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Osteoarthritis pain: What are we learning from animal models?

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Abstract

All experimental models of osteoarthritis (OA)-like joint damage are accompanied by behaviors indicative of pain. In experimental knee OA, evoked pain responses to exogenously applied stimuli suggest that animals become sensitized to mechanical stimuli. Neurobiological techniques, including electrophysiology and *in vivo* calcium imaging, confirm that joint damage is associated by peripheral sensitization to mechanical stimuli. Several mediators present in the OA joint can cause peripheral sensitization, most notably the neurotrophin, nerve growth factor. Furthermore, experimental OA is associated with neuro-inflammation in the peripheral and central nervous systems, including macrophage infiltration of the dorsal root ganglia and microglial activation in the spinal cord. Increasingly, researchers are employing models that are slowly progressive, and this approach has revealed that distinct pain mechanisms operate in a time-dependent manner, which may have important translational significance.

While the study of pain in experimental OA is rapidly evolving, applying increasingly sophisticated techniques to assess pain and unravel the neurobiology of its genesis, important gaps and limitations in our current approaches exist, which our research community needs to address.

Keywords

Osteoarthritis; Animal models; Mouse models; Rat models; Pain; Pain-related behaviors; Sensitization; Neuroinflammation; Innervation

Introduction: Why do we need to model OA pain in animals?

Chronic pain represents an enormous individual and societal burden in large parts of the world, with the back and the joints being most commonly affected (1) (2). Pain is the primary reason why people seek medical care (2). Osteoarthritis (OA) in particular is globally a major source of chronic pain. The most recent update of the Global Burden of

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Disease estimated that nearly 242 million people were living with symptomatic OA of the hip and/or knee (3).

OA is a chronic disease that mainly affects knees, hips, hands, and spine. Articular cartilage breakdown, subchondral bone remodeling, osteophyte formation, and synovitis contribute to progressive joint damage and result in functional limitations, often accompanied by pain. There are no cures that halt progression of OA joint damage, and treatment focuses largely on pain management. Standard pharmacological approaches include acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), centrally acting drugs such as duloxetine, and opiates. Unfortunately, these drugs often do not provide adequate pain relief, and their chronic use is associated with considerable toxicity (4). An urgent need exists for the development of targeted therapies that are efficacious and safe, but substantial lacunae in our understanding of the mechanisms of pain associated with joint damage hinder their development.

Basic mechanisms that initiate and maintain chronic pain have been exhaustively reviewed elsewhere (5) (6). In order to elucidate which mechanisms operate in OA, and how exactly they drive the genesis and maintenance of chronic pain in this context, studies in animal models may provide substantial value in generating novel insights, as we will discuss in this narrative review. We performed a PubMed search using the keywords “osteoarthritis”, “animal models”, “rats”, “mice”, “pain”, “pain behaviors”, “sensitization”, “neuroinflammation”, and “innervation”. From this literature, several key observations emerged that provide important insights into the pathobiology of OA-associated pain and guide directions for future research.

1. Models for the study of osteoarthritis in laboratory animals

OA joint damage can be modeled in different species using a variety of induction techniques. These models have advantages and limitations, as has been extensively reviewed (7–9). Surgical destabilization of the knee is often used to mimic injuries that occur in human knees. The most commonly used surgical techniques are transection of the anterior cruciate ligament (ACLT) or medial meniscal injury (partial or complete meniscectomy, meniscal tear, meniscal destabilization), leading to altered mechanical loading of the joint. In addition, closed non-invasive injury models have been developed to induce OA-like damage following a mechanical insult, with or without concurrent ACL rupture (9). Another category of models uses intra-articular injection of agents that disrupt metabolism in order to trigger joint damage. For example, monosodium iodoacetate (MIA) injected into the joint cavity inhibits glycolysis in chondrocytes, which causes chondrocyte death and results in inflammation, and leads to joint damage that mimics end-stage OA. Collagenase is sometimes injected intra-articularly, which destabilizes the joint and causes inflammation, again resulting in OA-like joint damage. In recent years, there have been efforts to mimic OA associated with obesity, for instance by feeding the animals a high-fat diet (10). In addition to these induced models, there are many inbred mouse strains and other laboratory animals that develop spontaneous OA with age, for example the Dunkin Hartley guinea pig and the STR/ort mouse (11).

2. How are these models used for studying pain associated with OA?

There is a vast literature on animal models of OA, but studies that incorporate pain as an outcome remain few and far between. A PubMed search for “osteoarthritis animal models” conducted on January 6, 2018 revealed 2964 papers, while searching for “osteoarthritis pain animal models” yielded 495 papers, going back to 1975, and replacing “animal” by “mouse” yielded another 20 papers focusing on OA pain. More than half of these 515 papers were discarded, because they were review articles, or they were not in animals or did not discuss pain or OA. The remaining 250 papers were divided into two groups: papers published before and after 2008 (the cut-off was chosen since 2008-2018 spans a decade). For each paper, it was determined which animal models and which pain assays were used, and what the general aims and methods were. Results are summarized in Table 1.

From Table 1, a few interesting trends can be observed. For one, the MIA model clearly has always been the most popular model for the study of OA pain, accounting for 41% of all studies before 2008, and 54% since then. The model was first described in 1987 as a means to induce OA-like joint damage (12), but it was not until 2003 that reports of associated pain behaviors were published (13) (14). Evidently, most of what we know about *in vivo* mechanisms of pain in experimental OA is based on observations in this model.

Pain-related outcomes are increasingly incorporated into OA animal studies. For example, studies aiming to test the efficacy of an intervention for slowing down structural joint damage now often include a pain-related outcome (Table 1). These pain outcomes range from assessing behaviors to applying ever more sophisticated neurobiological techniques in order to deepen our understanding of the mechanisms that initiate and maintain pain in OA.

Traditionally, preclinical pain research has focused on eliciting a specific type of pain using a targeted injury. An example is intra-articular injection of carrageenan, which triggers inflammation and long-lasting hyperalgesia (15). Such an approach may shed light on mechanisms of inflammatory pain, but it does not inform us on the contribution of these mechanisms to pain in OA. The past decade has witnessed significant changes in the way the research community approaches modeling OA as a disease. Increasingly, more disease-specific models are employed. Surgical models are generally considered more translationally relevant for OA joint pathology than the MIA model, especially for the early stages of disease (discussed in (7)). Slowly progressive models of OA may be key for exploring the bidirectional relationship between structural joint damage and pain. The chronic progressive nature of OA should be an important consideration when studying its pathophysiological mechanisms. It can be anticipated that mechanisms of pain will differ in early *vs.* late stages, and this is likely to have translational significance for efficacy of targeted therapies (as shall be discussed later). Indeed, in recent years, researchers have been increasingly monitoring pain in a longitudinal fashion (Table 1).

2.1. Experimental OA is associated with pain-related behaviors

In all models of OA joint damage, the presence of pain has been reported at some point. Various methods have been used to assess if animals experience pain or discomfort in the affected joint or elsewhere (Table 2). In OA patients, pain has a clear mechanical component; for example, knees hurt when walking or climbing stairs, and this can be an early sign of OA (16) (17). Lastly, quantitative sensory testing in OA patients has demonstrated reduced thresholds to mechanical stimuli, at the affected joint as well as at remote sites (18). Hence, behavioral testing in OA models most often focuses on sensitivity to mechanical stimuli.

Table 2 summarizes pain behaviors that have been assessed in OA models. Several recent reviews describe the strengths and limitations of these techniques, and discuss how they should be optimally performed (19, 20). Pain behaviors reported in experimental models can be broadly grouped into 4 categories. (1) The majority of studies assess evoked pain behaviors, where a response to an external mechanical or thermal stimulus is recorded. Most often, a mechanical stimulus is applied to the hindpaw, using von Frey filaments, effectively measuring referred pain and not pain in the knee. Mechanical allodynia in the hindpaw can be readily detected in the MIA model and in surgical models (20). Hyperalgesia in the affected knee has also been reported, where a force is applied to the knee and a response (vocalization or withdrawal) is recorded. (2) Weight-bearing asymmetry between the arthritic and the contralateral hindlimb can be assessed using an incapacitance tester. Weight-bearing deficits have been observed in various models, including MIA and joint instability models (20); (3) Gait analysis has become a widely available technique, most often assessing spatiotemporal gait parameters (reviewed in (21)). Gait patterns provide information about mobility and limb function, but they can also reveal pain, since the animal may alter its gait to protect an affected limb from pain when walking (21); (4) Assessment of spontaneous pain: in recent years, efforts have been made to try and determine if animals experience spontaneous pain. Several methods have been developed, such as activity monitoring (for example through video recording or LABORAS platforms) (20), burrowing (22), and conditioned place preference testing (23).

It is worth emphasizing that, although only a fraction of studies attempt to measure pain, it appears that some form of pain is always present and this throughout the duration of the study (both in early and late stages of disease), even if pain is not readily evident. Its presence should always be considered for ethical reasons but also for scientific reasons, since it remains unknown how pain affects the progression of OA. This clearly represents a gap in our current research approaches to OA as a disease, and animal models offer a tremendous opportunity for exploring this relationship.

2.2. Animal models of OA are characterized by peripheral sensitization to mechanical stimuli

Evoked pain responses in OA animals are indicative of sensitization—Pain responses to mechanical stimuli, as described above, suggest that joint neurons become sensitized in the course of OA. Carrageenan or complete Freund's adjuvant (CFA)-induced inflammation in the knee, for example, or the antigen-induced arthritis (AIA) model, are accompanied by mechanical knee hyperalgesia (pain evoked by gentle pressure to the knee or by movement in the normal range) (24) (25). Likewise, models of knee OA are characterized by hyperalgesia to mechanical stimuli at the affected knee, as has been reported after partial meniscectomy (26), after destabilization of the medial meniscus

(DMM) (27), and after intra-articular MIA (28) (29), which is suggestive of peripheral sensitization to mechanical stimulation.

Neurobiological techniques confirm peripheral sensitization to mechanical stimuli—Sensitization of joint afferents can be objectively quantified through electrophysiological recording of neuronal activity. In models of inflammation, *in vivo* recording of activity of joint afferents has shown that high-threshold C and Aδ afferents become sensitized to mechanical stimuli applied to the joint, and that mechano-insensitive (silent) nociceptors become mechanosensitive (30). In healthy rats and guinea pigs, as well as in MIA-treated rats, noxious outward rotation of the knee increased firing of joint afferents compared to non-noxious rotation (31–33). Furthermore, the firing rate of C and Aδ afferents was increased after intra-articular MIA compared to controls, and this in response to both non-noxious and noxious knee rotation (33). Finally, a recent study used *ex vivo* electrophysiology to demonstrate that 3 weeks after MIA injection, mechanosensitive ion channels on knee-innervating nociceptors were sensitized to a negative pressure stimulus (29). Intra-articular injection of the mechanosensitive ion channel blocker, GsMTx4, reversed knee hyperalgesia at this time point (29).

Consistent with electrophysiological findings, we recently reported peripheral sensitization in the DMM model, adapting a newly developed *in vivo* calcium imaging technique where sensory neuron activity in response to mechanical stimuli is monitored in real time. Using Pirt-GCaMP3 mice (which encode the fluorescent calcium reporter protein, GCaMP3, in sensory neurons), one can monitor calcium $[Ca^{2+}]_i$ responses of hundreds of neurons within the dorsal root ganglia (DRG) in live, anesthetized mice in an unbiased fashion, without determining *a priori* which type of fiber to record (34). We visualized responses in the L4 DRG (where the cell bodies of knee afferents reside) and found that, 8 weeks after DMM, increased numbers of DRG neurons responded to physical stimuli directed toward the operated knee or ipsilateral hind paw, compared to sham-operated mice. This correlated with the presence of knee hyperalgesia and mechanical allodynia (34). These mechanosensitive neurons were small-to-medium sized, consistent with C and Aδ fibers. In addition, the magnitude of the response of the responding neurons was similar in both sham and DMM mice, suggesting that peripheral sensitization occurs through recruitment of additional neurons, as opposed to through increased intensity of the response of individual neurons. These newly recruited neurons may be ‘silent nociceptors’ that have become mechanically sensitized, or they may be indicative of nociceptors becoming polymodal, such that they now respond to mechanical forces in addition to other stimuli like heat, cold or chemicals (35). We anticipate that the use of such novel neurobiological methods to monitor neuronal mechanosensitivity will provide a powerful new way of screening novel therapeutic agents that treat OA pain by reducing the excitability of the set of nociceptors recruited in association with joint damage.

Mediators in the OA joint cause peripheral sensitization—These observations in experimental models indicate that joint nociceptors are sensitized in the presence of joint damage. This begs the obvious question: how does this happen? As has been reviewed elsewhere, nociceptors express a broad array of receptors (36), such as cytokine receptors, pattern recognition receptors, G protein-coupled receptors (GPCRs, including receptors for chemokines, the PGE_2 receptor, the bradykinin receptor, and the histamine receptor), as well as the receptor for nerve growth factor (NGF), TrkA. Activation of these receptors can result in modulation of transient receptor potential cation channel subfamily A member (TRPA) 1, transient receptor potential vanilloid (TRPV) 1, the mechanosensitive Piezo2 channel, and voltage-gated sodium channels ($Na_V1.7$, $Na_V1.8$ and $Na_V1.9$), leading to hyperexcitability, *i.e.* peripheral sensitization.

One molecule present in OA joints appears to be key in peripheral sensitization of nociceptors, and this is the neurotrophin, NGF. A large body of literature has shown that NGF sensitizes nociceptors (37) and clinical trials with humanized monoclonal antibodies that bind NGF are ongoing for OA. While these trials suggest remarkable efficacy for OA pain, an ill-understood side effect can occur in patients treated with anti-NGF therapy, which is rapidly progressive OA (discussed in (38)).

NGF is present in the joints of animals with OA (39) (40) (41), where it exerts a profound sensitizing effect. For example, NGF administered into the facet joint in naïve rats induces behavioral hypersensitivity and spinal neuronal hyperexcitability (42), and injecting NGF into the rat knee causes weight-bearing asymmetry (43). An interesting study showed that OA knees are more sensitive to NGF-induced pain compared to non-OA knees (44), where intra-articular injection of NGF into rat knees with experimental OA produced a more prolonged augmentation of weight-bearing asymmetry compared to control knees. This coincided with increased expression of the NGF-receptor, TrkA, in the DRG during experimental OA (44). In concordance with these pro-algesic effects of NGF, neutralizing antibodies against NGF have been reported to be analgesic in different animal models of OA, in prophylactic as well as in therapeutic protocols, including in the MIA (45) (46) (22, 47) and the rat MMT model (48). Similarly, an oral TrkA inhibitor was efficacious in a rat surgical model (49). These studies support the clinical trial results that blockade of NGF signaling is effective in treating OA pain, but some of these studies also found more rapid cartilage degeneration, synovitis, and possibly subchondral bone changes, particularly when anti-NGF treatment starts in the earlier stages of disease (38). The mechanism of this effect on joint structure clearly needs further exploration.

Increasingly robust evidence indicates that NGF plays a key role in sensitization in the OA joint, but other mediators present in the joint can also contribute to sensitization, including cytokines, chemokines, prostaglandins, bradykinin, or TLR ligands such as disease-associated molecular patterns, including S100, matrix fragments, *etc.* (reviewed in (50)). We recently reported that a specific 32-mer fragment of aggrecan, generated by the orchestrated action of ADAMTS- and MMP-mediated cleavage of the aggrecan core protein, directly excites DRG sensory neurons through TLR2. Intra-articular injection of the 32-mer fragment provoked knee hyperalgesia in wild-type but not *Tlr2* null mice. Blocking the production or action of the 32-mer in transgenic mice prevented the development of knee hyperalgesia in the DMM model, suggesting that the aggrecan 32-mer fragment may be a mediator of OA-associated joint pain (51).

In vivo evidence that different potentially sensitizing molecules contribute to OA-associated pain remains scarce, and the relative contributions of these different molecules have not at all been elucidated.

2.3. Experimental OA is associated with neuro-inflammation in the peripheral and central nervous systems

Animal models of OA have been used to study the role of macrophages in joint damage (52, 53), but how macrophages in the OA joint may potentially contribute to joint pain has not yet been studied. Other immune cells in the joint have recently been implicated in experimental OA pain, specifically mast cells (54). When MIA was injected into the knee of transgenic mice harboring a TrkA gain-of-function mutation, increased TrkA receptor signaling resulted in increased pain, accompanied by higher numbers of macrophages and mast cells in the synovial fluid. A close anatomical connection between mast cells and peptidergic C-fibers in the synovium suggests a role for mast cell-to-nociceptor communication in OA pain (54). Mast cells release histamine, which may contribute to nociceptor sensitization (36) and they can release NGF and respond to it (maturation, degranulation) (55).

While pro-algesic effects of macrophages and immune cells within the OA joint remain largely unexplored, it has long been known that neuro-immune interactions in the pain pathway are essential for the initiation and maintenance of chronic pain (56). In models of neuropathic pain, a large body of work describes the neuro-immune changes that occur both peripherally and in the central nervous system (CNS). Peripheral nerve injury causes an immune response in the DRGs, with infiltration by neutrophils, T-cells, and macrophages. Bi-directional signaling between these immune cells and sensory neurons dynamically modulates pain (56). Furthermore, inflammatory cells resident to the CNS, microglia and astrocytes, also respond to peripheral nerve injury (57). Microglia are considered the resident macrophages of the CNS. After peripheral nerve injury, these cells undergo phenotypic changes into a pro-inflammatory activated phenotype (“microgliosis”), with an increase in CD11b immunoreactivity. Activated microglial cells promote chronic pain through the production of cytokines and chemokines (57).

Inflammatory models are also characterized by neuro-immune responses in the neuraxis. For example, intraplantar injection of CFA results in infiltration of macrophages in the DRGs (58). This also occurs in AIA, without any evidence of nerve damage, and correlates with pain-behaviors (59). Neuro-inflammation is now also being reported in disease-specific OA models. Starting 8 weeks after DMM surgery, L4-DRG are infiltrated with F4/80 macrophages, a time-point at which CCL2 and its receptor, CCR2, are upregulated in DRG neurons, concurrently with onset of locomotion-induced pain (60). *Ccr2* null mice show less macrophage infiltration into the DRG than wild-type mice after DMM surgery, and they are protected from persistent pain (60). In agreement with these findings in *Ccr2* null mice, a recent study demonstrated that pharmacological blockade of CCR2 was sufficient to reverse weightbearing deficits in the DMM model (61).

Microgliosis has also been reported in inflammatory models, such as after intraplantar or intra-articular administration of CFA (62), as well as in OA models. In the rat, dorsal horn microgliosis appeared as early as day 3 after administration of MIA, coinciding with secondary mechanical allodynia (63). In a mouse study, MIA caused secondary allodynia by day 3, maintained for 28 days. At both time points, the number of dorsal horn microglial cells was enhanced in MIA compared with controls (64). Thus, in the MIA model, microgliosis develops quite rapidly. In contrast, in the murine DMM model, microgliosis does not occur until the later stages of the disease (8 and 16 weeks after surgery), coinciding with the onset of persistent pain behaviors (65).

In summary, neuro-immune changes in the DRG and dorsal horn indicate that both the peripheral and central nervous system react to OA joint pathology. Importantly, when DMM surgery is performed in *Adamts5* null mice, which do not develop OA joint damage or associated mechanical allodynia in this model (66) (67), these neuro-immune changes do not occur (65) (and unpublished observations), suggesting that protecting the joint prevents peripheral sensitization and subsequent changes in the CNS.

2.4. Distinct pain mechanisms operate in a time-dependent manner

It is becoming increasingly clear that OA pain is heterogeneous, on the basis of its location, precipitating factors, and responsiveness to NSAIDs and other medications. Many patients can report more than one type of pain, and the pain experience changes as disease progresses (68) (69). Remarkably, as the field of modeling pain associated with experimental OA is progressing, this heterogeneity is also becoming more evident in OA models. The type of pain behaviors present may be dependent on the model, as has been reported for thermal allodynia, which is detected in more inflammatory models such as collagenase-induced OA (70) but absent up to 8 weeks after DMM (67). Furthermore, one study monitored pain following intra-articular MIA *vs.* partial meniscectomy (MNX) and revealed that MIA rats displayed persistent robust secondary mechanical allodynia and hyperalgesia, whereas partial MNX was associated with milder and slower-onset allodynia, without hyperalgesia. Joint damage was similar in both models, and the authors concluded that "the type of joint damage rather than the absolute extent is important in generating a behavioural pain response" (71). This was confirmed in an independent laboratory (72). Different induction methods all lead to end-stage OA, but the pathological processes to reach that point may differ, and these may therefore be associated with different pain behaviors. Careful studies in experimental models provide an opportunity to address such issues, and hence shed light on structural correlates of joint pain.

Table 1 reveals that in the last decade, more studies assess pain-related behaviors at different stages of the disease. From such studies, it is emerging that the type of pain-related behaviors, their response to therapy, and the mechanisms involved are dependent on the stage of the model. For example, in rat MIA, NSAIDs reverse weight-bearing deficits, paw and knee hyperalgesia in the first 2 weeks after induction (71, 73, 74). In contrast, in later stages, only centrally acting drugs such as morphine and gabapentin are effective (71, 74, 75). One study confirmed that naproxen, an NSAID, blocked spontaneous neuronal activity from joint afferents only during the early phase (74). These time-dependent effects are also present in surgical models. After partial meniscectomy in the mouse knee, Knights and colleagues (26) observed mechanical hypersensitivity in 2 phases: an early phase was reversed by the NSAID, diclofenac. Pain then resolved for several weeks, followed by a second phase of NSAID-insensitive but morphine-responsive pain. Interestingly, during the pain-free interval, hypersensitivity could be unmasked by the opioid antagonist, naloxone, indicating that reduced pain during this period was due to endogenous opioids. The latter was also reported in the DMM model, where spontaneous pain behaviors are delayed until 8 weeks after surgery (76) (60). Here, administration of naloxone resulted in pain 4 weeks earlier than in vehicle-treated mice, again suggesting that delayed pain in this model is the result of increased endogenous opioid function. Expression of the μ-opioid receptor in the peripheral nerves innervating the joint was transiently increased after DMM (76).

To complement these pharmacological studies, we have utilized DREADD (Designer Receptor Activated by a Designer Drug) technology to selectively inhibit nociceptors at different time points after DMM surgery (27). We used the DREADD receptor engineered for neuronal silencing, Pdi, which is selective for the synthetic ligand, clozapine-N-oxide (CNO), and expressed it in $Na_V1.8$ neurons (the majority of which are nociceptors). Administering CNO to these $Na_V1.8$-Pdi mice blocked knee hyperalgesia and secondary mechanical allodynia at the early stages of disease, but silencing nociceptors was no longer effective during the later stages (>8 weeks after DMM). In contrast, morphine, a drug that activates inhibitory GPCRs in both the peripheral and CNS, was still effective in late-stage disease (27). Together, these results suggest that at the later stage of the DMM model, targeting the peripheral nervous system alone may be insufficient to inhibit pain.

3. How can we use animal models to fill in key gaps in our understanding of OA pain?

The study of pain in experimental OA is rapidly evolving, using increasingly sophisticated techniques to assess pain and unravel the neurobiology of its genesis. However, important gaps and limitations in our current approaches exist, which our research community needs to address in order to study OA pain in laboratory animals with the rigor it deserves. Some pressing examples are briefly discussed below:

The sensory innervation of the joint changes in the course of OA

Anatomical studies (predominantly in rat and cat knees) have used microscopy to describe joint innervation and reveal that, except for articular cartilage, all joint tissues are extensively innervated by sensory and sympathetic neurons (77, 78). Information on the sensory innervation of the OA joint is scant, and was recently reviewed elsewhere (79). In brief, it appears that there is a loss of peptidergic fibers in inflamed synovium, while there may also be neuronal sprouting in the painful joint. Intra-articular injection of CFA into the mouse knee causes ectopic sprouting of nerves (80, 81). Treatment with anti-NGF reduced pain-related behaviors, as well as neuronal sprouting of nerve fibers (but had no effect on increased density of blood vessels or macrophages), suggesting that ectopic sprouting occurs in the arthritic joint and may be involved in pain generation (81). Nerve growth also appears to accompany increased vascularization of certain tissues in OA, including the meniscus, osteophytes, and subchondral bone. Vascular channels that breach the tidemark between the subchondral bone and articular cartilage (osteochondral channels) may contain both sympathetic and sensory nerves, which may contribute to pain (82).

Clearly, there is a pressing need for a deeper understanding of joint sensory innervation, and how it changes during the course of OA. Based on the limited information available, it appears that extensive remodeling of sensory innervation is an integral part of the OA disease process. However, detailed information is lacking and the factors that mediate these processes need further clarification in order to determine their importance for OA pain.

OA is a heterogeneous disease, with multiple risk factors

Although there are many risk factors for OA, including joint injury, aging, obesity, and genetic predisposition, the majority of preclinical research has focused on joint injury models in relatively young animals. Few studies have examined the pain phenotype in aging or obesity models, but the studies to date suggest that pain behaviors may present differently. A recent study in MIA mice compared pain behaviors and microgliosis in young *vs.* old mice, and observed that both were attenuated in aged mice (83). Two obesity model studies observed that different high-fat diets influenced strength but not spontaneous activity (84) (85).

Clinically, there has been an increased push for classification of phenotypes to aid clinical practice and clinical trial design (86). It will be important for animal model research to follow suit.

OA affects women and men

Unfortunately, animal studies are often limited to one sex, and this is most often the male sex. For example, only male C57BL/6 develop OA after DMM (87). This represents a severe limitation of preclinical models, not only because OA and associated pain are more common in women, but also because there is increasing evidence from animal models that mechanisms of chronic pain drastically differ between male and female mice (88).

Chronic pain is associated with functional reorganization of the brain

As functional MRI methods are being increasingly adapted to small animals, initial studies demonstrate that connectivity in the brain also changes in rat models of persistent pain in similar ways as in humans (89) (90). This suggests that preclinical OA models are likely relevant for teasing out the role of the CNS in osteoarthritis pain and for testing novel analgesics, which will offer tremendous opportunities.

Conclusion

Evidence from experimental models suggests that (1) OA-like joint damage is associated with sensitization and pain-related behaviors, whichever induction method is used; (2) joint damage appears to be driving pain and sensitization; (3) multiple mediators in the OA joint are capable of sensitizing nociceptors through binding specific receptors; (4) joint damage causes neuroinflammation in the peripheral and central nervous system; and (5) it is also increasingly evident that the progressive nature of OA pain may be reflected in preclinical models, which reveal that mechanisms of pain are different in early *vs.* late stages of the disease. Clearly, such observations have translational significance, not just for unravelling basic mechanisms but also for testing new drugs. Furthermore, important gaps remain in our understanding of basic mechanisms of joint pain, and severe limitations in the way we chose to model this pain. In order to make significant progress in this area, interdisciplinary research between OA researchers, pain researchers and neurobiologists. Meaningful translation of the findings will require better integration with clinical research. We anticipate that there are exciting times ahead for our field.

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Practice points

- All animal models of osteoarthritis that have been assessed thus far are accompanied by pain-related behaviors and by signs of sensitization to mechanical stimuli.
- Nerve growth factor along with other mediators in the OA joint such as cytokines, chemokines, prostaglandins, bradykinin, and disease-associated molecular patterns (DAMPs) can cause peripheral sensitization.
- Experimental OA is associated with neuro-inflammation in the peripheral and central nervous systems, including macrophage infiltration of the dorsal root ganglia and microglial activation in the spinal cord.

Research agenda

- Increasingly, researchers are employing models that are slowly progressive, and this approach has revealed that distinct pain mechanisms operate in a time-dependent manner, which may have translational significance.
- The majority of preclinical research has focused on joint injury models in relatively young animals, often only males. Future studies should examine the pain phenotype and mechanisms in experimental osteoarthritis associated with aging or obesity, and should work to develop models for female animals.
- Testing efficacy and mechanisms of novel analgesics will require the use of sophisticated animal models and behavioral assays, and this in a temporal fashion. Effect of analgesia on joint structure should also be evaluated.

Table 1

Overview of published papers "Osteoarthritis pain animal models/mouse models" PubMed search Jan 6, 2018.

	% Before 2008 (total=36)	**% Since 2008 (total=214)**
MIA model	41%	54%
Surgical model	28%	33%
Collagenase-induced OA	N/A	3%
Other OA-relevant models (ageing, obesity)	3%	3%
Inflammatory models *	16%	6%
Large animals	19%	7%
Two models side-by-side	5%	8%
Includes neurobiology	25%	35%
Assesses more than one behavior	16%	32%
Pain assessed at more than one time point	25%	40%
Assesses pain and joint damage in same animals	33%	43%
DMOAD testing with pain as secondary outcome	5%	11%

*These include intra-articular administration of CFA or carrageenan in order to trigger joint damage and pain. MIA = mono-iodoacetate; DMOAD = disease-modifying osteoarthritis drug.

Table 2

Methods that have been reported for the assessment of pain and/or sensitization in laboratory animals with experimental OA

Classification	Test	Measurement Device
Evoked pain behaviors	Mechanical allodynia in the hindpaw	von Frey monofilaments
Evoked pain behaviors	Knee hyperalgesia	apply force to the knee, e.g. with a PAM device or by bending the knee
Evoked pain behaviors	Thermal hypersensitivity	Hot/cold plate
Weightbearing deficits	Static weightbearing	Incapacitance meter
Weightbearing deficits	Dynamic weightbearing	Dynamic weightbearing apparatus
Gait	Spontaneous	Catwalk, painting paws
Gait	Forced	*e.g.* Treadscan
Spontaneous pain behaviors	Activity monitoring	*e.g.* by video recording or on a LABORAS platform
Spontaneous pain behaviors	Conditioned place preference	Conditioned place preference chambers
Spontaneous pain behaviors	Burrowing	Custom built device