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Original Investigation

A comparative study of early stage arthritis in three experimental rat models☆

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ABSTRACT

Objective: To assess osteoarthritis in rat models at an early stage (7 days after induction).
Materials and methods: This is a retrospective study comparing results from previous experiments. The models compared were the following: (a) anterior cruciate ligament transection model (CLX) and an adjuvant-induced arthritis model in two varieties (b) sub-plantar (ASP), and (c) intra-articular (AIA). Seven days after osteoarthritis (OA) induction, an analysis was made of the clinical, histological, radiological, and serological inflammatory markers (IL-1β, IL-4, IL-6, TNF-α, MMP-2, and MMP-9).
Results: The AIA model produced significant differences in several parameters, when compared to the control group. However, the levels of IL-1 were higher in all OA models than in the baseline group, being more pronounced in the CXL and AIA groups ($p < 0.001$). Surprisingly, the lowest value for IL-4 was observed in the AIA group ($p < 0.001$ vs. baseline group). Furthermore, the most elevated values of MMP-2 were observed in the ASP model.
Conclusions: Although arthritis rat models are used and compared interchangeably as if they were the same, it is shown in this work that at an early stage the models behave quite different in most of the studied variables.

Estudio comparativo de la fase temprana de artritis experimental en 3 modelos de ratas

R E S U M E N

Palabras clave:

Osteoartritis

Modelo animal

Rata

Inflamación

Citoquinas

Metaloproteasas de matriz

Objetivo: Comparar y caracterizar modelos de osteoartritis inducida en ratas en una fase temprana (7 días luego de la inducción).

Materiales y métodos: Este es un estudio retrospectivo que compara resultados de experiencias previas. Se compararon los modelos de: a) corte del ligamento cruzado anterior (CLX), y artritis inducida por adyuvante en sus 2 variedades, b) subplantar (ASP) y c) intraarticular (AIA). Las variables analizadas fueron: estado clínico, histología, radiología y marcadores séricos de inflamación (IL-1β, IL-4, IL-6, TNF-α, MMP-2 y MMP-9).

Resultados El modelo: AIA presenta diferencias significativas en diversos parámetros cuando se compara con el grupo control. Además, los niveles de IL-1 fueron elevados en todos los modelos de osteoartritis respecto al basal, siendo más pronunciados en los grupos CLX y AIA ($p < 0.001$). Por otra parte, el valor más bajo de IL-4 fue observado en el grupo AIA ($p < 0.001$ frente al grupo basal). Además, los valores más elevados de MMP-2 fueron observados en el modelo ASP.

Conclusiones: Si bien se usan y se comparan de manera indistinta los modelos de artritis en ratas como si fueran similares, en este trabajo demostramos que en un estadio temprano los modelos se comportan bastante diferentes en la mayoría de las variables estudiadas.

Introduction

Arthritis in its various nosological presentations is a disease that exhibits a progressive course, with some periods of remission, causing pain and usually presenting as sequels. In human medicine, rheumatoid arthritis is of particular importance due to its incidence, whereas in veterinary medicine, the sport horses have arthritis of chronic and progressive course with sporadic exacerbations, usually due to mechanical overload related to the sporting activity. The adequate management of osteoarthritis (OA) would allow reducing the high economic losses caused by the early withdrawal of animals from the sports competition.

For the study of arthritis both in humans and in horses, scientists have been working for a long time with murine models of arthritis, with the purpose of understanding the pathophysiology of the disease and assessing the usefulness of anti-arthritic drugs. However, there are several models of arthritis in rats that keep a relationship with the diseases studied in humans and other species, but they have not been well characterized neither from the point of view of the early response in their clinical, histological and radiological aspects, nor in terms of their serum inflammatory profile. Considering the regulations corresponding to the rational use of laboratory animals,[1] there arose the possibility to compare retrospectively the results of different experiments carried out in our laboratory based on the use of some of the models proposed for the study of arthritis.

In this work, we compared 3 murine models, which although they are widely spread in experimental arthritis, it has not been previously clarified as to which is the type of arthritis that each one best represents, and it has not been notified either which are the most relevant complementary methods for the study of each of these arthritis.

That is, on the one hand, these models have been used, indistinctly, to assess both acute and chronic phenomena, and in terms of the determination of molecular markers of inflammation, there are contradictions in the information for each model.

Currently, the role that biomarkers would play in OA is uncertain, and this is largely due to the diversity of arthritis models that have been used. The biological validation and utilization of molecular biomarkers could be very useful for the clinical practice in the diagnosis and monitoring of OA, provided that it is known how the levels of these biomarkers vary according to the different presentations of OA and how their levels are associated with each other.

In this work, we compared 3 models that we have used, these are: transection of cruciate ligaments (CLX) and adjuvant-induced arthritis in 2 modalities, intra-articular (AIA) and sub-plantar (ASP).

The CLX model would suppose a type of chronic arthritis produced by the wear of the joint facets as a consequence of the instability produced in the injured joint; this model could correspond to a good model of the sports wear and tear due to overtraining.

On the other hand, adjuvant-induced arthritis has been a model widely used to induce the pathogenesis of rheumatoid arthritis,[2] likewise, this model can be used to resemble other types of reactive arthritis that are usually very frequent in veterinary medicine. Arthritis can be easily induced by subcutaneous inoculation of *Mycobacterium tuberculosis* H37Ra (Mtb) inactivated by heat and suspended in oily excipient. Moreover, the adjuvant-induced arthritis model has been used as a general model of inflammation which allows evaluating the use