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Intra-articular administration of hydrogen sulphide ameliorates severity of experimental osteoarthritis

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Purpose: Progressive cartilage destruction leading to joint malfunction is one of the most prominent features of osteoarthritis (OA). At present this pathology has no cure and current treatments are mostly symptomatic, not being 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. The purpose here was to evaluate the effects of administering an H_2S-producing compound, intra-articularly, in an experimental model of OA.

Methods: Experimental OA was induced in a rodent (Wistar female rats) model by transection of the medial collateral ligament and removal of the medial meniscus of the left knee. The right knee was employed as control. Animals were randomized into three groups (6 rats per group). In one group (intra-articular sulphide, IS), GYY4137, a well-known H_2S producing compound, was delivered intra-articularly (200 μM in saline, 50 μl), with one single injection at day 7. The second group (intra-articular control, IC) received vehicle (saline) also in one single injection (50 μl, at day 7) serving as treatment control. The third group received no treatment and served as surgical control (C). Macroscopy clinical evaluation of the animals was performed at days 0 (before surgery), 7, 15 and 40 (euthanasia) including indirect evaluation of pain levels using a Rotarod performance test. Histopathological changes in articular cartilage and synovium were evaluated using a semi-quantitative scoring system (Mankin Score, MS) and a synovitis grading system (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 (Table 1). After 40 days, animals in the C group showed no significant improvement in either of these parameters. In the intra-articular control (IC) the number of falls had returned to pre-surgical levels, and in the animals that received intra-articular H_2S (IS), results were significantly better with respect to both day 0 and both control groups (C and IC) (Table 1). 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 (Table 2). 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 H_2S vs the Control group, both when considering TP or FC separately, and for the compartment as a whole (Table 2). Synovial inflammation was evaluated with the Krenn score, and no significant differences were found among the three groups.

Conclusions: This study demonstrates that a single dose of a H_2S-producing compound (200 μM GYY4137 in 50 μl saline) administered intra-articularly can reduce the severity of cartilage destruction in an experimental model of OA as compared to no treatment or a vehicle control. Further, results from the performance test suggest that exogenous H_2S administration in this manner also leads to a reduction of pain levels in the animals. Thus, these results confirm the potential of H_2S as a pharmacological treatment in OA, and provide encouragement to investigate this possibility in OA patients through clinical trials.

Table 1. Number of falls within a 5-min period, and time to first fall (s) for the three groups.

Group	Falls (n ± sd)				Time to 1st fall (s)			
	T0	T7	T15	T40	T0	T7	T15	T40
C	0.83 ± 0.75	4.00 ± 0.89#	4.00 ± 0.89#	3.67 ± 1.75#	233.7 ± 77.8	57.17 ± 35.39#	90.3 ± 67.5#	77.8 ± 40.2#
IC	1.67 ± 1.03	3.33 ± 1.75	2.17 ± 0.98	2.00 ± 0.89	209.2 ± 78.2	31.67 ± 11.74#	90.8 ± 20.9#	143.3 ± 50.3
IS	1.33 ± 0.82	4.00 ± 1.55#	2.50 ± 1.05	0.00 ± 0.00#*$	265.3 ± 58.8	78.50 ± 65.90#	196.3 ± 81.3*$	300.0 ± 0.0*$

C: control group; IC: intra-articular control (saline); IS: intra-articular sulphide (IS, 200 μM GYY4137). n = 6 in each group. #P<0.05 with respect to T0; *P<0.05 with respect to C; $$P$<0.05 with respect to IC.

Table 2. Mankin Score grading of cartilage destruction.

Group	Medial compartment	Lateral compartment	MTP	MFC	LTP	LFC	Whole joint
C	12.50 ± 0.6	4.0 ± 0.0	12.5 ± 0.7	12.5 ± 0.7	4.0 ± 0.0	4.0 ± 0.0	8.3 ± 4.6
IC	10.0 ± 1.7*	7.3 ± 4.0	9.7 ± 2.3	10.3 ± 1.2	6.7 ± 4.0	8.0 ± 1.7	8.7 ± 2.6
IS	7.0 ± 1.3*	3.8 ± 1.7	7.7 ± 0.6*	6.3 ± 1.5*	3.0 ± 0.0	4.5 ± 3.5	5.7 ± 2.3

C: control group; IC: intra-articular control (saline); IS: intra-articular sulphide (IS, 200 μM GYY4137); M: medial; L: lateral; TP: tibial plateau; FC: femoral condyle. n = 3 in each group. *P<0.05 with respect to C.