

Focus Article

An Overview of Animal Models of Pain: Disease Models and Outcome Measures

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Abstract: Pain is ultimately a perceptual phenomenon. It is built from information gathered by specialized pain receptors in tissue, modified by spinal and supraspinal mechanisms, and integrated into a discrete sensory experience with an emotional valence in the brain. Because of this, studying intact animals allows the multidimensional nature of pain to be examined. A number of animal models have been developed, reflecting observations that pain phenotypes are mediated by distinct mechanisms. Animal models of pain are designed to mimic distinct clinical diseases to better evaluate underlying mechanisms and potential treatments. Outcome measures are designed to measure multiple parts of the pain experience, including reflexive hyperalgesia measures, sensory and affective dimensions of pain, and impact of pain on function and quality of life. In this review, we discuss the common methods used for inducing each of the pain phenotypes related to clinical pain syndromes as well as the main behavioral tests for assessing pain in each model.

Perspective: Understanding animal models and outcome measures in animals will assist in translating data from basic science to the clinic.

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Pain, both acute and chronic, remains a significant health problem despite tremendous progress in understanding its basic mechanisms. The Institute of Medicine⁸⁷ reports that more than 100 million Americans experience chronic pain—more than heart disease, cancer, and diabetes combined. Further, pain costs the United States half a trillion dollars annually, measured in terms of health care usage, lost wages, and impact on quality of life. Despite the prevalence and impact of pain, it is extremely difficult to treat, and few basic sci-

ence advances have been effectively translated to the clinical setting over the last several decades.

Animal models of nociception (pain) date back to the late 19th century and have been crucial in our understanding of pain processes.²⁰² Since then, there have been a large number of animal models of disease developed to better understand pain from a variety of disease states, both acute and chronic, and these have proven useful in further advancing disease-specific questions and processes.^{14,16,75,165,208} It has become increasingly clear that pain is a heterogeneous phenomenon that differs widely based on the affected tissue (skin, muscle, joint, viscera, etc)^{78,137,172} and the mechanism of injury (thermal, mechanical, inflammatory, neuropathic, etc).^{50,125,166}

Animal models of nociception have 2 important components: the method of insult and the subsequent endpoint measurement. The most appropriate models,

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whether an injury, application of chemical agents, or other manipulations, should produce nociception by recapitulating the mechanisms of specific clinical conditions. Similarly, measures of nociceptive behavior not only must detect pain-like responses but should do so in a manner consistent with the clinical experience of pain. Measures of reflexive behaviors such as withdrawal thresholds to noxious stimuli have been used for decades to examine mechanisms of pain. These have clearly proven useful in advancing our understanding of the physiological basis of nociception; identification of neurotransmitters, receptors, intracellular messengers, and genes involved in pain behaviors; and better understanding of existing pharmacologic and nonpharmacologic pain treatments.^{10,37,50,56,208,209} Further, over the last several decades, the pharmacologic action (eg, efficacy, potency, duration of action) of a broad spectrum of analgesics to reduce reflexive sensory responses in rodent models of acute nociception and chronic pain have demonstrated consistent correspondence to human analgesia.²¹¹

It is clear that other behavioral tests can also produce valuable information that may not be gained solely from reflexive tests. As pain is a multidimensional experience¹²³ that includes a sensory experience of pain that can be dissociated from unpleasantness, it is useful to have measures that assess spontaneous pain behaviors, cortical processing and decision making, and physical activity levels (reviewed below). Further, because pain has a significant impact on function and quality of life,⁸⁷ measures that reflect these more complicated consequences of pain in animals will also help improve our understanding of mechanisms and diseases.

There has recently been significant debate over the most appropriate animal models of pain and which behavioral measures should be used. This debate focuses on the failure of the translation of basic science data into effective analgesics and has led to a reexamination of the utility of animal models of pain and behavioral measures for screening new potential analgesics. One well-known failure is that of the neurokinin-1 receptor antagonists (substance P).⁷⁷ Several reasons have been suggested for these failures.¹²⁶ One concern is the reliance of studies on reflexive measures, and it has been suggested that additional measures of supraspinal integration that use nonreflexive pain behaviors should be included, such as operant learning measures, spontaneous nocifensive behaviors, and quality of life or physical activity measures. Another concern is the use of animal models of disease that do not reflect the clinical condition the experimenter is trying to model, such as using inflammatory pain in animals to study chronic low back pain. Despite the failures, successes based on animal models have been noted, including the use of tumor necrosis factor- α antibody therapy for rheumatoid arthritis and targeting N-type calcium channels (ziconotide) and potentially nerve growth factor antibodies (tanezumab) for chronic pain.^{2,7,95,167} Other therapies may provide mixed results, as seen in targeting TRPV1 with systemic antagonists. This has proven difficult because of significant side effects (ie, hyperthermia), but desensitization of TRPV1 channels

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with capsaicin creams does significantly reduce pain in several different pain conditions (for review see⁸⁹).

The argument presented here is that animal models should be based on 1) understanding the clinical disease presentation and pathology (ie, face validity) and 2) behavioral measures that assess issues particular to that disease. For example, osteoarthritic knee pain generally involves mild pain while resting (spontaneous pain) but significant pain with movement (evoked pain). On the other hand, people with neuropathic pain generally have significant spontaneous pain as well as pain with touch or pressure (evoked pain). Therefore, multiple outcome measures should be examined in animal studies, and these outcomes should reflect behavior observed in the pain condition in humans for which the experimenter is studying.

It should be pointed out as well that failure of an analgesic to relieve symptoms in a clinical trial is not necessarily directly attributable to a basic failure of the research effort in animals. As with animal models, clinical trial design should also consider basic research findings, and multiple outcomes measures should be considered that include not only resting pain but movement pain, hyperalgesia, function, and quality of life measures. Each of these constructs is unique and may reflect a different outcome. As an example, using a nonpharmacologic treatment (transcutaneous electrical nerve stimulation [TENS]), Sluka and colleagues have repeatedly shown a measured reduction of hyperalgesia (increased sensitivity to evoked pain measures) in animal models of disease.¹⁷⁵ On the other hand, a great majority of clinical trials have measured spontaneous pain in human diseases.¹⁷⁵ Although TENS had no effect on spontaneous pain in postoperative pain, osteoarthritis, or fibromyalgia, it significantly reduced walking pain and hyperalgesia in these populations.^{44,155,199} Most clinical trials rely on measures of subjective pain ratings, yet because pain impacts nearly all aspects of a person's life, including function, activity, and quality of life, it is not always clear which of these changes (or lack thereof) in pain ratings was the main driving factor. We propose that clinical trials should incorporate not only pain measures at rest but also evoked pain measures and function and quality of life measures. Indeed, experts in clinical pain research, under the name IMMPACT (Initiative on Methods, Measurement and Pain Assessment in Clinical Trials), proposed guidelines for the measurement of pain treatment outcomes across multiple domains: pain, physical function, emotional function, global improvement, symptoms, and adverse events.^{57,195}

Thus, the present review is designed to give a better understanding and brief review of the available animal models of disease, which include inflammatory, neuropathic, muscle, joint, visceral, cancer, and postoperative pain. We will provide a general overview of available models and assessment of their usefulness. We will also review measures of pain behaviors in animals and will include evoked/reflexive, spontaneous, and affective pain behaviors as well as measures related to function and quality of life. Having a better understanding of both the disease models and the behavioral measures will assist

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