**Q8. Can we identify pain mediated by nociceptive mechanisms, neuropathic, and nociplastic mechanisms in experimental models of OA?**

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**RESPONSE:** YES. Nociceptive pain can be readily identified in OA models, while identifying neuropathic and nociplastic pain is more challenging.

**LEVEL OF EVIDENCE:** Varies based on mechanism. Nociceptive mechanisms – Strong evidence; Neuropathic mechanisms – Moderate evidence**;** Nocipastic mechanisms –Limited evidence.

**RATIONALE:**

**Methods:** PubMed searches for "osteoarthritis pain AND rat" and "osteoarthritis pain behavior AND mouse" produced a total of 1314 and 926 results respectively (search made 5.1.2026). Search narrowed: "osteoarthritis nociceptive AND mouse" (96 results) "osteoarthritis nociceptive AND rat" (206 results), "osteoarthritis neuropathic AND mouse" (38 results), "osteoarthritis neuropathic AND rat" (76 results), "osteoarthritis nociplastic AND mouse" (1 result), "osteoarthritis nociplastic AND rat" (2 resuls).

**Nociceptive mechanisms:** Defined as processes underpinning the detection and response to a painful stimulus following the activation of sensory nociceptors. These peripheral, spinal and brain mechanisms occur without overt nervous system damage, responses are stimulus dependent and include processes that result in reversible peripheral and central sensitization. Pain states exhibiting nociceptive mechanisms have functional descending inhibitory control pathways.

**1) Sensory afferent morphology, spontaneous and evoked responses of sensory neurones and spinal neurones.** Models of OA exhibit nociceptor neuroplasticity in the damaged knee joint, including sprouting in the synovium and the subchondral bone and increased $Na_V1.8$+ innervation at later stages of the DMM model[1,2]. In this model, development of pain behaviour is associated with increased sensory nerve fibres and DRG expression of calcitonin gene-related peptide (CGRP)[3]. Increased CGRP and TrkA immunoreactivity in DRGs innervating subchondral bone and knee joint was positively correlated with subchondral bone damage score, but not cartilage degeneration in MIA rats[4]. The percentage of CGRP-positive cells in medium/large cells was significantly increased in MIA rats[4]. Knee joint mechanosensitive afferent fibre recordings suggest C-fibre contributions to spontaneous pain behaviours, and A fibre contributions to stimulus-evoked pain behaviour in MIA rats[5]. Increases in joint afferent firing frequency are MIA dose related[6]. However, at the population level, studies of multiple retrogradely labelled joint afferents did not identify increased spontaneous activity in PMX mice[7]. Knee joint levels of multiple pro-nociceptive molecules and receptors are increased in mouse models of OA[8] and local administration of nociceptive molecules increased the movement-evoked activity of joint afferent sensory nerves[9] and spinal neuronal responses in MIA rats[10]. Alterations in high-threshold mechanosensitive ion channel properties in MIA mice contribute to peripheral sensitization[11]. Evidence for spontaneous firing and spinal sensitization, which is maintained at the spinal level, is strong in the MIA model[12-15]. Supported by increased contributions of Nav1.7 and 1.8 within nociceptive pathways in OA models at peripheral and central levels, and increased spinal voltage-gated calcium channel contributions[16-19]. Mixed evidence is evident for altered markers of central sensitization, protein levels of c-Fos and p-ERK1/2 and IBA-1 and GFAP were not altered in the spinal cord of DMM mice[3] but are increased in MIA rats[20]. Evidence for altered top-down control of spinal excitability, with increased RVM contributions and increased opioid sensitivity at later stages in the MIA model[21].

**2) Pharmacological interventions supporting nociceptive mechanisms.** Strong evidence includes the ability of morphine, tramadol and oxycodone to reduce MIA-induced behavioural responses

(movement-evoked pain behaviours, lowered mechanical thresholds and heat hyperalgesia)[22, 23]. Strong evidence from blockade of the archetypal nociceptive channel, TRPV1. Intra-articular TRPV1 antagonism attenuates MIA-induced WB asymmetry[24], intra-arterial antagonist administration reduces mechanically-evoked firing of joint afferents in MIA rats and reversed the lowered mechanical thresholds[24]. Spinal TRPV1 antagonism inhibits spontaneous and evoked responses of nociceptive specific and WDR neurones in rat models of OA[15].

**Neuropathic Mechanisms:** neuropathic pain is defined as arising from a lesion or disease of the somatosensory system. OA models display several neuropathy-like features, yet discrimination of neuropathic mechanisms from other mechanisms requires converging lines of supporting evidence.

**1. Peripheral Nerve Injury:** Activating Transcription Factor (ATF3) expression in ipsilateral DRGs is an indicator of neuropathy across OA models1–4. ATF3 is absent in intact DRGs, but induced by peripheral axotomy (not by inflammation5), and can be co-expressed with Growth Associated protein 436 during regeneration. ATF3 is reported in the MIA model1–4, where its expression is dose-dependent6,7. High MIA doses produce biphasic expression with strong early peaks (6), which may reflect MIA-induced acute toxicity1. More convincing evidence for neuropathic mechanisms is low dose MIA (0.3mg) induced delayed persistent low-level ATF3 expression at later timepoints, compared to high dose MIA6. Reduced intra-epidermal fibre density7 and reduced retrograde labelling of knee afferents suggests nerve fibre retraction from the joint 8, sympathetic sprouting1, and afferent nerve demyelination, which appears earlier and more prominently in the MIA model, compared to the MMT model9–11. Note evidence for sex differences in nerve injury and behavioural changes in PTOA models12.

**2. Central neuroinflammatory mechanisms**: These occur in non-neuropathic pain states and therefore cannot be attributed specifically to neuropathic mechanisms. In OA models, spinal gliosis is reported from week one onwards, and often parallels ATF3 expression in DRGs1,2,7,14. However, gliosis can precede detectable nerve injury15. Glial inhibition can attenuate mechanical hypersensitivity, but not cold hypersensitivity1, suggesting gliosis alone is insufficient to drive neuropathic mechanisms. MIA and surgical (ACLT/DMM) exhibit changes reflective of central sensitization16–19. In the MIA model, dorsal horn c-Fos induction occurs only in the presence of ongoing NSAID-resistant pain behaviour, and A- and C-fibre–evoked responses are amplified without threshold shifts, consistent with central hyperexcitability rather than altered peripheral sensitivity20. High MIA doses can recruit supraspinal descending facilitation20, consistent with neuropathic mechanisms. Although central sensitization implicates a neuropathic component, overlap with nociceptive mechanisms limits specificity of mechanisms.

**(3) Behavioural hypersensitivity and (4) Pharmacological profile:** Behavioural pain readouts of OA models lack mechanistic specificity per se, however secondary mechanical7,23and cold1,7,23,24hypersensitivity are strongly suggestive of neuropathic mechanisms, especially when co-supported by markers of neuropathy (ATF3 expression7) and pharmacological verification9,25. Pharmacological responsiveness does require caution as commonly used neuropathic pain drugs, (SNRIs and anticonvulsants such as gabapentin) exert broader central modulatory effects, not univocally confirming neuropathic mechanisms. Evidence for neuropathic mechanisms is strengthened when neuropathic-pain drugs have beneficial effects in NSAID resistant models of OA9,25.

**Nociplastic mechanisms:** Distinct from nociceptive and neuropathic pain, mechanisms may include augmented CNS pain and sensory processing and altered pain modulation, symptoms may include more widespread or intense pain than expected given the amount of identifiable tissue or nerve damage, as well as CNS-derived symptoms (fatigue, sleep, memory, and mood problems). Two papers were identified from the pubmed search[X][Y], but upon scrutiny provided no supporting evidence. Widening the search to the aforementioned symptoms, provided evidence of alterations in sleep patterns in MIA rats, increased negative affective behaviors, changes in circadian patterns, persistent cognitive impairments, and late development of depressive-like behavior in MIA mice.

**Commented [VC1]:** I am excluding this model as not considered model of OA and limited space Additionally, nerve-injury oriented approaches like LPA models, demonstrate demyelination and widespread ATF3 induction within the DRGs, without overt inflammation9,13. While effectively modelling peripheral neuropathy the high proportion of damaged nerves (~50% of assessed DRG neurons) raises questions about clinical comparability.

**Commented [VC2]:** I would remove this Behaviourally, several studies in MIA models support a biphasic pattern characterized by an early phase, transient resolution, and later re-emergence of pain-related phenotype6,7,21 consistent with an initial inflammatory stage (e.g. increased inflammatory cytokines) 22, followed by a delayed neuropathic contribution supported by neuropathy markers, as described above.

**Commented [VC3]:** Predictive and concurrent validity of pain sensitivity phenotype, neuropeptidomics and neuroepigenetics in the MI-RAT osteoarthritic surgical model in rats - PubMed
NLRP3 inflammasome activation in sensory neurons promotes chronic inflammatory and osteoarthritis pain - PubMed

**Commented [VC4]:** Sex differences in sleep pattern of rats in an experimental model of osteoarthritis - PubMed

Sleep pattern in an experimental model of osteoarthritis - PubMed

**Commented [VC5]:** Blockade of the Sigma-1 Receptor Relieves Cognitive and Emotional Impairments Associated to Chronic Osteoarthritis Pain - PubMed

**Commented [VC6]:** Differences in multidimensional phenotype of 2 joint pain models link early weight-bearing deficit to late depressive-like behavior in male mice - PubMed

Supraspinal neuroinflammation and anxio-depressive-like behaviors in young- and older- adult mice with osteoarthritis pain: the effect of morphine - PubMed

**Conclusion:** There is a very high level of evidence of pain mediated by nociceptive mechanisms from many studies of various experimental models of OA in mice and rats. Although less widely studied, there is substantial evidence for neuropathic mechanisms in experimental models of OA, however not all evidence is equal and should be triangulated to increase confidence. Behavioural evidence is essential but should be supported by appropriate correlates of neuropathic mechanisms that are temporally aligned with structural changes to the joint and nerves. There are very few studies of nociplastic mechanisms and the supporting evidence for these mechanisms in experimental models of OA is scarce, which aligns with the limited evidence of these mechanisms in models of neuropathic pain.

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