Intra-Articular Treatment with Recombinant Human Bone Morphogenetic Protein 7 (rhBMP-7) Attenuates the Development of Post-Traumatic Osteoarthritis in Rats

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Introduction

Several experimental animal models have been developed for human osteoarthritis (OA) and used to study the pathophysiological efficacy of disease and symptom modifying OA drug candidates in various species. (1) One of these candidates is recombinant human bone morphogenetic protein 7 (rhBMP-7). (2) It is a bone-inducing agent used currently in clinical practice to enhance bone formation in spinal fusions and during fracture repair. In preclinical studies, rhBMP-7 has been shown to attenuate the development of degenerative changes induced by anterior cruciate ligament transection in rabbits and by excessive running in rats and to repair cartilage damage in rabbits, goats, sheep, and dogs. In this study, we characterized the effects of intra-articular rhBMP-7 treatment on the development of post-traumatic OA induced by surgical medial meniscal tear (MMT) and medial collateral ligament transection (MCLT) in rats. (3)

Aim of the Study

The objective of this study was to characterize the effects of intra-articular rhBMP-7 treatment on the development of post-traumatic OA induced by surgical MMT and MCLT operation in rats.

Materials and Methods

Surgical preparation. Male Lewis rats, body weight, static and weight-bearing limbs were measured as a whole. OA was induced by a 6-mm incision at the patellar ligament insertion. OA surgery was performed under general anesthesia. Animal care and handling was performed according to the guidelines of the Institutional Animal Care and Use Committee. The use of animal models is justified by the advances in understanding of the disease and the potential for developing effective treatments. The study was approved by the Ethical Committee of Turku University, and all experiments were conducted in accordance with the guidelines of the Finnish Ministry of Agriculture and Forestry.

Statistical analysis. All data are presented as mean ± standard error of mean (SEM). All the data were normally distributed with a skewness of approximately zero and p-values < 0.05 were considered statistically significant. Statistical analysis was performed using two-way analysis of variance (ANOVA), followed by a Tukey’s post-hoc test (GraphPad Prism, version 5.0). The significance level was set at p < 0.05.

Study Design

Static Weight Bearing

Body Weight

Degenerative Changes in Knee

Static Mechanical Allodynia

Representative Knee Images

Study Findings

In MMT+MCLT rats, paw weight bearing and withdrawal threshold were decreased in operated hind limbs at the beginning of treatment and after 2 weeks of treatment. Treatment with rhBMP-7 improved paw weight bearing and increased paw withdrawal threshold. In MMT+MCLT rats treated with vehicle, from mild to marked degenerative changes were observed in medial tibial plateau. Changes in articular cartilage included focal cartilage degeneration as well as cartilage degeneration at the outer 1/3 of the plateau. Treatment with rhBMP-7 prevented the decrease in articular cartilage matrix and significant cartilage degeneration as well as cartilage degeneration volume and lesion depth ratio especially at the inner and middle 1/3 of the medial tibial plateau.

Conclusions

Intra-articular treatment with rhBMP-7 at 0.25 μg/wk demonstrated a focal chondroprotective activity in the rat MMT + MCLT model of post-traumatic OA. This supports the development of rhBMP-7 as a potent disease modifying OA drug candidate for human OA.

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References


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