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A new mixture of hyaluronic acid and Adelmidrol reduces joint damage in a model of rheumatoid arthritis

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Abstract

Introduction Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease of synovial joints characterized by cartilage degeneration and bone destruction, leading to pain and widespread hyperalgesia[1].Synovial inflammation, together with increased oxidative stress, results in degradation of hyaluronic acid (HA) with decreased concentration of its joint content and changes in its molecular weight distribution [2].These changes profoundly affect joint lubrication and exacerbate cartilage damage, ultimately perpetuating the inflammation-pain cycle[2].Although disease-modifying anti-rheumatic drugs and steroidal / non-steroidal anti-inflammatory drugs can reduce RA inflammation, long-term use is frequently associated with poor tolerability, and a variety of side effects, reinforcing the unmet need for RA[3].Here we investigated a novel association of high-molecular-weight HA(HMW-HA) and the palmitoylethanolamide analogue Adelmidrol in a well-established model of RA, i.e., antigen-induced arthritis (AIA) in mice

Methods Balb/C male mice were immunized with subcutaneous injection of methylated bovine serum albumin (mBSA) on day 0. Fourteen days later, mice were challenged with an intra-articular (i.a.) injection of mBSA in the left femur-tibial joint [3]. On post-injection day (D) 3,7,14 and 21, mice received the study treatment (1% HMW-HA and 2% Adelmidrol, namely Hyadrol®, i.a. injections) or the corresponding vehicle. On D21, histological damage (comprising infiltration of inflammatory cells, bone erosion, and cartilage damage) was scored on H&E-stained sections based on a semiquantitative 0 (normal)-to-5(severe) scale [4]. The mast cell (MC) number, synovial immunohistochemistry for NGF and levels of hyaluronidase in joint tissues (EALISA) were evaluated. The serum concentration of pro-inflammatory cytokines (TNF-α,IL-1β) and low-molecular-weight (LMW)-HA as well as enzymatic antioxidants (i.e., SOD,CAT,GPX) were measured. One- or two-way ANOVA followed by Bonferroni test for multiple comparisons was used for data analysis. A p-value < 0.05 was considered significant

Results The histological damage of the affected joint, MC number, NGF expression and hyaluronidase levels were all significantly decreased in animals treated with 1% HMW-HA and 2% Adelmidrol compared to vehicle-treated ones. Moreover, AIA-induced increase in serum levels of proinflammatory cytokines and LMW-HA were significantly counteracted by the study treatment. Finally, the antioxidant status was significantly increased in response to treatment

Conclusion The present results show for the first time that i.a. injections of 1% HMW-HA and 2% Adelmidrol significantly decreased arthritis severity in an experimental model of RA.The recently discovered antioxidant protection by Adelmidrol against oxidative degradation of HA[5],together with the recovered antioxidant status shown in the present study, may be the main mechanisms underlying the observed beneficial effects. The present promising results allow to envisage the i.a. use of 1% HMW-HA and 2% Adelmidrol as a novel candidate to improve disease severity in rheumatic patients

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