HYLAN G-F 20 ATTENUATES KNEE PAIN IN RAT MODEL OF OSTEOARTHRITIS

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INTRODUCTION: Osteoarthritis (OA) is an age-related joint disease characterized by progressive degeneration of articular cartilage and development of chronic pain. Although a number of experimental OA models have been employed to investigate the underlying etiologies of the cartilage degeneration [1, 2], there have been relatively few investigations to study the chronic knee pain in animal models of OA. Moreover, employing these models in the assessment of the analgesic efficacy of putative therapeutics remains largely unexplored. Hyaluronic acid (HA), a major component of synovial fluid and cartilage matrix, is used for treatment of OA patients via intra-articular administration. However, even though a clinical benefit of HA has been demonstrated in patients, the mechanisms underlying this therapeutic benefit remain elusive. Therefore, the objective of this study was to measure pain behaviors in a rat model of surgically-induced OA [3] and then utilize the model to evaluate the analgesic efficacy of Hylan G-F 20 for its ability to provide pain relief.

METHODS AND MATERIALS:

Animals and Treatments: Adult male Sprague-Dawley rats (Harlan Sprague Dawley, Inc., Indianapolis, Indiana, USA) weighing approximately 275 ± 50 g were used as test subjects and allocated to 5 treatment groups, with 10 rats per group. Surgically-induced OA was produced by medial meniscectomy (MSX) of the right knee [1] in 4 groups, while a fifth group underwent sham procedure to serve as a control. The 5 treatment groups were as follows: 1) MSX + 3 intra-articular (IA) injections of lactated ringers solutions (LRS) 14, 21, and 28 days post-MSX; 2) MSX + 3 IA injections of 0.04 mg Hylan G-F20 (Genzyme Corporation, Cambridge, MA) 14, 21, and 28 days post-MSX; 3) MSX + a single IA injection of 0.06 mg cortisone per rat (triamecinolone acetonide) on day 14 post-MSX; 4) MSX + 5 mg/kg morphine sulfate s.c. (Sigma) on behavioral testing days 3, 10, 15, 22, 29, 36, 43, and 50; 5) Sham + 3 intra-articular (IA) injections of LRS days 14, 21, and 28.

Behavioral Testing: All animals underwent behavioral analysis for mechanical allodynia prior to MSX, and again on days 3, 10, 15, 22, 29, 36, 43, and 50 days post-induction of OA. For groups receiving IA injections, the injections were administered 24 hours prior to the allodynia testing. Animals treated with morphine sulfate were tested approximately 30 minutes following the subcutaneous administration of drug. Mechanical allodynia was measured using von Frey filaments applied to the plantar surface of the hind limb. The withdrawal threshold was determined according to Chaplan’s “up-down” method [4] involving the use of successively larger and smaller filaments to identify the 50% response threshold.

RESULTS: Previous studies in our laboratory have demonstrated histological evidence of OA lesions following MSX (Figure 1). Analysis of mechanical allodynia revealed significant increases in sensitivity that began within 72 hours post-surgery and persisted over the entire course of the experimental period. Morphine was able to reverse allodynia at each time point providing evidence that this behavior was pain related. Two weeks following OA induction the animals were treated by intra-articular injection of Hylan G-F20 (once a week for 3 weeks) or steroid (once) and tactile allodynia measured on day 3, 10, 15, 22, 29, 36, 43 and 50. Both IA treatment reversed allodynia on day 21, 28 and 35 respectively (Figure 2). The study demonstrates the ability of Hylan G-F20 to provide pain relief comparable to that seen with steroid.

CONCLUSIONS: OA pain is a complex process involving both peripheral and central sensitization. HA has been used to treat OA pain but its mechanism of action remains elusive. This is partly due to lack of animal models to evaluate pain in osteoarthritis. We have reproduced and employed rat models of OA pain to evaluate the analgesic properties of HA. We observe that IA HA provides pain relief in this model comparable to that of IA steroid in terms of pain behavior. This result suggests that this model could provide us with a tool to understand how HA influences the molecules involved in induction and maintenance of chronic arthritic pain. This model will also be useful in developing and evaluating drugs for relieving OA pain.

REFERENCES