Changes in epiphyseal bone, subchondral bone plate and epiphyseal trabecular bone in surgically and chemically induced rat models of osteoarthritis

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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. The preclinical efficacy has been determined by numerous microscopic scoring systems and joint pain assessments. Recently, the histopathology initiative of Osteoarthritis Research Society International (OARSI) presented recommendations for histological OA assessment in different species in order to standardize preclinical efficacy studies. Recommendations for rat samples focus on articular cartilage, synovium, joint capsule, and growth plate. When studying treatment effects on osteoarthritic rat bone, the histological OA assessment should be completed with the analysis of epiphyseal bone, subchondral bone plate and epiphyseal trabecular bone.

Aim of the study
This study characterized changes in epiphyseal bone, subchondral bone plate and epiphyseal trabecular bone and assessed knee joint discomfort, pain and degenerative changes in four rat OA models, induced by intra-articular monooiodacetate (MIA, 1 mg), medial meniscal tear combined with medial collateral ligament transection (MMT + MCLT), anterior cruciate ligament transection combined with partial medial meniscectomy (ACLT + pMMx), and ACLT alone.

Methods

Animal experimentation: Unilateral OA was induced in the knee joints of 3-month-old male Lewis rats (body weight 330 - 380 g) using the following rat OA models: 1) MIA at 1 mg, 2) MMT + MCLT, 3) ACLT + pMMx, and 4) ACLT. Body weight, static weight bearing and static secondary mechanical alldynia were followed during the in-life phase of the study. Knee joints were harvested at two time points in each model, as follows: at 2 and 4 weeks in the MIA model, at 3 and 6 weeks in the MMT + MCLT model, at 4 and 8 weeks in the ACLT + pMMx model, and at 5 and 10 weeks in the ACLT model.

Knee joint analyses: Static weight bearing was determined as hind paw weight distribution by incapacitation Tens (Linton Instrumentation, Norfolk, UK) and static mechanical alldynia as paw withdrawal threshold by von Frey filaments (0.02-15.0 g; North Coast Medical, Morgan Hill, CA, USA). Histological OA assessment was performed by OARSI rat scoring system and histological bone analysis separately in epiphyseal bone, subchondral bone plate and epiphyseal trabecular bone in three coronal sections obtained from the weight-bearing area of medial tibial plateau at 200 µm intervals and stained in Toluidine blue.

Study design

Fig. 1. This study included four rat OA models. Body weight, static weight bearing, static secondary mechanical alldynia and degenerative knee changes including changes in osteoarthritic bone were analyzed as presented above.

Rat MIA Model

Rat MMT + MCLT Model

Rat ACLT + pMMx Model

Rat ACLT Model

Summary

- Rat MIA model exhibited a reduction in the amount of epiphyseal bone, subchondral bone plate and epiphyseal trabecular bone at 2 and 4 weeks.
- This reduction in bone mass was associated with mild to moderate degenerative changes and a reduction in paw withdrawal threshold.
- Rat MMT+MCLT model demonstrated an increase in the amount of epiphyseal bone, subchondral bone plate and epiphyseal trabecular bone at 3 and 6 weeks.
- This gain in bone mass was observed together with moderate to severe degenerative changes and a reduction in paw withdrawal threshold.
- Rat ACLT+pMMx model showed an increase in the amount of epiphyseal bone and epiphyseal trabecular bone at 8 weeks.
- This increase in bone mass was associated with moderate to severe degenerative changes and a reduction in paw withdrawal threshold.
- Rat ACLT model exhibited a reduction in the amount of epiphyseal bone and epiphyseal trabecular bone at 5 weeks and in the amount of subchondral bone plate at 5 and 10 weeks.
- This decrease in bone mass was associated with mild to moderate degenerative changes and a reduction in paw withdrawal threshold.

Conclusions

The amount of epiphyseal bone, subchondral bone plate and epiphyseal trabecular bone decreased in the chemically induced rat OA model (MIA) and in the surgically induced rat OA model (ACLT) exhibiting mild to moderate OA changes. The amount of epiphyseal bone, subchondral bone plate and/or epiphyseal trabecular bone increased in the surgically induced rat OA models (MMT+MCLT and ACLT+pMMx) exhibiting moderate to severe OA changes.

Acknowledgements

The authors are grateful to Johanna Örling, Anniina Luostari, Natalia Hablained-Kirillov, Riikka Kytömaa, Suvi Suutari and Jani Seppänen for their expert technical assistance.

References