Administration of intra-articular hydrogen sulphide reduces the severity of osteoarthritis *in vivo*

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Purpose: Osteoarthritis (OA) results in progressive cartilage destruction leading to joint malfunction. Current treatments, mostly symptomatic, are not able to stop or retard the progression of the disease. Hydrogen sulphide is a small gaseous molecule that has shown to prevent cartilage degradation as well as to exert anti-inflammatory effects in in vitro models of OA, and is the active component of sulphurous minero-medicinal waters. The purpose here was to evaluate the effects of administering an H2S-producing compound, intra-articularly, in an experimental model of OA.

Methods: Experimental OA was induced in Wistar rats by transecting the medial collateral ligament and removing the medial meniscus of the left knee. Right knees were used as control. Animals were randomized into 3 groups (6 rats per group). Group 1 (intra-articular sulphide, IS): A single intra-articular injection of GYY4137 (200 µM in saline, 50 µl) at day 7. Group 2 (intra-articular control, IC): A single intra-articularly injection of vehicle (saline, 50 µl) at day 7. Group 3 (Surgical control, C): No treatment. Gross evaluation of the animals at days 0 (before surgery), 7, 15 and 40 (euthanasia) included indirect evaluation of pain in a Rotarod performance test. Histopathological changes in articular cartilage and synovium were evaluated with the Mankin Score (MS) and the Krenn Score (KS), respectively.

Results: Seven days after surgery animals in all 3 groups showed worse performance in the Rotarod test, with significant increases in the number of falls (except IC) and reductions in the time to first fall. After 40 days, animals in the C group showed no significant improvement in either of these parameters. In the intra-

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articular control (IC) the number of falls had returned to pre-surgical levels, and in the animals that received intra-articular H2S (IS), results were significantly better with respect to both day 0 and both control groups (C and IC). Times to 1st fall were also significantly better in the IS group versus C and IC groups both at days 15 and 40.

Cartilage deterioration as a result of surgery was evaluated with the Mankin Scoring system. Tibial plateaus (TP) and femoral condyles (FC) in both the medial (M) and lateral (L) compartments in each knee were evaluated. There were no significant differences among groups in the lateral compartment, neither when considering TP and FC separately nor for the compartment as a whole. Conversely, scores in the medial compartment were significantly better in the animals treated with intra-articular H2S vs the Control group, both when considering TP or FC separately, and for the compartment as a whole).

Synovial inflammation was evaluated with the Krenn score, and no significant differences were found among the three groups.

Conclusions: Exogenous H2S administered intra-articularly (200 μM GYY4137 in 50 μl saline) can reduce the severity of cartilage destruction in an in vivo model of OA as compared to no treatment or a vehicle control. H2S also led to a reduction in pain levels as demonstrated by a performance test. Thus, these results confirm H2S as a potential treatment in OA, and provide encouragement to investigate this possibility in OA patients through clinical trials.