



- **FACT SHEET No. 4**

## **Animal Models of Osteoarthritis Pain**

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Animal models enable investigation of the mechanisms behind osteoarthritis (OA) pain and help develop novel treatments. However, OA models have largely been developed to reflect structural pathology, and only recently has their validity as models of human OA pain been explored in detail. Differences between OA pain models may reflect the differences in pain experiences between individual patients with OA.

Animals develop OA spontaneously—for example, Dunkin Hartley Guinea pigs, STR/ort mice, dogs, horses. However, the progression of development can be unpredictable, or appropriate controls are unavailable. Surgical models (e.g., meniscal and/or cruciate ligament transection, or joint destabilization) and chemical models (e.g., intra-articular injection of sodium monoiodoacetate) of OA have been developed to investigate the mechanisms underlying OA pathology and pain. At later phases, these models display characteristics of established OA in humans (osteophytes, cartilage damage, subchondral bone remodeling, pain behavior), though the early pathogenesis might differ between the models and man.

OA is a chronic disease, and therefore acute inflammatory pain models (e.g., following intraplantar or intra-articular injection of carrageenan) have limited translational relevance to human OA. Chronic inflammatory joint models, either mono-articular (e.g., following intra-articular injection in sensitized animals of Freund's complete adjuvant (CFA) or methylated bovine serum albumin) or polyarticular arthritis (e.g., systemic FCA or collagen-induced arthritis models), are also used to study the mechanisms underlying joint pain and may have relevance to aspects of OA pain.



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Murine and rat models of knee OA exhibit weight-bearing asymmetry, resembling the tendency for patients to avoid weight bearing on an osteoarthritic knee. In addition, these models exhibit lowered hind-paw withdrawal thresholds to punctate mechanical stimulation, resembling reduced mechanical pain thresholds that have been observed distant to the arthritic joint in people with knee OA.

Other behavioral endpoints, including reduction in hind-paw grip strength, changes in innate behavior (such as burrowing), and vocalization on direct pressure or torque applied to the arthritic joint, are interpreted as indicating pain in these models in the rat. Arthritis pain behavior in dogs and other large animals has largely been assessed by gait analysis, although quantitative sensory testing is increasingly used in these animals. Although changes in behavioral responses are interpreted as indicating OA pain, it must be remembered that some of these behaviors, such as change in gait, will be influenced by other factors, such as joint instability and alterations in proprioception.

Animal models of OA pain have been used to explore functional, cellular, and biochemical changes within pain pathways, from the joint up to the brain. These models of OA pain exhibit both peripheral and spinal sensitization, as demonstrated by electrophysiology. Joint inflammation, driven by increases in pro-inflammatory mediators, such as cytokines and growth factors, contribute to the sensitization of the sensory afferents and increase nociceptive output from the joint. Changes in gene expression in the cell bodies of the sensory fibers, alterations in neuromodulator release, and neuroimmune interactions with microglia and astrocytes in the spinal cord are associated with OA pain behavior. Models of OA pain are currently being used to explore the contribution of descending facilitation and inhibition in the regulation of spinal excitability associated with OA.

The translational validity of animal models of OA and the development of novel analgesics for subsequent use in man remains to be established. The demonstration that analgesics displaying efficacy in randomized controlled trials in OA patients also reduce pain behavior in animal models of OA, supports the utility of these models. Furthermore, novel analgesic strategies in development clinically, such as blocking nerve growth factor, reduce pain behavior in animal models. However, translational validity remains limited, and several drugs have shown effects in animal models but failed to significantly improve pain in man. Further refinement of animal models and their assessment, as well as better understanding of which phenotypic clinical OA subgroup is modeled by a particular animal model, will improve their translational utility in the future.

## References

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