Gene 537 (2014) 184–188

Contents lists available at ScienceDirect

Gene

journal homepage: www.elsevier.com/locate/gene

Review

Pain assessment in animal models of osteoarthritis

Margaret J. Piel [a], Jeffrey S. Kroin [b], Andre J. van Wijnen [f], Ranjan Kc [c], Hee-Jeong Im [c,d,e,*]

[a] *Comparative Medicine Consultants, Chicago, IL 60631, USA*
[b] *Department of Anesthesiology, Rush University Medical Center, Chicago, IL 60612, USA*
[c] *Department of Biochemistry, Rush University Medical Center, Chicago, IL 60612, USA*
[d] *Department of Orthopedic Surgery, Rush University Medical Center, Chicago, IL 60612, USA*
[e] *Department of Internal Medicine (Section of Rheumatology), Rush University Medical Center, Chicago, IL 60612, USA*
[f] *Department of Orthopedic Surgery & and Molecular Biology, Mayo Clinic, Rochester, MN 55905, USA*

ARTICLE INFO

Article history:
Accepted 30 November 2013
Available online 10 December 2013

Keywords:
Rodents
Dogs
Horses
Rabbits
Guinea pigs

ABSTRACT

Assessment of pain in animal models of osteoarthritis is integral to interpretation of a model's utility in representing the clinical condition, and enabling accurate translational medicine. Here we describe behavioral pain assessments available for small and large experimental osteoarthritic pain animal models.

Contents

1. Introduction

Animal models of osteoarthritis (OA) include those that develop spontaneously or are surgically or nonsurgically (chemically) induced, all of which can provide insights into the molecular, pathological, or biochemical progression of changes in the joint during OA. Chronic pain is a hallmark of OA, and its evaluation in any animal model is integral to assessing the relevance and utility of that model in translation research. OA pain is typically localized and related to movement

Abbreviations: BPI, basic pain inventory; CBPI, canine basic pain inventory; DWB, dynamic weight bearing; GUVQuest, Glasgow University Veterinary School questionnaire; LABORAS, Lab Animal Behavior Observation Registration and Analysis System; OA, osteoarthritis.

* Corresponding author at: Cohn Research BD 516, 1735 W. Harrison, Rush University Medical Center, Chicago, IL 60612, USA. Tel.: +1 312 942 3091; fax: +1 312 942 3053.
E-mail address: Hee-Jeong_Sampen@rush.edu (H.-J. Im).

0378-1119/$ – see front matter
http://dx.doi.org/10.1016/j.gene.2013.11.091

or weight-bearing of the affected joints. In animal models, these joints are typically the knee and/or hip joint.

Pain is difficult to evaluate objectively because of the inherent variability in the individual's interpretation of the sensory input. This variability represents the emotional and cognitive components of pain perception. In addition, little correlation exists between the objective measures of OA (e.g., radiologic or pathologic changes) and the degree of chronic pain experienced by the individual. Many assessments of pain in OA animal models are behaviorally based, and may require that the animals be acclimatized to any apparatuses before testing. Measures for assessing pain in animals can be direct or indirect. Indirect measures include static or dynamic weight-bearing, foot posture, gait analysis, spontaneous movement, and mechanical/thermal/cold sensitivity. Direct measures include hind limb withdrawal test, knee compression force, struggle threshold angle of knee extension, knee tissue edema, vocalizations after stimulation of the affected knee, and brain imaging.

2. Pain assessment methods for osteoarthritis models in small animals

Small animals (primarily mice and rats but also rabbits and guinea pigs) are used extensively in OA research, and a large repository of historical data, especially in rats and mice, exists to which research data can be compared. Their small size and typically lower cost for purchase and maintenance compared with large animals make them attractive animals in which to model OA. Some small animals, such as mice, can be genetically altered to enable the study of specific modulators in the development of OA, and while others, such as the Duncan Hartley guinea pig, can spontaneously develop OA. Methods used to assess pain in rodents include those that are mechanically, anatomically, or chemically based.

2.1. The rotarod test

This is a performance test that utilizes a rotating rod onto which a rodent is placed. The rotating rod creates forced motor activity so as to evaluate functional parameters, such as balance and coordination, by measuring riding time (seconds) or endurance. Each animal is trained for 5 min at a constant speed of 4 rpm on the rotarod (Rotamex, Columbus Instruments). The first trials start at least 1 h after training. Every day, each animal receives a number of trials, separated by 30 min, at speeds accelerating from 4 to 40 rpm (with a 4 rpm increase every 30 s). Each animal is tested for a number of consecutive days (typically 3). Each trial is finished when the animal falls off the rotarod. The latency to falling off the rotarod is recorded and used in subsequent analyses (Fig. 1).

2.2. Computerized incapacitance meter system

The dynamic weight bearing (DWB) system is a computerized incapacitance meter (similar to gait analysis) in which behavioral observations are made on the animal during free ambulation on four paws, which is consistent with normal gait in quadrupeds. Computerization obviates observer bias. This test evaluates weight redistribution associated with pain. Redistribution of body weight to a portion of the paw surface is quantified as OA-induced impairments in paw positioning. During data capture, raw data for each paw is synchronized with images from a video camera, and the averaged values are encrypted and recorded on a computer that has a sampling rate of 10 Hz. This provides for accurate and non-biased pain assessment. The weight distribution of the animal, per limb, can be shown for each time period, with the mean and the variation coefficient (Fig. 2).

Fig. 1. The rotarod test.

2.3. Gait analysis—CatWalk® (Noldus)

The Catwalk method is an automated quantitative gait analysis that allows the objective and rapid quantification of individual paw parameters as well as parameters related to inter-limb coordination (Gabriel et al., 2008). Briefly, light from a fluorescent tube is sent through a glass plate. Light rays are completely reflected internally. As soon as anything, e.g. a rat's paw, is in contact with the glass surface, light is reflected downwards. It results in a sharp image of a bright paw print. Locomotion can be considered as a daily life activity, i.e. it is a voluntarily initiated movement, repeated several times a day. Daily use of the painful limb can lead to habituation, which further results in a subsequent attenuation of the behavioral gait adaptation. Analysis of all gait parameters is performed through the use of an appropriate software program.

2.4. Assessment of spontaneous behavior

Spontaneous exploratory activity is measured as a method to assess ongoing pain (Kroin et al., 2006; Martin et al., 2004). Animals are tested in clean, clear vivarium plastic cages (42 × 25 × 20 cm) enclosed in a cage rack. The Photobeam Activity System (San Diego Instruments, San Diego, CA) uses adjacent beams which are 5 cm apart and beam interruptions are recorded automatically. One set of photo-beams is

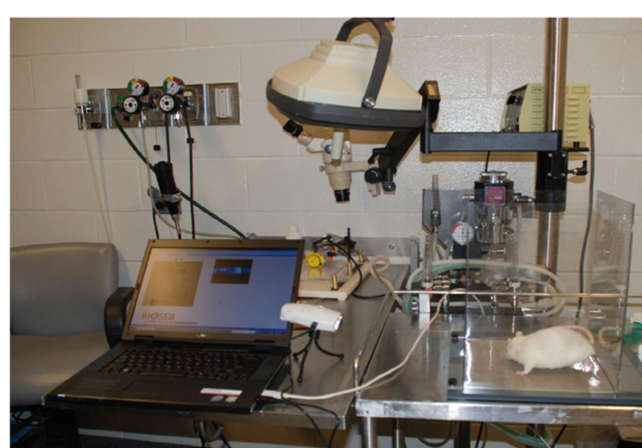

Fig. 2. Computerized incapacitance meter system.