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Review

A commentary on modelling osteoarthritis pain in small animals

A.M. Malfait †‡*, C.B. Little §, J.J. McDougall ‖¶

† Department of Medicine, Section of Rheumatology, Rush University Medical Center, Chicago, IL, USA
‡ Department of Biochemistry, Rush University Medical Center, Chicago, IL, USA
§ Raymond Purves Bone and Joint Research Laboratories, Kolling Institute of Medical Research, Institute of Bone and Joint Research, University of Sydney at Royal North Shore Hospital, St Leonards, NSW 2065, Australia
‖ Department of Pharmacology, Pain Management & Perioperative Medicine, Dalhousie University, Halifax, Nova Scotia, Canada
¶ Department of Anaesthesia, Pain Management & Perioperative Medicine, Dalhousie University, Halifax, Nova Scotia, Canada

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SUMMARY

Objective: To describe the currently used animal models for the study of osteoarthritis (OA) pain, with an emphasis on small animals (predominantly mice and rats).
Outline: Narrative review summarizing the opportunities and limitations of the most commonly used small animal models for the study of pain and pain pathways associated with OA, and discussing currently used methods for pain assessment. Involvement of neural degeneration in OA is briefly discussed. A list of considerations when studying pain-related behaviours and pathways in animal models of OA is proposed.
Conclusions: Animal models offer great potential to unravel the complex pathophysiology of OA pain, its molecular and temporal regulation. They constitute a critical pathway for developing and testing disease-specific symptom-modifying therapeutic interventions. However, a number of issues remain to be resolved in order to standardize pre-clinical OA pain research and to optimize translation to clinical trials and patient therapies.

Pain and disability are the primary symptoms for patients who suffer from osteoarthritis (OA), representing one of the major health burdens in the industrialized world (reviewed in[1]). Current symptom management approaches (non-steroidal anti-inflammatory drugs (NSAIDs), viscosupplementation, opiates, corticosteroids) are largely inadequate, because of their limited efficacy, particularly for severe OA pain, and the plethora of safety issues with prolonged treatment. Ultimately, uncontrolled pain is the primary motive for total joint replacement (TJR)[2] and even after TJR a significant portion of subjects report persistent pain of unknown origin[3]. Effect sizes of NSAIDs, the most commonly used painkillers in OA, are small to moderate and often close to those of placebo[4,5]. Serious side effects associated with chronic use of NSAIDs have been extensively documented[6]. Recently, blockade of Nerve Growth Factor (NGF) was reported to be strongly analgesic in knee OA[7] but an unexpected side effect was encountered in seemingly accelerated OA, especially in patients who were taking concomitant NSAID therapy[8]. These issues underscore the significant gaps in our current understanding of OA pain: firstly, the molecular pathways that generate and maintain the pain but also the relationship between joint pathology and pain and whether this changes with disease stage, progression or initiating cause ("trigger").

Currently used animal models for the study of OA-associated pain

Filling in these considerable shortcomings in our knowledge will require that clinical research in OA patients is complemented by studies in disease-specific animal models of OA. Clinical studies provide important data on *association* between clinical symptoms (i.e., pain) and particular tissue pathologies, genetic differences (e.g., SNPs), psychosocial determinants, etc., and these can be described "risk factors". Ascribing a *causal relationship* between a specific molecular, cellular or pathological event and OA pain, requires therapeutic or prophylactic modification of that factor with a measurable change in the onset, severity or progression of the pain. In the absence of such interventions for patients with OA, defining the key changes that cause OA pain needs to be investigated in preclinical models where such factors can be prophylactically or therapeutically targeted (e.g., specific genetic mutations).

* Address correspondence and reprint requests to: A.M. Malfait, Department of Medicine, Section of Rheumatology, Rush University Medical Center, Chicago, IL, USA

E-mail address: anne-marie_malfait@rush.edu (A.M. Malfait).

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The number of research papers specifically aiming to evaluate pain and pain mechanisms in animal models of OA is surprisingly small, relative to the extent of the medical problem it represents. A Pubmed search conducted on March 31 2013 using the search terms “osteoarthritis pain” yielded 13,391 results whereas adding the keyword “animal models” revealed just 240 papers, only 113 of which were original reports on pain in OA animal models. On the contrary, a search for “animals models of OA” resulted in 1737 papers (3/25/2013), describing a plethora of models, including spontaneous and induced disease (using at least 20 induction methods) in variably aged male and female animals of some 10 different species (reviewed in[9–11]). The majority of these studies aimed to investigate the pathophysiological mechanisms of OA joint pathology and/or test potential disease-modifying therapies. It remains unclear whether any one of the array of models and or species is superior and more predictive of translation to humans, both with regard to disease mechanisms and therapeutic targets. Nevertheless, our understanding of the cellular and molecular pathways that regulate the initiation and progression of structural joint damage in OA has advanced enormously as a result of findings from animal models.

The number of OA models/induction methods used to study pain, and the animals (species, age, gender) in which they have been examined is much more restricted than for studies of structural pathology[12]. The animal models used to study OA pain and the techniques to assess pain in the papers retrieved from the PubMed search, are listed in Table I. The opportunities and limitations associated with the most commonly used models are discussed, in addition to well-established and emerging techniques for evaluating pain. We will briefly discuss evidence of neuronal degeneration in pre-clinical models, while specific mechanisms of pain uncovered in animal models are reviewed in detail elsewhere in this special issue[13]. We have focused this discussion largely on studies in small animals (mouse, rat, guinea pig) as these represent the most commonly used species for OA pain investigation, as is becoming the case in all pre-clinical medical research (understanding animal research http://understandinganimalresearch.org.uk/). There is no evidence to suggest that pain outcomes in small animals better replicate human disease than other species used (e.g., dog, sheep, horse), and these larger animals may provide more anatomically and biomechanically useful models of humans, particularly for evaluation of potential non-pharmacological symptom-modifying OA therapies (e.g., surgery, physical therapy). In dogs and horses in particular, pain and disability associated with OA is a significant clinical problem, and thus findings in these

Table I
Animal models of OA and changes in nociception/pain reported

Model	Species	Changes in nociception/pain outcomes reported
MIA	Rat (knee)	- Mechanical hypersensitivity (progressive) in hindpaw[14] - Weight-bearing deficit[14] - Altered gait[15] - Diminished hindlimb grip force[16] - Cooling hypersensitivity[17] - Vocalization in response to knee bend[15] - Conditioned place preference[18] - Locomotive changes, including rearing (assessed by photocell)[19] - Depressed wheel-running[20] - Altered sleep patterns[21]
	Mouse (knee)	- Diminished locomotion during forced exercising[22] - Mechanical hypersensitivity[23]
	Guinea Pig (knee)	- Altered weight-bearing[24] - Mechanical allodynia[24]
Surgical models (Instability inducing)	Rat ACLT	- Gait changes[25] - Weight-bearing deficits[26] - Mechanical allodynia[26]
	Rat MMT	- Weight-bearing asymmetry[27] - Mechanical allodynia[27]
	Mouse DMM	- Mechanical allodynia (von Frey) early on, maintained for 16 weeks; absence of thermal allodynia up to 8 weeks post DMM[28] - Late-onset altered behaviour on Laboras platform (reversible with indomethacin)[29,30] - Late-onset weight-bearing deficit[30];
	Mouse partial medial MNX	- Vocalization upon knee compression[31] - No weight-bearing deficit[31] - Secondary mechanical allodynia and hypersensitivity[31] - Cold hypersensitivity[31]
	Rabbit Partial MNX	Changes in weight-bearing[32]
	Dog ACLT	Altered gait and locomotion[33]
	Dog Groove model	Altered gait[34]
	Sheep MNX, DMM	Altered gait[35]
	Horse osteochondral fragment plus exercise (carpus)	Altered gait; reduced mechanical nociceptive threshold (joint flexion)[36]
Obesity-associated OA	Mouse	Changes in locomotion[37] Mechanical allodynia/hypersensitivity[37] Anxiety-like behaviours[37]
Other	Rat Collagenase-induced arthritis	Mechanical and thermal allodynia[38]
	Mouse Collagenase-induced arthritis	Changes in weight distribution[39]

References in this table represent a selection from the 113 papers revealed by the Pubmed search in addition to hand-selected papers that were missed in the search or appeared after the search date. Abbreviations used: ACLT = anterior cruciate ligament transection; DMM = destabilisation of the medial; MMT = medial meniscal tear; MNX = meniscectomy.