In-vitro Inflammatory Knee Pain: Of Mice and Men

Sampurna Chakrabarti[1], Luke A. Pattison[1], Kaajal Singhal[1], David C. Bulmer[1], @fluorescence_SC Deepak R. Jadon[2], and Ewan St. John Smith[1] @psalmotoxin

[1]Department of Pharmacology, [2]Department of Medicine

Highlights:

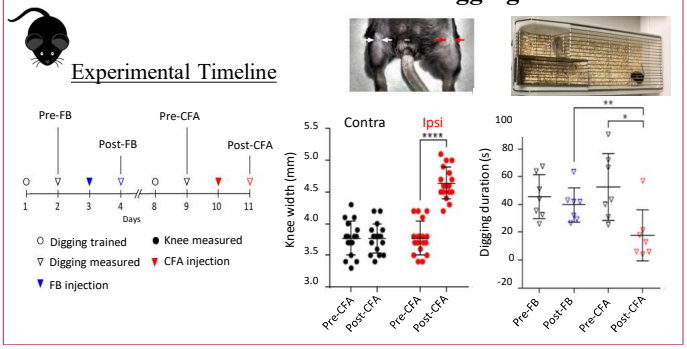
- Mice display reduced natural digging behavior after complete Freund's adjuvant (CFA) induced knee inflammation.
- Knee-innervating dorsal root ganglion neurons are more excitable after inflammation.
- After inflammation, knee neurons show upregulation of the heat-sensing ion channel, transient receptor potential vanilloid 1 (TRPV1) and a TRPV1 blocker reverses the CFA-induced reduction in mouse digging behaviour.
- Synovial fluid from osteoarthritic patients directly increases sensory neuron excitability and dysregulates transient receptor potential channel signalling.

Introduction:

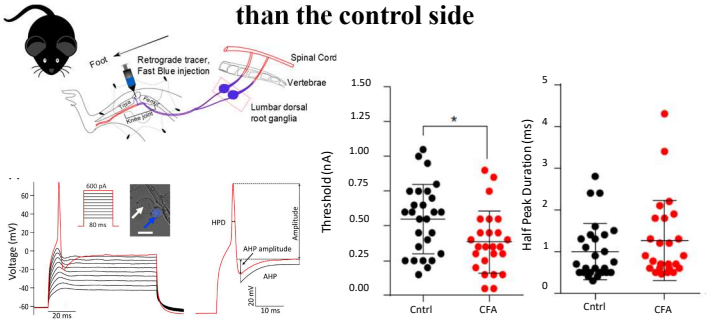
- Knee arthritis is a leading cause of disability with pain being a defining clinical symptom.
- Digging is an ethologically relevant rodent behavior that models spontaneous pain in human arthritic patients [1].
- Complete Freund's adjuvant- (CFA) induced knee inflammation is an important model for studying inflammatory arthritis, but only partially recapitulates human arthritis and hence have limited translational potential [2].
- Synovial fluid in osteoarthritic patients contain inflammatory mediators, many of which can sensitize the nerves innervating the knee [3]. These nerves have their cell bodies in the dorsal root ganglia.
- Knee neurons can be activated by transient receptor potential (TRP) channel agonists, capsaicin (TRPV1), cinnamaldehyde (TRPA1) and menthol (TRPM8). These TRP channels transduce noxious stimuli and are important for sensory neuron chemosensitivity [4].

Stimulating sensory neurons with synovial fluids obtained after routine synovial fluid aspirations from arthritic patients can be used to identify new, clinically relevant targets of arthritic pain.

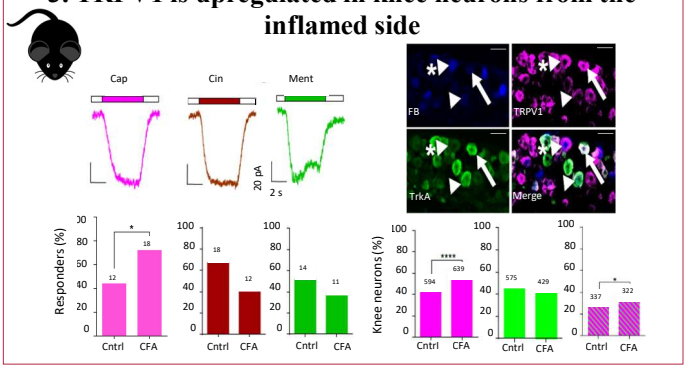
1. Knee inflammation decreases digging behavior



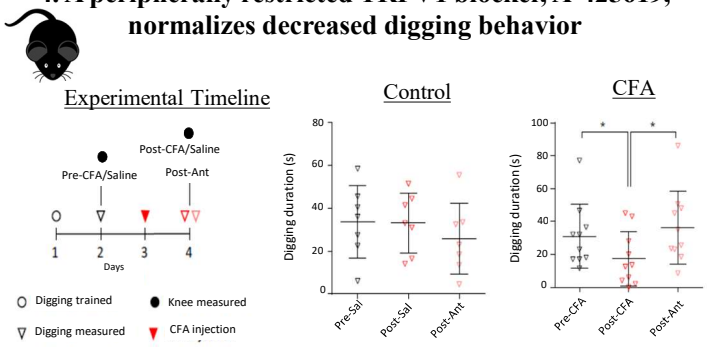
2. Knee neurons from the inflamed side are more excitable than the control side



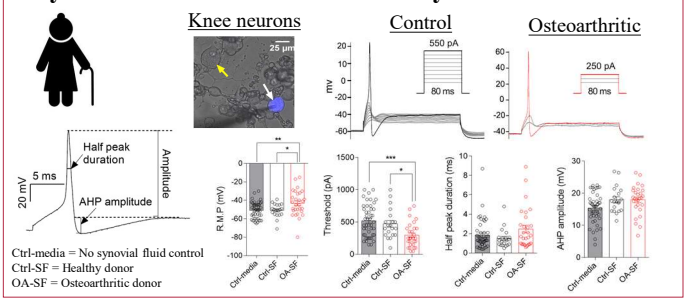
3. TRPV1 is upregulated in knee neurons from the inflamed side



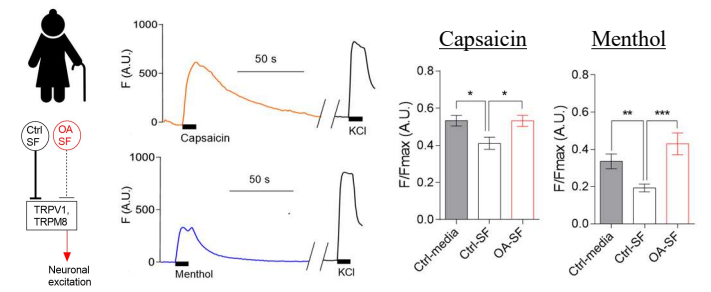
4. A peripherally restricted TRPV1 blocker, A-425619, normalizes decreased digging behavior



5. Incubation with osteoarthritic, but not healthy synovial fluid increases excitability of knee neurons.



6. Incubation with osteoarthritic synovial fluid dysregulates TRP channel activity



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References: [1] Deacon 2006, Nat Protoc 1, 122-4 [2] Gauldie et al. 2004, J Neurosci Meth 139, 281-91 [3] Leung et al. 2017, Osteoarthritis Cartilage 25, 1420-7 [4] Chakrabarti et al. 2018, Neuropharm 143, 49-62