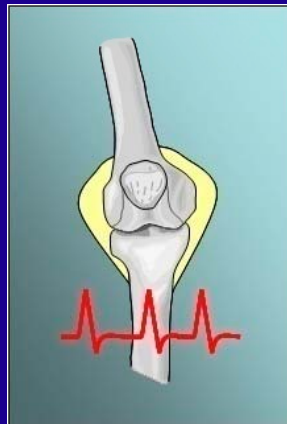


# ENDOCANNABINOID ENHANCEMENT BY LOCAL INJECTION OF THE FATTY ACID AMIDE HYDROLASE INHIBITOR URB597 REDUCES NOCICEPTION IN AN ANIMAL MODEL OF OSTEOARTHRITIS

Niklas Schuelert (PhD)

Dept. of Physiology & Pharmacology

University of Calgary

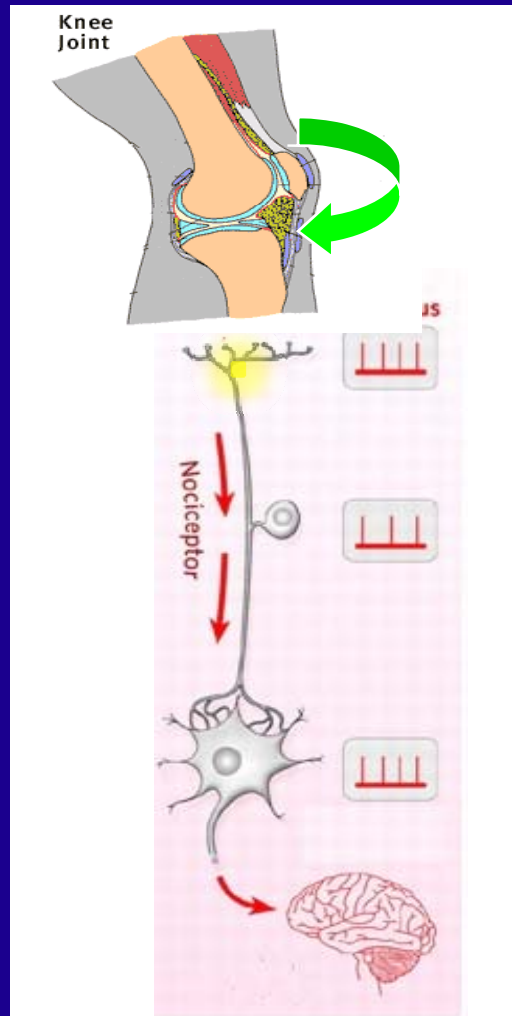


# Disclosure statement

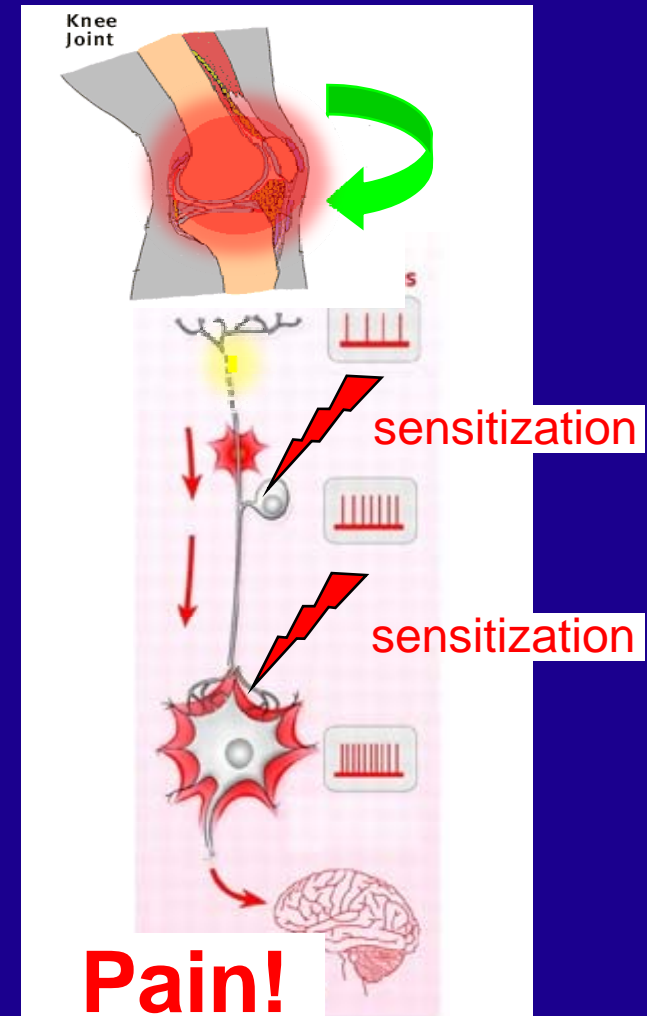
- Collaboration with Eli Lilly (USA)
- Contract with AstraZeneca (UK)

# Osteoarthritis sensitizes nerves

Normal knee joint

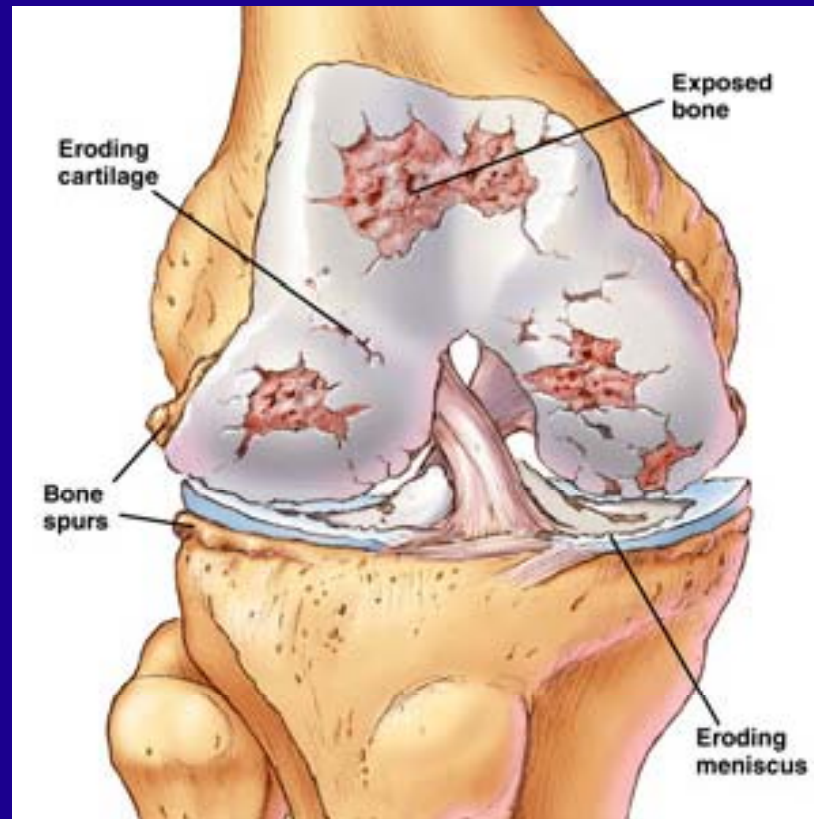


Arthritic knee joint



# Osteoarthritis

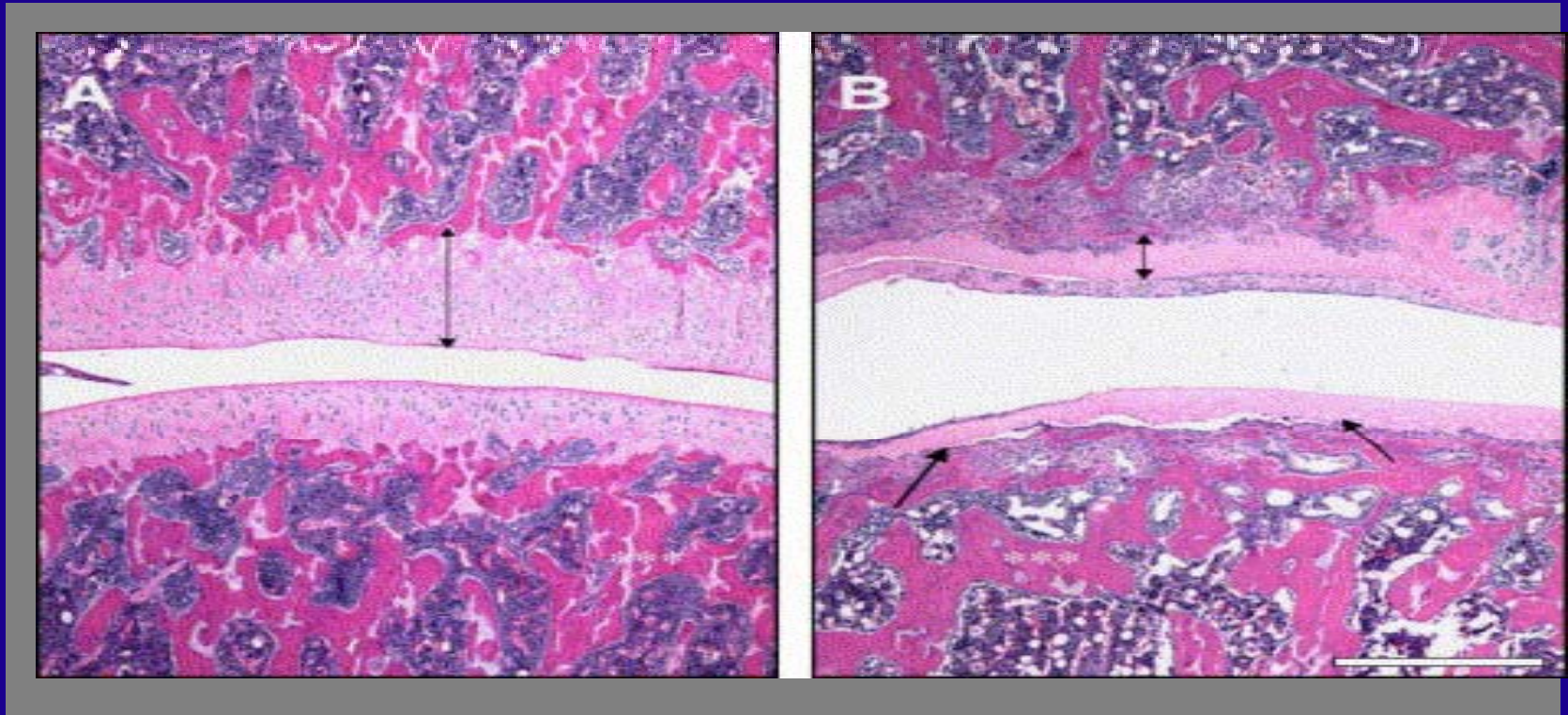
Osteoarthritis is a degenerative joint disease characterized by the breakdown of articular cartilage, the formation of osteophytes (bone spurs), and the production of osteophytes. OA is a chronic condition that causes pain and structural changes associated with OA.



# MIA rat model of Osteoarthritis

control

MIA treated

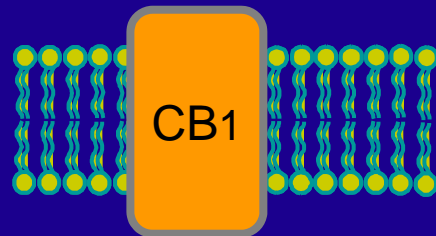


- Intra-articular Injection of 3mg sodium monoiodoacetate (MIA) into joint inhibits glycolysis
- disruption of chondrocyte metabolism
- cartilage degeneration after 14 days

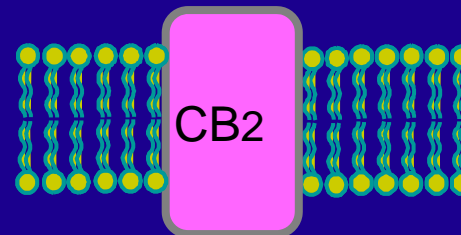
*Pomonis et al (2004)*

# Cannabinoid receptors

- Cannabinoids (CBs) act on various regions in the nervous system, suppressing nociceptive transmission
- Two CB receptor subtypes have been identified:



CNS, peripheral nerve terminals



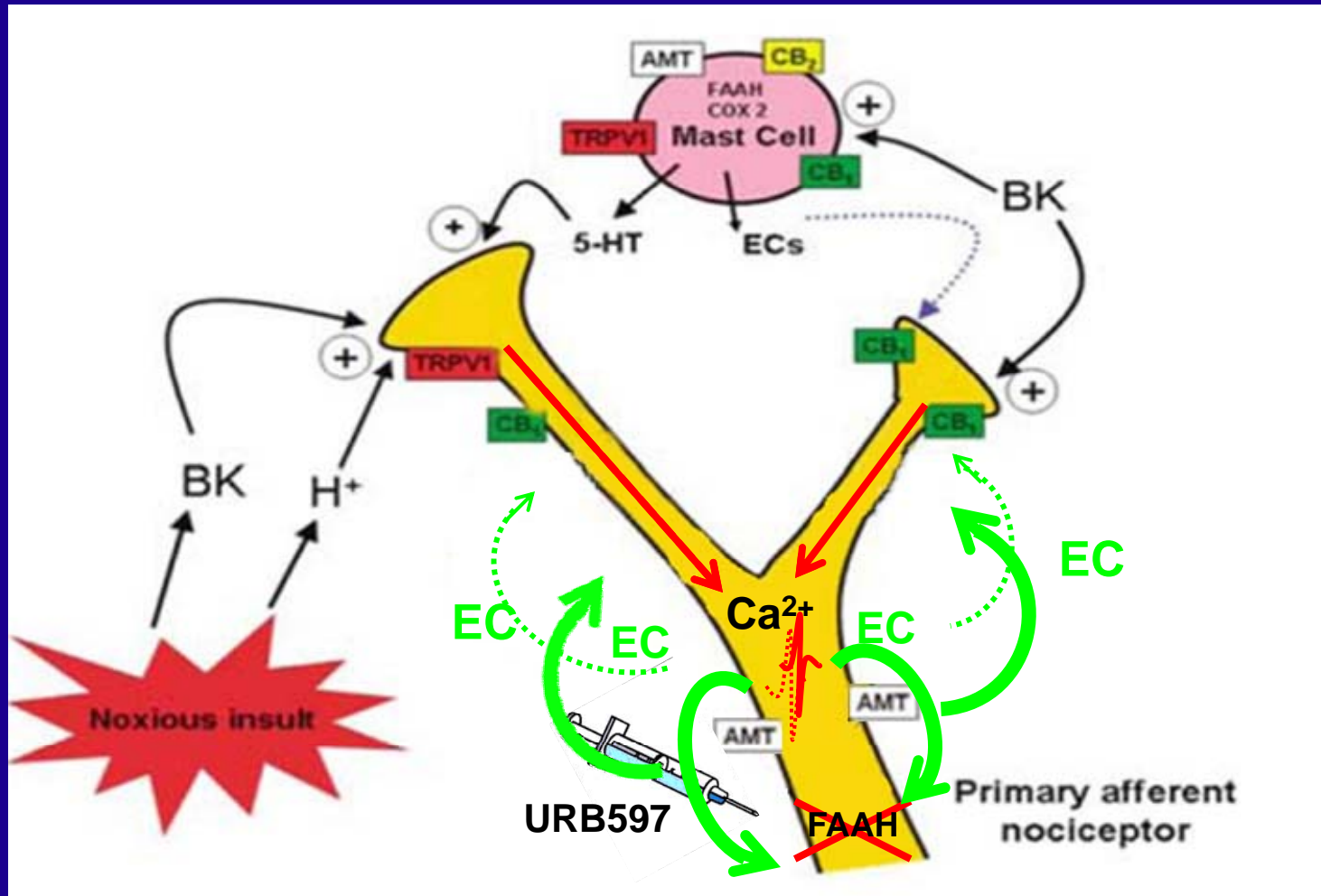
Immune system

- A major limitation on the use of CB agonists as therapeutic agents are their side effects resulting from the activation of central CB<sub>1</sub> receptors

# Endocannabinoids

- Endocannabinoids (ECs) are released on demand (no storage in secretory vesicles) and act locally on the pre-synaptic neuron (retrograde signalling)
- Increased neuronal activity that occurs during noxious stimulation of the pain pathways is believed to drive the synthesis of ECs
- Rapid termination of ECs limits the level of analgesia
- Targeting ECs rather than the receptor as an alternative approach to achieve analgesia without central side effects

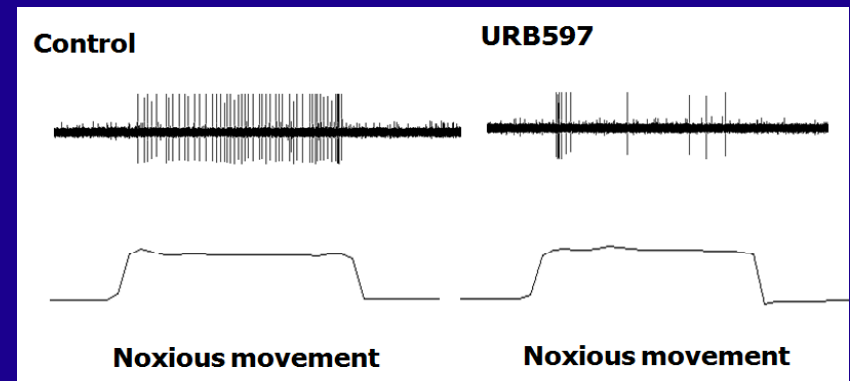
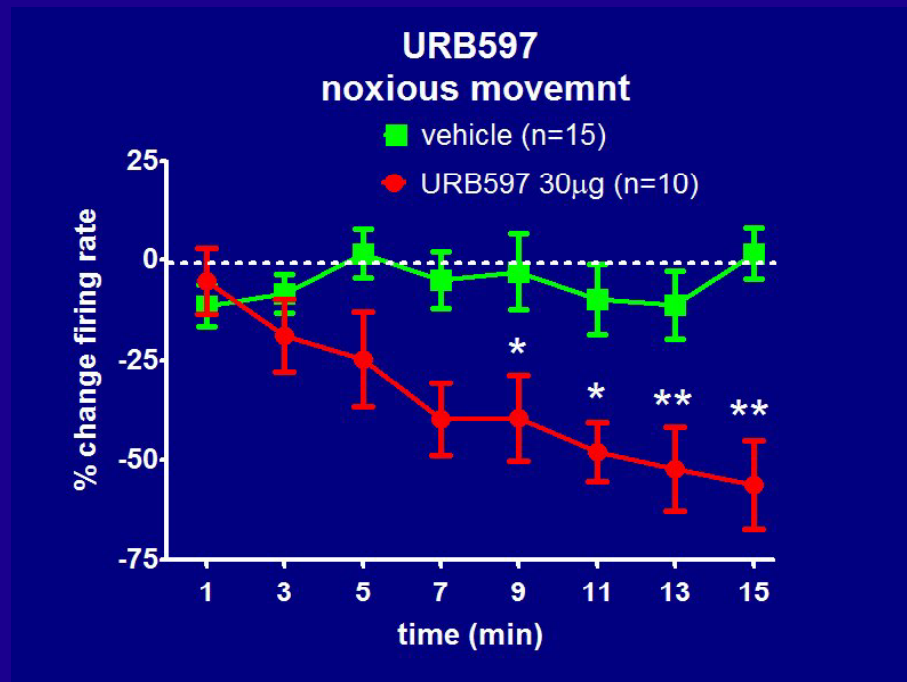
# Endocannabinoids



Modified from  
Jhaveri et al. 2007

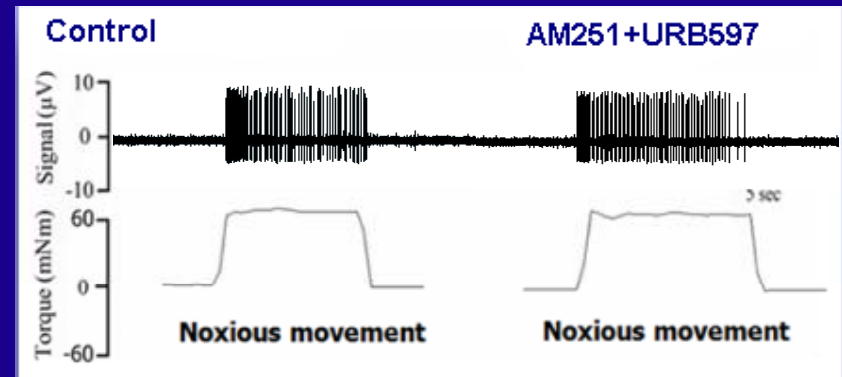
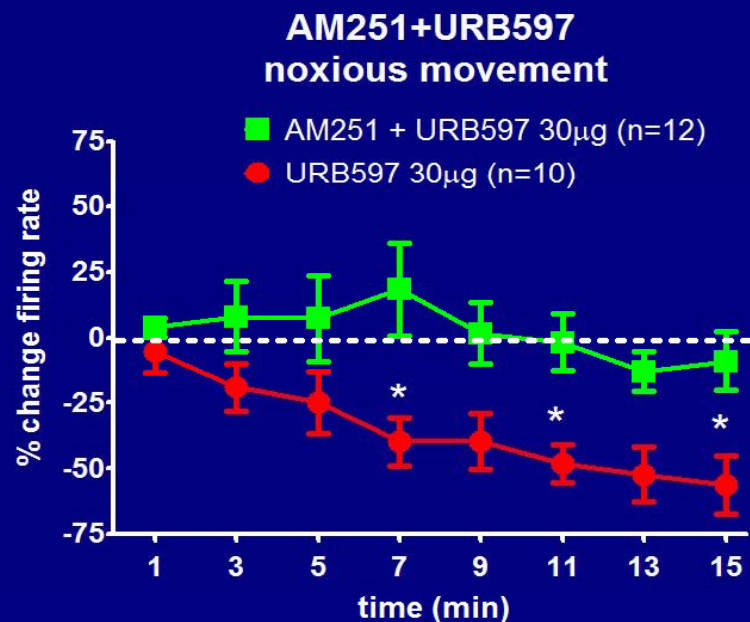
- URB597 is an active site inhibitor of FAAH. URB597 is a potent inhibitor of FAAH, and its inhibition of FAAH is associated with increased levels of endocannabinoids (ECs). URB597 also modulates nociceptive responses mediated by TRPV1 receptor agonists (Jhaveri et al. 2007)

# URB597 MIA model



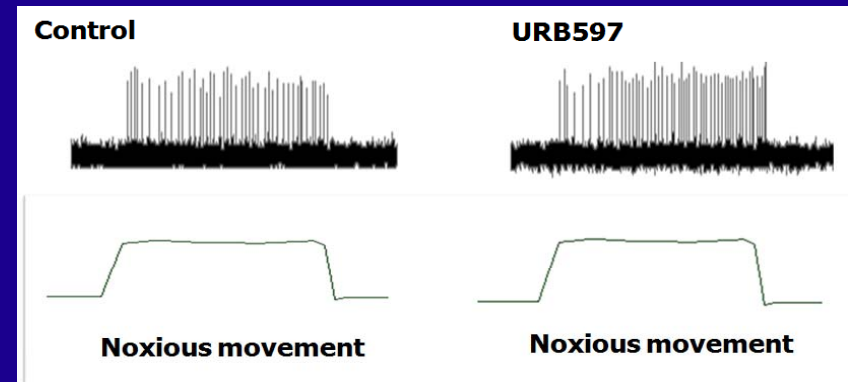
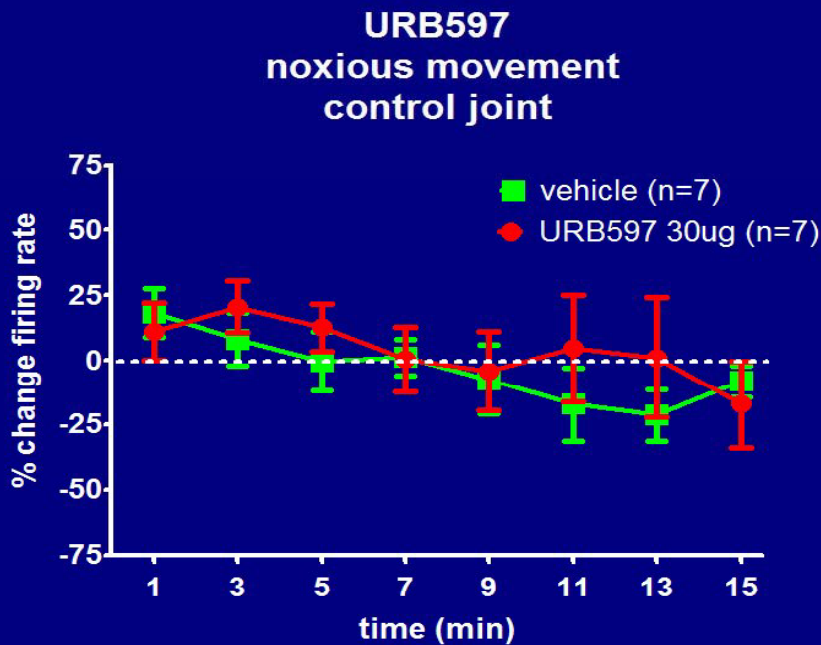
**URB597 (30  $\mu$ g/100 $\mu$ l bolus) reduces mechanosensitivity of afferent nerve fibres by up to 56%**

# CB<sub>1</sub> antagonist + URB597 MIA model



Co-administration of the CB<sub>1</sub> antagonists AM251  
abolishes effect of URB597

# URB597 control rat



URB 597 has no effect in the control joint  
→ no endocannabinoid release?

# Conclusion

- Local intra-arterial injection of URB597 into the OA joint of MIA rats alleviates peripheral sensitization of knee joint afferents and reduces pain transmission during noxious movement of the joint
- URB597 has no effect on nerve activity in control joints
- Systemic administration of CB1 antagonists AM251 abolishes the analgesic effect of URB597, confirming that the effect is mediated via CB1 receptors
- We anticipate that these findings could lead to the development of more effective analgesics for serious pain conditions in OA

# Acknowledgements

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A H F M R



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