

Development of Behavioral Measures of Osteoarthritis-induced Pain in Rabbits

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ABSTRACT

Osteoarthritis (OA) is a painful and disabling disease affecting millions of patients worldwide. The existing drug therapies for OA reduce pain, but are only moderately effective. The broad objective of our work is to develop OA pain models to both better understand the pathogenesis of OA-induced pain and assess potential analgesic agents. The specific objective of the work described is to establish behavioral methods to measure OA induced spontaneous pain in rabbits, species that are not commonly used for pain studies, using weight bearing and rearing assessments. Weight bearing was evaluated by placing rabbits in a chamber, specifically designed so each hind paw was resting on a separate transducer pad, to accurately measure the difference in weight distribution between ipsilateral and contralateral limbs. Rearing assessment was accomplished by placing rabbits in spacious chambers, where animals could freely move, and measuring the number of rearing episodes over a fixed period of time. This allowed utilizing a well characterized surgical model of OA in rabbits - anterior cruciate ligament transection (ACLT) that closely resembles post-traumatic OA in humans, as well as taking advantage of relatively large joint volume for assessment of intra-articularly delivered therapies.

Author Keywords

Osteoarthritis, pain, osteoarthritis-induced pain, behavioral measure, ACLT, rabbit, weight bearing, rearing.

INTRODUCTION

Despite exciting progress in the understanding of molecular and cellular mechanism of osteoarthritis, chronic pain

which is the most prominent symptom of this disease remains a challenging entity to treat. This in part owes to lack of optimal models and assays for measuring OA-induced pain in animals. To date, most of preclinical studies use rat models and evoked stimuli to measure osteoarthritis-induced pain. Here, we provide an analysis of pain in rabbits – species that are not commonly used for behavioral studies of pain. We have utilized anterior cruciate ligament transection (ACLT) - surgical model of osteoarthritis, which closely mimics post-traumatic OA in humans. To assess behavior signs of pain we have used weight bearing and rearing assays. These assays allow to measure ongoing, spontaneous pain – a common clinical complaint and an important target for new drug development.

METHODS

To model OA, rabbits were anesthetized and after skin incision, joint was fully exposed, ACL was identified, apprehended with a micro-dissecting hook, and transected. The procedure predictably resulted in chondrocyte loss and lesion formation, characteristic of OA, which was confirmed histologically. A separate group of animals underwent sham surgery. To assess the development of pain-like behavior in rabbits we have utilized weight bearing (WB) and rearing tests. WB was measured using an incapacitance tester, where rabbits were placed in the holder specially designed to maintain the animal comfortably positioned on two separated sensor plates. In the absence of hind paw injury animals apply equal weight on both hind paws, indicating a postural equilibrium. After unilateral hind paw tissue injury, a change in the weight distribution on the sensor can be detected, with less weight applied by the injured paw. After acclimation in the chamber for 5-10 min, five consecutive readings that did not require a shift in animal position or any other manipulation were taken. Additionally, to measure changes in rabbit activity in response to joint injury, rabbits were placed in an enclosed chamber (2.5×2.5 ft.) and the number of rearing episodes was recorded over a 15 min period of time.

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RESULTS AND CONCLUSIONS

Experimental results from WB analysis demonstrate a clear differentiation between naïve and OA animals that is statistically significant, thus indicating that weight bearing is an accurate and reproducible method that can be used to measure pain-like behavior in rabbits. On the contrary, rearing assessments were not able to detect differences between ACLT and sham groups and concluded that rearing is not a sensitive enough tool for the analysis of behavioral signs of pain in rabbits. Pharmacologic characterization of the validity of weight bearing for the detection of pain with commonly used analgesics is in progress.

Ethical Statement

Male New Zealand White rabbits (~3000 g at the start of the study) housed individually in ventilated cages with free access to food and water, were used for this study. Rabbits were maintained in temperature and humidity controlled animal rooms on a 12 h light/dark cycle in an Association for Assessment and Accreditation of Laboratory Animal Care accredited facility. All experiments have been approved by the Institutional Animal Care and Use Committee at Genzyme Corporation and are in strict accordance with the ethical guidelines laid down by the International Association for Study of Pain.