Introduction
Several experimental animal models have been developed for human osteoarthritis (OA) and used to study the preclinical efficacy of disease and symptom modifying OA drug candidates in various species. One of these candidates is recombinant human bone morphogenetic protein 7 (rhBMP-7). 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 and medial collateral ligament transection (MMT + MCLT) in rats.

Methods

Animal experimentation: The study was conducted using male Lewis rats (body weight range 360-425 g). Unilateral OA was induced in their right knee joints by surgical MMT and MCLT operation. Treatment was started one week after the operation and continued once a week for 5 weeks. Rats were treated intra-articularly with rhBMP-7 0.25 μg/week and with vehicle at 0.05 ml/week. Treatment effects on body weight and OA symptoms were followed during the study. After 6 post-surgery weeks, rats were terminated and their knee joints were harvested. Knee joint analysis: Joint discomfort and pain were used as OA symptoms. The joint discomfort was determined as static weight bearing and measured as hind paw weight distribution using Inacapacity Tester (Linton Instrumentation, Norfolk, UK). The joint pain was determined as static mechanical alldynia and measured as paw withdrawal threshold using von Frey filaments (0.02 - 15.0 g). North Coast Medical, Morgan Hill, CA, USA). Microscopic QA assessment was performed using the recommendations of the OARSI histopathology initiative in these coronal sections obtained from the weight-bearing area of medial tibial plateau at 200 μm intervals.

Statistical analysis: All results are presented as mean ± standard error of mean. If the assumptions of parametric tests were fulfilled as such or after appropriate data transformation, one-way analysis of variance and linear contrasts of means were applied for evaluating statistical significances of measured parameters. Otherwise, statistical significances were evaluated using non-parametric Kruskal-Wallis and Mann-Whitney U tests.

Body weight

Conclusions

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

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References