Phenotypic Characterization of Mechanical Sensitivity in Mice Following Medial Meniscal Destabilization as a Model of Osteoarthritis

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Introduction: Pain is the primary concern of the osteoarthritis (OA) patient, yet the systematic study of OA pain has been largely ignored. There is no simple relationship between structural joint damage and pain (1). Only recently have researchers started to study pain behavior in animal models of OA (e.g., the rat monooiodoacetate model). Conversely, the inflammatory assays commonly used by pain researchers (e.g., formalin, carrageenan) are not particularly relevant to OA. The present study endeavors to bridge the two "silos" of pain and OA research, by looking for the interaction of OA and pain sensitivity in mice during the course of knee OA induced by destabilization of the medial meniscus (MMD). Our goals were to characterize pain-related behavioral changes in the mouse MMD model, and to establish the association between behavioral changes and structural changes in the knee joint.

Materials and Methods: Surgery - Destabilization of the medial meniscus was performed in 8-12-week old CD-1 mice of both sexes (housed 4/cage), as described (2). Surgery was performed in the right knee only. Sham surgery was performed in age and sex-matched control mice. Sham surgery was identical to MMD, except that the medial meniscus remained intact;

Mechanical allodynia - Before surgery and at 2-week-intervals thereafter for 56 days, mice were tested for their withdrawal thresholds to von Frey filaments applied to the plantar surface of both hindpaws, using the up-down psychophysical method of Dixon (3). Mice were placed individually in transparent Plexiglas cubicles (5 cm x 8.5 cm x 5 cm high) placed atop a perforated metal floor with 5-mm diameter holes placed 7 mm apart, and habituated for 2 hours before testing commenced.

Nylon monofilaments (Stoelting Touch Test Sensory Evaluator Kit; fibers #2-#9, 0.015 g-1.3 g) were firmly applied to the hindpaw (alternating the side of the body being tested) until they bowed for 5 s. The presence or absence of a clear withdrawal response in that 5-s response was scored. After no less than 30 seconds, the next stronger or weaker fiber was applied, as necessary.

Results: As shown in Figure 1, we observed a robust and progressive decrease in withdrawal threshold in the ipsilateral hindpaw (first statistically significant on post-operative day 28, p<0.01). No significant interactions with sex were observed. Mice undergoing sham surgery displayed no significant changes in withdrawal thresholds at any time point (Fig. 1). A similar pattern of results was observed in C57BL/6 mice (data not shown).

Discussion: In conclusion, MMD in CD-1 mice leads to robust mechanical allodynia, measurable within 2 weeks post-surgery. Correlation with histological findings in the knee joints is currently under investigation. In addition, we are performing MMD surgery in ADAMTS-5 deficient mice, which are resistant to OA in this model, in order to test nociception in comparison with wild types.


Acknowledgements: The authors would like to thank Dr. C. Little, Sydney, Australia, for his help with the implementation of the MMD surgery.

(IMAGE 1)

Fig. 1. Withdrawal thresholds to mechanical stimulation of the right plantar hindpaws of CD-1 mice after MMD or sham surgery of the right knee.