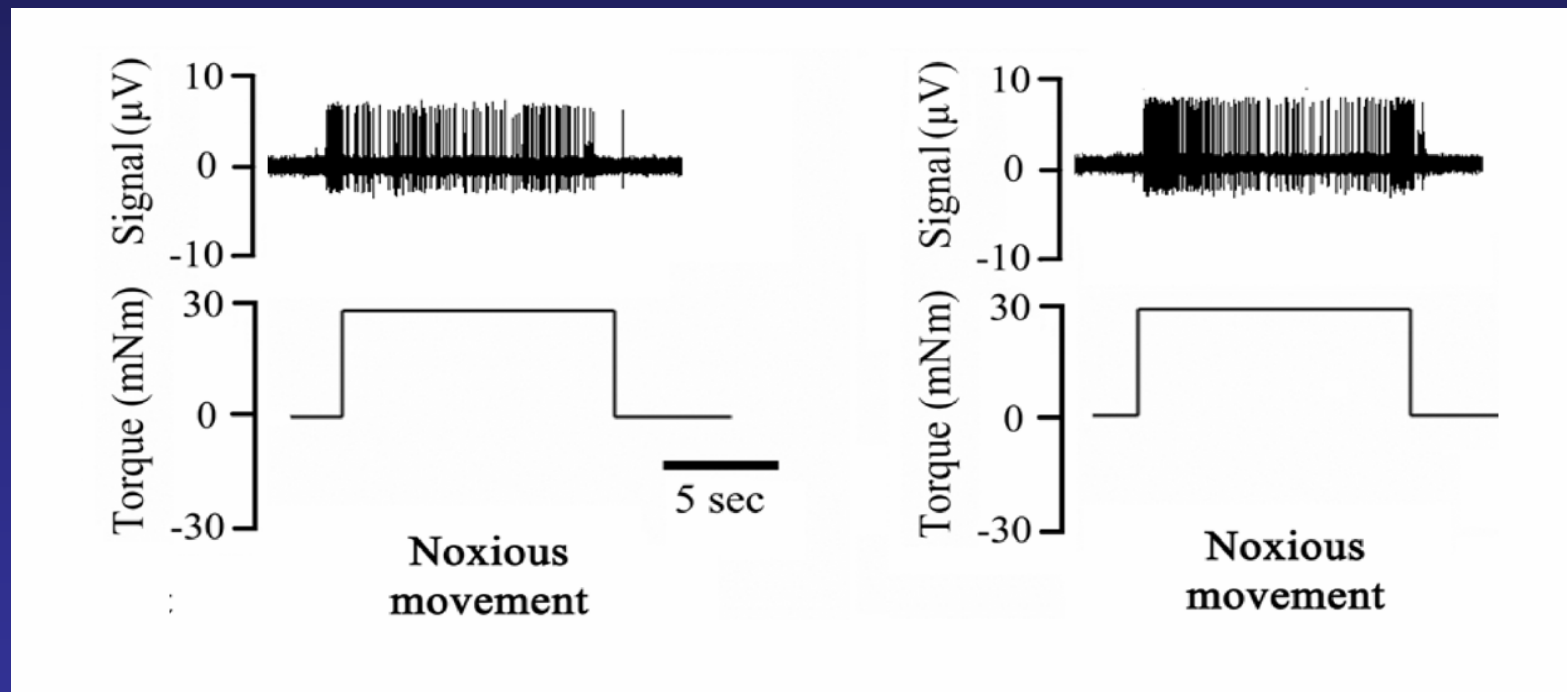
?

- Does local application of cannabinoid CB<sub>2</sub> agonist GW405833 reduce joint pain in a rat model of osteoarthritis?

# CB2 agonist GW405833 OA joint

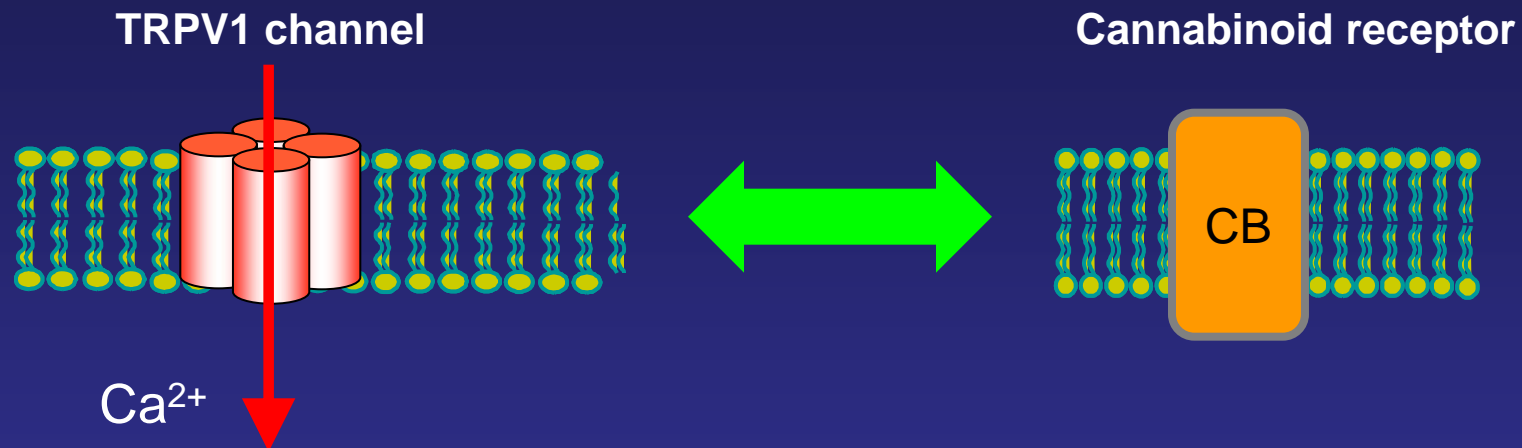
control

GW405833



GW405833 causes sensitization of afferent nerve fibres in the osteoarthritic knee joint

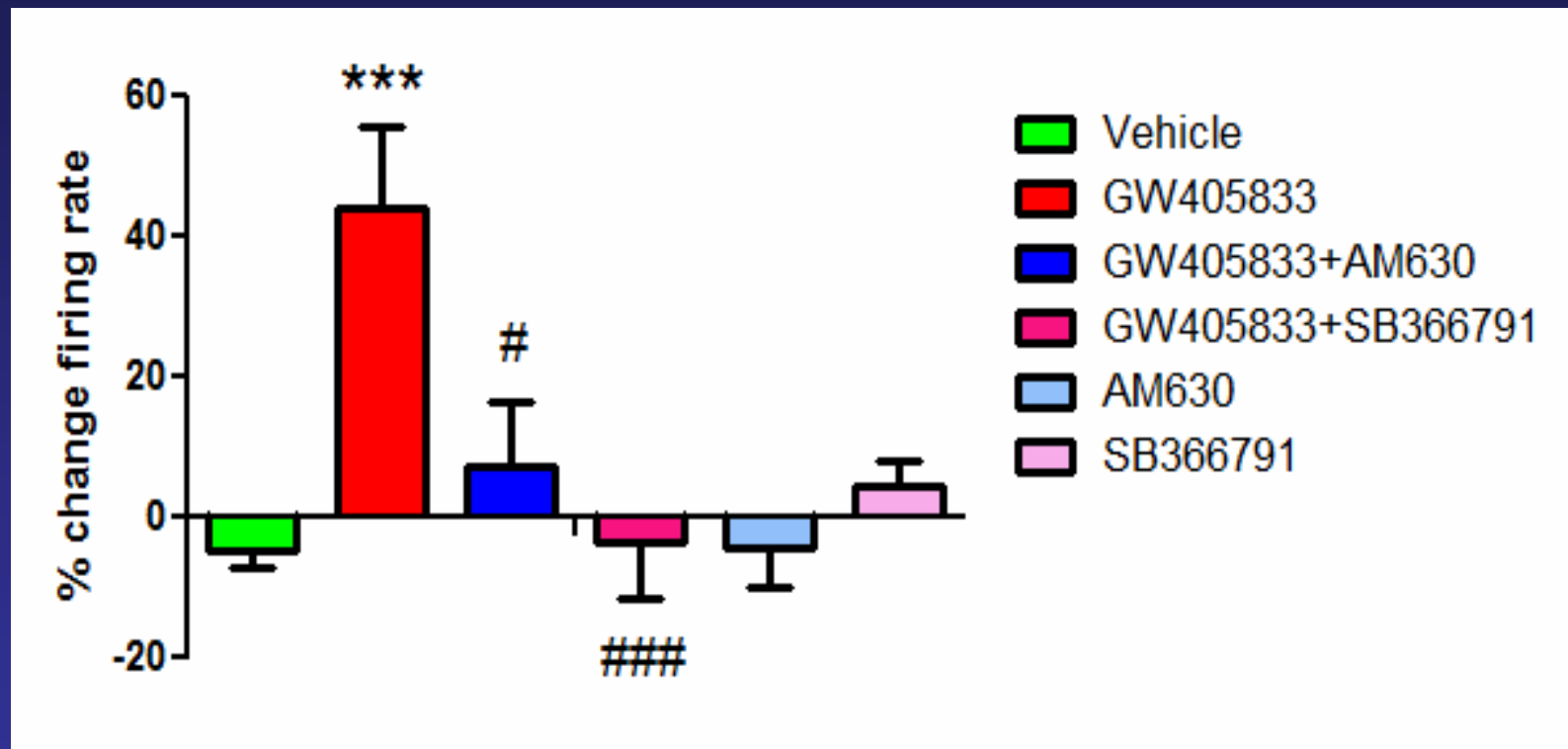
# Transient receptor potential vanilloid 1 (TRPV1)



- Involved in the transmission of pain (located on C-fibres)
- Activated by endogenous CBs (Anandamide)
- CB receptors and TRPV1 are functionally connected

*(Ahluwalia et al. 2003; Costa et al. 2004)*

# CB2 agonist GW405833 OA joint



Sensitizing effect can be blocked by co-administration of the CB<sub>2</sub> antagonist AM630 or the TRPV1 antagonist SB366791

# Conclusion

- The CB<sub>2</sub> agonist GW405833 reduced sensory nerve fibre activity in control joints but induced sensitization in OA joints → phosphorylation of TRPV1 channel?
- Both, the CB<sub>2</sub> receptor as well as the TRPV1 channel seem to be involved in mediating this sensitizing effect
- Findings correlate with behavioural study showing increase of pain after GW405833 application in the OA joint
- Peripheral activation of CB<sub>2</sub> receptors by GW405833 is unsatisfactory for treating OA pain due to its paradoxical effect on peripheral CB<sub>2</sub>/ TRPV1 receptors

# Acknowledgements

- Dr. Jason McDougall
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A H F M R



ALBERTA HERITAGE FOUNDATION  
FOR MEDICAL RESEARCH



CANADIAN  
ARTHRITIS  
NETWORK

